Inside: Ten years of RCSI research

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RCSI DEVELOPING HEALTHCARE LEADERS WHO MAKE A DIFFERENCE WORLDWIDE

Acknowledgements

Thank you to RCSI Alumni for their continued support to us as students – providing career advice, acting as mentors, enabling electives and research, and supporting the publication of the *RCSIsmj* since its inception in 2008.

We, as today's generation of students and tomorrow's generation of alumni, are very grateful for this ongoing support.

A special thanks to Professor David Smith for the time and encouragement he has given to the *RCSIsmj* Ethics Challenge and for his support of the annual debate.

We would also like to thank the Dean, Professor Hannah McGee, for her sponsorship, and Margaret McCarthy in the Dean's Office for her constant endorsement and assistance.

The *RCSIsmj* was extremely privileged to have a number of professors and clinicians involved in this year's journal club. We would like to thank the following for their support of, and participation in, the journal club and to express our appreciation of the time, knowledge and expertise they shared with us:

Dr Mark Murphy
Dr Frank Doyle
Mr David O'Brien
Prof. David Henshall
Prof. Gerard Curley
Prof. Arnold Hill
Prof. Sam McConkey
Prof. Fionnuala Breathnach

RCSIsmj contents

Life and how to live it

The growth and evolution of the *RCSIsmj* every year is much akin to our own journey from the embryo – starting off with endless potential and slowly developing the expected parts, growing into a recognisable entity that resembles in some ways the fully-fledged iterations of the past. However, like individual people, each edition undeniably takes on its own character in the process, developing unique themes as it matures; the *journal* you now hold is as alike to what it was at its inception as we are to our own baby pictures. Indeed, in this year's *journal* content we are led to consider life – and medicine – from embryo to life's very end.

We begin with the question of whether altering the germline is appropriate, by ethics challenge winner Katie Nolan. Staff writer Samar Atteih takes a global view of new treatments for cystic fibrosis from a young age, and Michelle Ohle discusses the implications of increasing life expectancy for children with chronic diseases. Moving into more adult issues, Matthew Patel recognises the global trend of increasing acceptance of cannabis use and discusses a seemingly paradoxical presentation of hyperemesis in a chronic cannabis user, while Deena Shah and Claire Gallibois review the ideal approaches to tackling jet lag for the growing number of global travellers. Anshuman Sood takes a long view on health after significant medical intervention, studying renal transplant recipients in his research on renal cell carcinoma. Continuing along the spectrum of age, Simrin Sennik investigates for the presence of different neurodegenerative pathologies in elderly patients with idiopathic normal pressure hydrocephalus. Finally, examining what makes a "good death" are Hugo Reynolds, who encourages advanced care planning, and Daniel O'Reilly, who reflects on two books dealing with the subject on a personal and medical level.

To lay bare the worst kept secret in scientific research, the whole process from start to finish is an exercise in trial and error. Dean Kamen, a modern inventor (including of the Segway) says: "The unintended consequence of redefining success as lack of failure is that we quickly become so risk averse and everything we do in life is only marginally better than what we did yesterday. Life is so short. We shouldn't waste any of it trying to do anything marginal".

We sincerely hope you find this edition as challenging and informative as we have in its making – and that you are also inspired to abandon the marginal in pursuit of the extraordinary.

Jenna Geers
Editor-in-Chief, *RCSIsmj* 2016-2017

Director's welcome

"If you always do what you always did, you will always get what you always got." – Albert Einstein

It is with great pride and joy that I welcome you to the tenth anniversary edition of the *RCSIsmj*. With every passing year, we have continued to receive more submissions for publication and this year was no exception. We continue to be overwhelmed with not just the quantity, but also the improving quality of submissions, making our job exceptionally difficult. I hope the staff next year finds themselves challenged even further!

Over the past decade, we have tried to continually innovate and improve our *journal* as we gradually find ourselves finely interweaving it into the fabric of the RCSI. During my first year, we cemented the now-popular journal clubs, while adding discussions to aid students to understand the publishing and peer review process, in addition to introducing interviews and book reviews. The following year we proceeded to get our scientific blog up and running, in line with the modern open access nature of research and medicine. This year we have inaugurated a section to celebrate our progress as a journal and as a college over the past decade, which we hope to continue in an abbreviated format in the future, for faculty to showcase their research and encourage students to play an increasing role in expanding the dynamic borders of our knowledge of medicine.

With this tremendous milestone for our *journal*, unfortunately my involvement with the *RCSIsmj* now comes to an end. I am tremendously grateful to this year's staff, without whom this task would be impossible. I am confident that I am leaving this task in safe and secure hands. We are also deeply indebted to the continued and necessary support from the Dean's office and the entire faculty at the RCSI. For those who have seen the *RCSIsmj* evolve over the years, we hope you are proud of your colleagues who have contributed to the *journal* and to the field of medicine. I am confident that you will be inspired and impressed by the work of your peers and our faculty this year as well. I am excited to follow the progress of the *journal* as it approaches its rebellious teenage years while we continue in our quest to make innovation ordinary.

Mohit Butaney
Director, *RCSIsmj* 2016-2017

Ethics challenge 2017/2018

BARIATRIC SURGERY FOR TEENAGERS

American doctors are debating whether to offer bariatric surgery to severely obese young people.[1] The market is huge; about three to four million teenagers are eligible, but only about 1,000 per year have the operation. The proportion of adolescents who are severely obese has nearly doubled between 1999 and 2014 – from 5.2% to 10.2% of all people aged 12 to 19.

On the other hand, bariatric surgery is sometimes the only thing that seems to work. "We're at a point in this field where surgery is the only thing that works for these kids but we don't know the long-term outcomes," Aaron Kelly, an expert in paediatric obesity at the University of Minnesota, told *The New York Times*.[2]

For many teens severe obesity is medically, socially and psychologically challenging. It is associated with type 2 diabetes, high blood pressure, sleep apnoea, acid reflux, fatty liver, high cholesterol levels, and depression. "I've had many patients tell me they'd rather be dead [than remain fat]," one doctor told the *Times*.[2]

However, many doctors are deeply sceptical of the health benefits of the surgical option; it has not proven spectacularly successful. According to the most recent studies, most participants shed about one-third of their weight and kept it off for at least five years, but two-thirds remained severely obese and some developed vitamin deficiencies as a result of the operation.

Doctors are thinking of offering the operation at an even younger age than adolescence, since diets, exercise and behavioural therapy just do not work. The longer doctors wait, the more likely it is that the obese teenager will become an obese adult. "It obviously is a controversial area," says Dr Marc P. Michalsky, of the Ohio State University College of Medicine.[2]

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2. Kolata G. 'Doctors Consider a Last Best Hope for Obese Teenagers: Surgery'. *The New York Times*, February 24, 2017. Available from: https://www.nytimes.com/2017/02/24/health/obese-teenagers-bariatric-surgery.html?_r=0.

This is the ninth instalment of the *RCSIsmj* Ethics Challenge. The editorial staff would like to congratulate Katie Nolan on her winning essay in the 2016/2017 Ethics Challenge. Please see page 6 for her submission.

We invite students to submit an essay discussing the ethical questions raised in the scenario presented. Medical ethics is an essential aspect of the medical curriculum and we hope to encourage RCSI students to think critically about ethical situations that arise during their education and subsequent careers. All essays will be reviewed by a faculty panel of experts and the winning essay will be published in the 2018 print edition of the *RCSIsmj*. The deadline for submission of entries will be separate from the general submission deadline for the 2018 edition of the *RCSIsmj*. Please visit our website at www.rcsismj.com for specific dates. Please contact us at editorsmj@rcsi.ie with any questions or concerns.

Submission guidelines

Please construct a lucid, structured and well-presented discourse for the issues raised by this scenario. Please ensure that you have addressed all the questions highlighted and discuss these ethical issues academically, making sure to reference when necessary. Your paper should not exceed 2,000 words.

Your essay will be evaluated on three major criteria:

1. Ability to identify the ethical issues raised.
2. Fluency of your arguments.
3. Academic quality with regard to depth of research, appropriateness of references and quality of sources.

Good luck!

The winning entry will be presented with a prize at the launch of the next issue.

ETHICS CHALLENGE WINNER 2016/2017

Gene editing

By Katie Nolan
RCSI medical student

Introduction

The 2016/2017 *RCSIsmj* Ethics Challenge presents the current state of gene-editing therapies and questions future directions.[1] Gene editing in its current form is very much a double-edged sword – promising a future with endless possibility for medical treatments while at the same time making us question our core beliefs about what is possible and what should be possible. Gene editing came to the fore in the last 20 years as the heralded solution to genetically inherited diseases, and has been making great strides in recent years. Superseding RNA interference techniques, early attempts at targeted gene editing were made with zinc finger nucleases, followed by transcription activator-like effector nucleases (TALENs).[2] More recent and more controversial advances use the CRISPR/CAS9 system. All three techniques utilise endogenous nuclease activity, derived from bacterial immune systems, to direct and excise mutated genes, or insert therapeutic genes, which can ameliorate a disease phenotype.[3,4]

Until recently, this work was carried out in somatic cell types or in pluripotent stem cells with a view to implanting augmented cells that could prevent a disease phenotype developing (e.g., medium spiny neurons in Huntington's disease).[5,6] This is the forefront of current therapeutic work; however, due to the complexity of the human genome and immune system, these techniques have limitations. Attempting to treat a disease once clinical manifestations are present is more difficult than before signs and symptoms manifest clinically. Hence, some scientists and doctors are calling for germline gene editing in gametes (sperm, ovum) and embryos, to eradicate disease-causing gene mutations before these cells replicate and perpetuate the mutations throughout every cell in the body.[7-9]

A definitive solution to inheritable genetic defects or gene mutations would revolutionise medicine but, hindered by our current level of knowledge, it could do so at a very high price. A topic of this magnitude is therefore a polarising subject in the medical community.

In 1997, the United Nations Educational, Scientific and Cultural Organisation (UNESCO) created the Universal Declaration on the Human Genome and Human Rights, which states that the human genome is the fundamental unit of humanity, and enshrines our human dignity and diversity.[10] UNESCO refers to the genome as the "heritage of humanity". In particular, UNESCO states that human dignity requires that we are not "reduced to our genetic characteristics", that we maintain respect for human diversity, and that the human genome does not become a source of "financial gain".[10] Gene editing of germline cells stands to contravene all of these rights and would require stringent regulation, regulatory enforcement and tightly-controlled research to delineate the procedures and the safety guidelines.

Should a temporary or permanent global ban on human germline editing be introduced, and if so, on what basis?

Science, by its nature, moves forward constantly. Owing to the potential benefits of gene editing, and with future advances in the techniques, a permanent ban on gene editing could limit therapeutic opportunity and hinder future therapeutic progress but would be unlikely to halt all progress. That being said, in its current guise and with limited future insight, a temporary global ban on germline editing could provide time for safety, efficacy and ethical guidelines to be developed, and refinement of techniques to be carried out, which would prevent breach of ethical rights.

Germline gene editing in 2016 simply cannot meet the ethical requirements set out by Beauchamp and Childress or the

Declaration of Helsinki (DOH). Beauchamp and Childress focus on four principles of medical practice, which protect the patient's right to understand and choose the safest treatment.[11] The DOH sets rules for conducting medical research in humans.[12] The International Summit on Human Gene Editing, held in 2015 by the National Academy of Sciences, called for a moratorium on germline editing until "safety and efficacy issues are resolved" and "there is a broad societal consensus on the application".[13,14] Indeed, research recently published in China on non-viable human embryos described the use of gene editing to potentially prevent the fatal blood disorder β-thalassaemia, and was a chilling insight into the risks of implementing gene editing without acceptable protocols.[15] The investigators reported that, of 86 manipulated embryos, only four contained the correct genetic material and the technique had caused many "off-target" mutations.[16] Before a temporary ban on gene editing could be removed, production of reproducible data on efficacy and safety in animal, stem cell, and somatic cell models using gene editing would be necessary. Even then, the first patient clinical trials would require tight regulation and lifelong monitoring in a small subset of people.

With the lack of knowledge surrounding gene editing in humans, and therapeutic changes in the genome, a patient or a patient's family may have difficulty in providing true informed consent for new therapies.

Respect for persons

Germline gene editing makes permanent and heritable changes to human DNA that children will carry into adulthood. Germline gene editing may cause "off-target effects", which cannot be controlled and which cannot be predicted. Germline gene editing therefore does not give the child carrying the mutations a chance to make a choice about their health and does not offer "respect for their capacity for self determination".[17]

Future offspring of gene-edited children could be considered to have diminished autonomy if they are directly harmed or at increased risk of disease events from genomic editing. Although this presents a special case, persons with diminished autonomy need to be afforded extra protections.[18]

This is not the first time that respect for autonomy has been waived in clinical genomics; the American College of Medical Genetics and Genomics policy statement from 2013 was found to encourage laboratories to run additional sequencing on patient samples in addition to the original purpose for which the samples were acquired, and further, that the doctor report any incidental findings to the patient.[19] Respect for persons also requires health professionals and law makers to act in a patient's best interests (beneficence) and to prevent harm to the patient (nonmaleficence) through ineffective treatment, loose guidelines or unsafe conditions.[11,20]

Balancing risks with benefits

The DOH states that research must minimise harm and put the health of the patient as a priority.[12] Germline mutations to remove a genetic disease could have disastrous future consequences for subsequent generations. Medicine cannot at this point adequately assess the risks of inaccurate editing, even if the immediate benefits appear worthwhile. The DOH also stipulates that all research must have careful assessment of predicted risks and burdens to individuals; it does not stipulate, however, who is equipped to make these assessments. Assessments would require dedicated panels of scientists (at the forefront of genetic research), doctors (capable of implementing new therapies) and policy-makers. Novel research is just that – novel – and proper assessment of future risks requires data across generations and population sets. Just this year, a new gene-editing technology similar to CRISPR was developed in China, called NgAgo.[21] So even before decisions are made as to how best to proceed with CRISPR, a newer technology has arrived. With more rapidly-developing techniques will come more questions and required evaluation. A safer alternative, pre-implantation genetic diagnosis, could identify embryos with the disease, and embryos fertilised *in vitro*, which are not diseased, could be implanted, diminishing the risk of genetic aberrations.[22]

Informed consent

Informed consent is required in clinical and experimental research to ensure that patients understand and consent to all associated risks and benefits. It is crucial to ethical and transparent research.[23] With the lack of knowledge surrounding gene editing in humans, and therapeutic changes in the genome, a patient or a patient's family may have difficulty in providing true informed consent for new therapies.[24] While doctors and scientists do not know the full possibility of future outcomes in humans, a patient or their parents will find it impossible to make a fully-informed choice.[25] Stem cell-based therapeutic research and biomedical research on animals have taught us that we can rarely accurately or fully predict outcomes in living organisms.[26,27]

Justice

A major concern in gene editing is determining which populations could avail of it. The ethical principle of justice requires that there be equitable distribution of healthcare and fair treatment of individuals.[28] Justice also addresses which diseases would take precedence for receiving new therapies. For instance, would monogenic diseases such as Huntington's disease or cystic fibrosis take priority over polygenic diseases with defined genetic risk factors, such as breast cancer?[29]

If germline gene therapy was approved, diseases prevalent in low-income countries (LICs) might not be considered a priority when deciding which diseases would be worthwhile therapeutic targets. Sickle cell anaemia affects about 3% of the population in Africa, and the question arises whether this prevalence would make sickle cell anaemia a priority for germline gene editing, and whether therapy would be distributed to areas of highest prevalence.[30] Ethics require that distributive justice be upheld throughout all countries;

however, in LICs it is questionable as to whether they would receive distributive justice without strict protocols being adhered to. As with *in vitro* fertilisation (IVF) and other reproductive health procedures, gene-editing therapeutics would be costly and could have limited availability in LICs, which may not have the facilities or the expertise to implement the technology.[31]

Another caveat is the question of who would pioneer this new therapy. The danger of the research being privatised and sold by companies at a high cost as a niche medicine market cannot be underestimated.[32] Doctors will need to be trained to implement gene therapy in public hospitals, where a broader population base can gain access. The question of privatisation of these niche medical therapies also raises the risk of large corporations exploiting developing countries in future trials and patient testing. The establishment of ethics committees in LICs should help to assuage this problem.[33] Compensatory justice needs to be assessed for future risks. Protocols, legislation and rules need to be established to determine whether the responsibilities to compensate patients for future adverse effects of gene abnormalities would lie with industry, the government or individual doctors.[34]

A study from 2014 found that of 39 countries analysed, 29 have a full legal ban on genetic editing. The USA has ambiguous rules; China, Japan and Ireland have a ban but lack legal enforcement. With the majority of countries exercising a ban on genetic manipulation in humans, a worldwide consensus on implementing new techniques would be required to allow germline editing as a therapeutic.[35]

Is there an ethical difference between using gene editing for the avoidance of severe inherited diseases or for enhancement of human capabilities?

As a doctor one's duty of care is to patients, to ensure that they are fully informed of their diagnosis, that they understand and consent to treatment, and that the benefits of treatment outweigh the risks.[36] If gene editing were regulated and shown to be effective in preventing a severe inherited form of a disease prevalent in a patient's family, then it may be ethically difficult to oppose. However, human enhancement poses many more ethical and moral dilemmas, and the use of gene editing for human enhancement is rejected by most scientists involved in therapeutic gene editing.[37] As with therapeutic germline gene editing, strict regulation is required to ensure fair distribution and confer benefits equally to patients.

A more ethically and morally pressing issue is the definition of "enhancement". While gene editing for an inherited disease would solve a single defect, enhancement has endless possibilities and would require much more stringent regulation. Article 6 of the DOH states that no person "shall be subject to discrimination based on their genetics".[10] Enhancement therapy could only create discrimination between rich and poor, enhanced and natural. Gene editing could be utilised to bolster a eugenics movement and promote racist ideals about "desired human traits".[38] In competitive sport, genetically-enhanced athletes would destroy the ethos of competitive sportsmanship and it is unlikely that any ethical or regulatory body would be equipped to legislate such a situation.[39]

Conclusion

If the human genome is the "heritage of humanity", then using advanced technology to alter it should only be done when we are confident that it can be done effectively and safely, and only with a view to preserving human life and dignity. Without this preparatory knowledge, we as a race cannot give informed consent, and we could be sacrificing our natural diversity.

Heralding this view, a recent forum held in California between scientists, industry, bioethics and lawmakers made recommendations for more transparent research to delineate and manage risks related to CRISPR and other methods.[40] This medical and scientific community needs to work with government and the wider public on the determination of policy and strategy for gene editing before committing the future of humanity to new therapies.

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Celebrating a passion for research

RCSI's Research Strategy focuses on translational health research – 'from bench to bedside to population' – because ultimately 'Today's research is tomorrow's healthcare'. We work to ensure that you, our undergraduate students, get a sense of the research culture of RCSI during your education here. The passion for research, and the great strides being made in their specialties, are evident from the testimonials of some of your senior professors in the following pages of this special 10th anniversary volume of the *RCSIsmj*.

Alongside their commentaries, I can add from my experience that the best research is conducted when differing disciplines bring their collective expertise together to address a specific health problem. The Department of Psychology, among others, has focused on researching the patient's perspective on health, illness and healthcare. Topics such as patient quality of life and family burden have become increasingly important research themes in many health conditions. RCSI has led on many Irish population health surveys – on general lifestyle, on sexual health and on ageing. We are also proud to co-host a national postgraduate PhD training programme in health services and population health (SPHeRE).

Student research is supported in numerous ways in the RCSI – in particular through the Research Summer School, where over 120 students annually get an opportunity to join research teams here. The student conference (ICHAMS: International Conference of Health and Medicine Students), now in its sixth year, is an example of RCSI student-led showcasing of undergraduate research work. The *RCSIsmj* is the perfect closing point to that triangle of opportunities to 'conduct, present and publish' research as a student. Since its inception in 2008 the *RCSIsmj* has provided a great platform for undergraduate students to showcase and publish your research. The success of the *RCSIsmj* comes from the skill, enthusiasm, and dedication of fellow students who serve as the *RCSIsmj* Executive Committee, the staff writers and the peer review team.

The *RCSIsmj* has gone from strength to strength. It has been wonderful to witness its growth over the last 10 years. As staff, we proudly and regularly present copies to external visitors – who (almost) don't believe such a quality publication could be student produced! We are happy to pass on the credit to you as student teams and contributors who have made this reputation of *RCSIsmj* possible. We celebrate the 10th anniversary edition. Well done to all who have been involved over the last 10 years; your contribution to the RCSI's overall research profile and reputation has been invaluable. Happy 10th birthday!

Professor Hannah McGee
Dean, Faculty of Medicine & Health Sciences

On the shoulders of giants

The landscape in clinical medicine and research today is vastly different than it was when the first edition of the *RCSIsmj* was published 10 years ago. Many of the innovations and gold standards of practice today will be obsolete in a decade's time. With the blistering pace of medical research and development in today's world, it can be easy to become distracted by cutting-edge technologies, or tucked away in a lab, immersed in niche scientific predicaments that have plagued clinicians for decades; we can easily lose perspective on the grander scheme and the significant progress already made. Therefore, it is occasionally necessary to take a step back and look at the road already travelled, in order to appreciate the direction we are travelling in!

The following pages contain reflections from some of the RCSI's senior faculty, who have been some of our biggest supporters over the past decade, providing their insights on progress in their own field over the past 10 years. They comment on their own experience and involvement in research in their respective fields, and many advise students to become part of the driving force behind medical research and continued innovation, in whichever area they choose. The Dean of Medicine, who has supported us at every turn over the past decade, has opened the discussion with a note to students on the central role that research plays in the RCSI's philosophy.

Sir Isaac Newton famously wrote: "If I have seen further, it is by standing on the shoulders of giants". It is this idea – to consciously appreciate the foundation from which we will spring to make further discoveries – which inspired the following segment. We hope you will, as we do, marvel at the discoveries of yesterday and become inspired to take up the mantle of research in your own careers.

Mohit Butaney and Jenna Geers

Respiratory medicine

Professor Gerry McElvaney, Head of Medicine

Progress in the last 10 years

In my areas of cystic fibrosis (CF) and alpha-1 antitrypsin deficiency (AATD) there have been a series of major breakthroughs, which we have been centrally involved in. The big breakthrough in CF has been the development of ion channel potentiators and correctors.

Professor Gerry McElvaney.

The first major study on ion channel potentiators for people with the G551D mutation was one of the most impressive responses to any medication that I have seen, targeting the basic underlying mechanism and showing almost immediate clinical benefits. The data from correctors is not as impressive as yet, but the concepts underpinning them are encouraging. In this period we were the first group to elucidate why women with CF do worse than men and this paper in the *New England Journal of Medicine* has encouraged people to evaluate this dichotomy in other lung and non-lung disorders. In AATD we were the first to show that MZs, who had previously been described as carriers, do have a significantly increased risk for chronic obstructive pulmonary disease (COPD) if they smoke. The importance of this is illustrated by the fact that there are approximately 10 million MZs in the US and 200,000 in Ireland. We also led the two major studies on AAT replacement therapy (*Lancet*, *Lancet Respiratory Medicine*), whereby plasma-purified AAT is given intravenously to people with the ZZ mutation. The results have been unequivocal, showing for the first time that AAT replacement slows down progression of emphysema in this population.

Ongoing research

The major areas of ongoing research in CF and AATD centre on therapeutic options such as improved correctors for CF, and new and improved therapies for AATD. In AATD, we are collaborating with colleagues in the University of Massachusetts to develop a gene therapy strategy and we are also working on aerosolisation of anti-elastase compounds, both of which would decrease treatment burden in AATD. We are also working on understanding the basic mechanism of disease in these two areas.

We have produced significant work on degranulation of neutrophils in CF and AATD, the effects of dysfunctional acidification along with proteomic analysis of biologic fluids and the auto-immune element in these conditions.

We believe this work will advance understanding and promote therapeutic interventions.

Advice

Go to a laboratory with a good track record of publication and mentorship. Be prepared to work very hard; this is not a nine-to-five, five-day-week job.

Read voraciously about your core area. Learn from those around you. Forget about instant gratification and PUBLISH. I didn't need this advice at the time as I already did these things – so this advice is for people wishing to come into my lab or others like it.

Breast surgery

Professor Arnold Hill, Head of Surgery

Breast cancer treatment has changed substantially over the last 10 years. Significant advances have included:

1. The increased range of reconstructive techniques available. Deep inferior epigastric perforator (DIEP) reconstruction is now more commonplace, and the use of special synthetic materials such as acellular dermal matrices have facilitated performing breast reconstruction with implant-based techniques.
2. The development of sentinel lymph node mapping has significantly reduced the volume of axillary surgery performed for breast cancer. Women who have a negative axilla no longer receive an axillary dissection. This has reduced the morbidity from breast cancer surgery substantially.
3. The advent of oncotype testing has reduced the quantity of chemotherapy administered to breast cancer patients by over 50% over the last number of years. Oncotype testing is a genetic test of the patient's tumour, which predicts the likelihood of the breast cancer recurring. A low oncotype score avoids the need for adjuvant chemotherapy. This has been a substantial benefit to patients with breast cancer over the last five years.
4. The area of family history in breast cancer has changed substantially. We now have a greater use of testing for BRCA1 and BRCA2 genes, and our knowledge in this area has been fine tuned with the advent of more sophisticated triaging of patients based on their family history. We now use the IBIS risk calculator score, along with the NICE scoring system for calculating breast cancer risk. It is likely over the coming years that the availability of genetic testing will substantially increase because of a reduced cost and this will lead to greater work in the area of breast cancer surgery. Women are considering the option of risk-reducing mastectomy more than previously.
5. Anti-HER2 therapy has substantially changed the nature of HER2-positive breast cancer. We now consider dual anti-HER2 therapy as standard, and the ever-expanding range of anti-HER2 therapies are increasing the response rate to HER2-positive breast cancers. HER2 positivity was traditionally thought of as a poor prognostic marker in breast cancer but because of the anti-HER2 therapies available this is now considered to be a good prognostic factor.

Our own area of breast cancer research, led by Professor Leonie Young and her team, has identified the coregulatory protein SRC1 as a significant player in determining the outcome from endocrine-resistant breast cancer. Marie McIllroy and her team have identified the role of the

Professor Arnold Hill.

androgen receptor in endocrine-resistant breast cancer. Ann Hopkins and her team have looked at the role of Jam-A in breast cancer metastasis. These three areas have enhanced our understanding of the biology of endocrine therapy for breast cancer.

It is an exciting time in the field of breast cancer research.

We have made many inroads into the disease, although there remains further work to be done.

Anaesthesia and critical care medicine

Professor Gerard Curley

Sepsis, the most common cause of death in intensive care, is implicated in one in 20 of all deaths for the population as a whole (UK data),[1] and up to one-half of all hospital deaths (US data).[2] In 2008-2009, 30,587 patients were hospitalised in Canada with sepsis, and 9,300 of these died. In Ireland, for 2013, up to 60% of all hospital mortality had a sepsis or infection diagnosis.[3] Mortality is 50-60% in patients with septic shock, for whom temporal improvements in mortality are slight at best.[4] Sepsis survivors spend significantly longer in acute care hospitals, have longer length of stays in ICUs than patients admitted with other diagnoses, and are also more likely to need extended care in other acute or long-term healthcare facilities upon discharge.[5] An estimated $14.6 billion USD were spent in the United States in 2008 in direct patient care of sepsis.[6] In Ireland, the total number of cases with a diagnosis of sepsis was 8,831 in 2013, which accounted for a total of 221,342 bed days with an estimated cost of €125 million.[3]

Professor Gerard Curley.

The cost to society in terms of loss of life, productivity, and loss of quality of life from physical and cognitive impairment due to sepsis is staggering. Despite over 15,000 patients studied, and over one billion dollars in study costs, effective sepsis therapy remains elusive.[6] A new therapy for sepsis would have obvious major human, economic and social benefit. There is an urgent need for innovation and discovery requiring improved ability to define appropriate molecular targets for preclinical development, and testing in relevant small and large animal and, where possible, human models, to determine the clinical value of novel agents for sepsis.

Several large phase III and IV clinical trials are currently underway in sepsis. In light of the substantial improvements in sepsis outcomes with advances in supportive critical care, the current trials seek to further optimise fluid, haemodynamic, and sedative management.

After many failures of strategies seeking to decrease the inflammatory cascades in early sepsis, the focus of immunomodulatory research has shifted to attempts to boost immunity during the later phase of immunoparalysis.

Recognising that multiple organ failure is responsible for much of the clinical burden of sepsis, early-stage research has increasingly focused on strategies to enhance endothelial and epithelial barrier function, bioenergetics, and active inflammation resolution pathways. One promising approach is the use of cell-based therapies such as allogeneic mesenchymal stem or stromal cells (MSCs), which have potent immunomodulatory, antimicrobial, bioenergetic, and barrier-enhancing effects.

These cells are currently being tested in phase II trials for acute respiratory distress syndrome (ARDS) in Ireland, the UK and the US, and in a Canadian phase I trial in sepsis (NCT02421484). Our laboratory here at the RCSI is investigating how MSCs communicate with immune cells, particularly macrophages.[7] We are also manipulating MSCs in order to develop a more advanced cellular therapeutic. My advice for young clinician scientists is to try to keep your mind open to complex and elaborate systems, and to solving the major questions in diseases like sepsis. Clinical medicine can highlight to us what we do not know, but research enables us to answer a biological question. The time of looking at a single molecule or gene is long past. We need to think about disease from a broader perspective. The more exposure you have to different approaches to solving the big questions in disease research, in terms of technical expertise, general and basic knowledge, the better you're going to do.

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Professor Tom Fahey.

General practice

Professor Tom Fahey

The greatest opportunity for general practice is also its greatest challenge. Over the last 20 years more people have been able to benefit from evidence-based preventive treatments that have improved their quality and quantity of life. However, with these benefits come challenges; the over-utilisation of diagnostic tests and treatments has led to the 'medicalisation' of society and accounts for the rising costs of healthcare throughout the world, and substantial drug-related iatrogenic harm.

For example, research from our group, the HRB Centre for Primary Care Research shows how much medicine we consume. In 2012, 60% of the >65 population in Ireland were taking ≥5 medicines compared with <20% in 1997, while 20% were taking ≥10 medicines in 2012 compared with 1% in 1997, according to a recent *BMJ* article. This level of medicine-taking is also associated with over one-third of the elderly population being exposed to a "potentially inappropriate medicine", a drug that causes more harm than good.

National initiatives such as the 'Too Much Medicine' campaign in the UK and the 'Choosing Wisely' campaign in North America are responses to the problems of overmedicalisation and overutilisation. Our research concerns itself with finding ways to support clinicians and patients in making evidence-based choices about the benefits and risks of medicines at an individual level. Young doctors embarking on their clinical careers need to appreciate that more medicine, particularly in the frail and elderly, is not always in the best interests of patients. In my own case, I have been fortunate that my postgraduate training in epidemiology has enabled me to practise medicine with reference to external evidence, and my advice to younger colleagues is to take notice of evidence-based medicine: it provides a structure and form to being a better doctor.

Epidemiology and public health medicine

Professor Ruairi Brugha

Training tomorrow's health professionals for the national and international market is the RCSI's core business. The local and global dimensions of doctor migration and retention have formed a core RCSI research area since 2005. A series of journal articles, supported by three grants from the Health Research Board (HRB), has charted the causes

and effects of the large-scale migration of foreign-trained nurses and doctors to Ireland. Recent and emerging papers are helping to unpack and understand the health system and medical workforce factors that account for large-scale emigration by Irish medical graduates. Emigration and its root causes account for Irish hospitals recruiting doctors from low- and middle-income countries that can ill afford to lose them.

What are the lessons and trends from this emerging body of research? Firstly, mixed methods, through the use of qualitative and quantitative research, explain and measure the factors that account for these migration trends. Secondly, there are ethical and economic dimensions to medical migration, and methodological challenges that we are tackling in our fourth HRB project, which is establishing a longitudinal study to capture the perspectives and intentions of doctors, some of whom have emigrated. Thirdly, sitting on two national Department of Health-led health workforce working groups and running annual policy dialogues with national decision makers provides opportunities for the research to directly impact on national policy and strategy.

The second area of health workforce research in the Department of Epidemiology and Public Health Medicine addresses the other side of the coin, by identifying and evaluating mechanisms to train and retain health workers that are affordable and appropriate to the needs of some of the poorest countries worldwide. Two studies, funded by the European Union (FP7 and H2020), focus on a second core business of the RCSI – making safe surgery available to district and rural populations of Africa. The cardinal feature and aim of the RCSI's health workforce is to tackle issues of great policy importance. President Mary Robinson has rightly described health workers as "the life-blood of the health system".

Professor Ruairi Brugha.

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Training tomorrow's health professionals for the national and international market is the RCSI's core business. The local and global dimensions of doctor migration and retention have formed a core RCSI research area since 2005.

Microbiology

Professor Hilary Humphreys

Hospital- or healthcare-associated infections (HCAIs) have increased in prominence during the last 10 years. Research, together with improved practice, have led to a decline in MRSA infection rates in many countries, including in Ireland, and the development of rapid detection systems to facilitate earlier interventions. However, an ageing population in most countries, improved survival from cancer and organ transplantation, the use of immunomodulatory drugs for many conditions such as inflammatory bowel disease, sub-optimal

Professor Hilary Humphreys.

professional practice such as in the area of hand hygiene, and inadequate healthcare infrastructure – e.g., overcrowding – all facilitate the emergence and spread of causes of HCAIs. Current research is focusing on improved surveillance to detect outbreaks earlier, the application of molecular techniques to better understand pathogenesis, and how to better influence human behaviour to optimise preventive strategies. In addition, there is a greater awareness of the need to better understand the host immune system and how that impacts upon presentation and prognosis. Innate components of the immune system may render some categories of patients more vulnerable than others, and vaccination against *Staphylococcus aureus* is possible in the future. We also need to improve our capacity to adequately decontaminate healthcare facilities where causes of HCAI have emerged and evolved to adapt to that micro-environment. Is it possible that we can develop a decontamination system, the equivalent of fumigation, that would be quick, easy, relatively inexpensive and non-toxic? There is also a need for systems to more rapidly detect multi-drug resistant bacteria such as carbapenem-resistant enterobacteriaceae (CRE), where there are multiple mechanisms and we need new agents that are effective in treatment. Currently, we have at most two to three agents that may be useful and in some countries there are no agents available. Given the capacity of microbes to evolve rapidly and cleverly, and the increasing concern among the public, patients and healthcare systems, research in HCAIs will continue to be important. It will be critical to focus on areas that will impact on patient care and use modern technologies.

Obstetrics and gynaecology

Professor Fergal Malone

Perinatal Ireland is an all-Ireland collaborative research network headquartered at the RCSI Department of Obstetrics & Gynaecology at the Rotunda Hospital, Dublin. This was the first group in Ireland to link the seven major academic obstetric hospitals as well as representatives of all seven medical schools on the island of Ireland to carry out research into women's and children's health. The questions Perinatal Ireland has explored in its research over the last 10 years include important and vital areas such as multiple gestation management, intrauterine growth restriction (IUGR), and prediction of abnormal labour. Results from this research have been presented in national and international circles, and published in prestigious journals the world over, and have made a tangible difference to the care and outcomes of women and children in Ireland and internationally. The ESPRiT study investigated optimal management of twin pregnancies by initially focusing on discordant twin growth, and defined the degree of twin size discordance that is associated with adverse outcomes. Several publications from this study contributed to national guidelines on optimal twin management, including frequency of foetal surveillance, timing of delivery and method of delivery. The Prospective Observational Trial to Optimise Paediatric Health in IUGR (PORTO) study defined the optimal method of diagnosing intrauterine foetal growth restriction, as well as the best surveillance programme for such pregnancies. Distinguishing between small but normal babies and small and at-risk babies is one of the most complex problems in modern obstetrics. Standard international practice has been to consider the lowest 10% by weight to be at the highest risk. The PORTO study found that it is effectively only the babies in the lowest 3% who are actually at the highest risk, and called into question whether having a foetus in the lowest 10% by weight alone really matters in predicting adverse outcomes.

The GENESIS study investigated whether foetal head circumference, either alone or in combination with other measurements or factors, can identify women who might need an unplanned caesarean section once labour has begun, or who may have a complicated delivery. The results demonstrated a range of accurate parameters that can predict cesarean delivery. The contribution of this research network to the development of national and international clinical guidelines, and the enthusiasm to conduct research that advances clinical care of mothers and their children, is the lasting legacy of the first decade of Perinatal Ireland's work, and hopefully will continue for decades to come.

Professor Fergal Malone.

Orthopaedics

Professor John O'Byrne

Orthopaedic and trauma surgery is a field that is changing rapidly. It is a field that combines surgical techniques with increasingly sophisticated biomechanical devices and increasing understanding of the biological processes in bone healing. The progress within my own field of joint replacement surgery in the last ten years has revolved around a more sophisticated patient pathway, with shorter hospital stay, less postoperative pain and more rapid rehabilitation. Work continues to develop more sophisticated implants with better bone fixation and better bearing surfaces.

Ongoing research, however, is in the biological processes that can encourage fracture healing, cartilage regeneration and spinal cord regeneration. Exciting research is taking place in all of these areas. Specifically, with Professor Fergal O'Brien and Professor Cathal Moran, I am involved in very sophisticated research developing an artificial substitute for bone and cartilage. This is at an advanced stage and ready for human trials.

When I graduated from medical school to pursue a career in surgery, I was very focused on gaining clinical and surgical skills and combining this with part-time research. Reflecting on this, I would advise my younger self to specifically take time out of clinical work and dedicate time to full-time research. I believe it is only by doing full-time research that one fully develops a comprehensive understanding of all the aspects that are involved. I believe that research should remain an integral part of a clinician's training and ongoing practice.

Professor John O'Byrne.

Paediatrics

Professors Alf Nicholson, Naomi McCallion, Martin White, Paul McNally, and Ms Katie O'Connor

The RCSI Department of Paediatrics is committed to pursuing excellence in teaching and research, with the academic staff conducting extensive research in a wide range of areas. Professor Nicholson believes identifying common paediatric problems is essential for students, and he has published a book in this field entitled *When Your Child Is Sick*, and co-authored a textbook, *Diagnosing and Treating Common Problems in Paediatrics: The Essential Evidence-Based Study Guide.* He has played a key role in the new National Model of Care for Paediatric Healthcare Services in Ireland. Over the last decade, paediatrics has made great strides in areas such as injury prevention and cystic fibrosis (CF), to name but a few. CF is more prevalent within Ireland than anywhere else in the world. Over the last 20 years, the gene for CF was discovered and there have been great advancements in the treatment of CF lung disease, with survival rates continuing to increase. However, there is still a significant gap in our knowledge and Professor Paul McNally's research looks at this. He and Dr Barry Linnane established the SHIELD CF programme, which is carrying out ongoing research into the causes of early lung disease in babies and children with CF. There is significant neonatal research being undertaken in the Department; Professor Naomi McCallion's main areas of research are in neonatal ventilation and haemostasis, with ongoing research into newborn transport and neonatal infection. In addition, she has an interest in educational research in paediatrics. Professor Martin White's work focuses on neonatal abstinence and nutrition. Professor El Khuffash is a leader in the

Professor Alf Nicholson.

field of functional echocardiography, pulmonary hypertension and management of PDA. Since 1930, Down syndrome has been regarded as one of the most important leukaemia-predisposing syndromes, and children with it have unique clinical features. Professor Aengus O'Marcaigh is pursuing ongoing research in myeloid leukaemia of Down syndrome. Dr Seamus Hussey's research interest is in the field of inflammatory bowel disease (IBD), which is particularly relevant in paediatrics, as approximately 25% of IBD presents in childhood and IBD can have long-term effects for paediatric sufferers extending into adulthood. He established the Determinants and Outcomes in CHildren and AdolescentS with IBD (DOCHAS) Study. The last decade also saw major advancements in medical information technology, particularly in relation to virtual learning and simulation training, which the Department has embraced. Young doctors should begin pursuing research early in their career and hone their skills. There are many opportunities – research attachments, summer research opportunities and research projects within the paediatric departments – which students are encouraged to get involved with.

Pathology

Professor Mary Leader

The three major developments in histopathology in the last ten years include the use of molecular markers in malignant disease, the discussion of patients with a malignant diagnosis at multidisciplinary meetings, and specialised reporting within histopathology departments. The ability to evaluate DNA and RNA in formalin-fixed, paraffin-embedded material has led to enormous advances, particularly in haematopathology. The recognition of specific molecular changes and the demonstration of altered proteins have led to the development of both immunohistochemical and molecular markers, which are very helpful in diagnosis and prognosis. Examples include cyclin D1 expression in mantle cell lymphomas, c-Myc translocation in Burkitt's lymphoma, t(14;18) translocation and BCL2 over-expression in follicular lymphoma, and many others. The histopathologist now has a major role in the identification of patients who may respond to targeted therapies. These act in a variety of ways including by blocking cell surface receptors, and by inhibiting tyrosine kinases, cell signalling pathways and cell replication. The most commonly used therapies include rituximab in B-cell lymphomas, Herceptin in breast carcinoma and also metastatic gastric carcinoma, and imatinib in chronic myeloid leukaemia and gastrointestinal stromal tumours. More recently, combined therapy with more than one of these agents is proving more effective in patients' maintenance of a response to therapy. Discussion at multidisciplinary meetings is now required for optimum management of patients with malignant disease. This facilitates full review of clinical, radiological and histopathological features, and advice on best management. It also facilitates detection of any errors that may have occurred during the work-up of the patient. The third major development in histopathology has been specialised reporting. This is most frequent in large departments where there are sufficient histopathologists to allow a special interest or 'lead role' in a particular area of histopathology. For example, some histopathologists report only on skin specimens, others report only breast cases and others report only GI pathology. In Ireland at present this is not feasible in many departments. The RCSI Histopathology Department's main research interests currently are molecular pathology. We develop and validate protocols for identifying molecular markers within neoplasms to allow an insight into histogenesis, diagnosis, prognosis and testing for a patient's response to specific targeted drugs. My advice to my younger self with

Professor Mary Leader.

Professor Mary Cannon.

regard to research would be, firstly, publish early in your career. This allows you to develop an interest in research and also it is vitally important for your CV. As far as possible, try and develop a research project where you are dependent on as few people as possible. Many research projects falter if research collaborators fail to deliver on their part of the project. Finally, upgrade your skills in statistics and try and understand what makes your paper attractive to publishers.

Psychiatry

Professors Mary Cannon, David R. Cotter, and Kieran C. Murphy

There has been huge progress in understanding the biological basis for mental illness over the last decade. One critical development is the knowledge that thousands of genes are responsible for mental disorders and significant progress has been made in identifying these genes.

In addition to genetic factors, another critical development has been our understanding that exposure to environmental factors, whether *in utero*, in childhood, in adolescence or in early adulthood is also crucially important. This has led to the realisation that the potential for major impact on disease outcome may be through modification of exposure to these environmental risk factors. The effect of these risk exposures on the synapse is one particular focus of this work. Another critical development is the growing awareness of the need to develop preventive measures and early interventions for mental illness. The first step is to examine childhood precursors and at-risk mental states for illnesses such as psychosis and depression. This area of research has really developed over the past decade but we still have much to learn. Developments in neuroimaging have revolutionised our understanding of how the brain works and studies over the past decade have confirmed and further delineated the neuroanatomical basis for mental disorders. Professor Murphy has contributed to numerous studies identifying the genetic basis for mental disorders and is a member of two international consortia – the Psychiatric Genomics Consortium and the National Institute of Mental Health (NIMH)-funded 22q11 Deletion Syndrome Brain and Behaviour Consortium. He has also examined the neuroanatomical basis for psychotic and other neurodevelopmental disorders. Professor Cotter is currently funded as a Health Research Board clinician scientist with a key focus to identify predictive plasma protein, lipidomic and metabolomic biomarkers of schizophrenia. He is also studying the synaptic changes in the brain in major mental disorders, and how the synapse is affected by environmental risk factors for schizophrenia and its treatments. Professor Cannon is funded by the Health Research Board and the European Research Council. She is investigating psychotic symptoms in young people, as these symptoms appear to indicate increased risk for later mental illness and also the neuroanatomical basis for these symptoms. However, up to one in five young people report such symptoms, so we need to refine our knowledge about these symptoms to identify those who are truly at risk.

Our advice to younger students is:

a. Give research a chance to see if it is interesting to you. It is not for everyone!
b. Obtain skills and training in biostatistics – a key component of research.
c. Start early – build up an academic CV during summer research placements and SSC modules.
d. Take up the opportunity, if it exists, to do an intercalated degree (PhD or BSc) during your medical training.
e. Understand that research is an important component of professional development for all branches of medicine.

Professor David R. Cotter.

Professor Kieran C. Murphy.

RCSI smj case report

Epidural labour anaesthesia in a patient with tropical spastic paraparesis

Abstract

Human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy (HAM), also called tropical spastic paraparesis (TSP), is a medical condition that is associated with symptoms including muscle spasms, sensory disturbances causing paraparesis, and weakness of the legs. It is estimated that 15-20 million people worldwide are infected with HTLV; however, the majority of individuals will be completely asymptomatic with no clinical signs or symptoms. This is the first case report detailing a patient with suspected seronegative TSP who received epidural analgesia during labour with no change in her neurological symptoms postpartum. The significance of this disease is twofold; TSP has many similarities to multiple sclerosis (MS), which has known possible complications during labour as well as postpartum, and additionally, the increasing prevalence of TSP reflects the importance of increasing awareness of the condition. TSP should not contraindicate neuraxial anaesthesia. Epidural labour analgesia is an acceptable option for patients with TSP. While there is mention in the literature regarding potential exacerbation of TSP postpartum, there are no reports on the safety of epidural anaesthesia for labour in TSP; thus it was felt that this case needed to be described, as TSP and MS share similar progressive neurological characteristics. Research Ethics Board approval was obtained and the patient gave consent for this case report.

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Introduction

Tropical spastic paraparesis (TSP), also known as human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy (HAM), is an immune-mediated disorder of the spinal cord.[1-3] HTLV-1 is the retroviral infection thought to cause TSP, which infects millions of people worldwide; however, less than 5% develop the neurological disease, TSP.[4,5] HIV-infected patients and drug users are at an increased risk of acquiring this infection, as sexual encounters and needles are common causes of disease spread.[3]

Non-infectious co-factors also contribute to the pathogenesis of this viral process. Therefore, TSP can be seronegative[6] and serological differences may be found.[1] This includes environmental interactions (rainfall levels and high humidity), toxins, and viruses.[6] The virus can be transmitted through blood, sex, breast milk and needles[1,7] and is the first retrovirus linked to human disease,[8] occurring mostly in patients from countries near the equator, such as those in South America, Africa, and the Caribbean islands.[9] It has also recently been reported in various other countries around the world, due to increasing world travel and immigration.[1] TSP usually presents as slowly progressive spasticity, weakness and pain of the legs, paraesthesia and bladder dysfunction.[8] The World Health Organisation (WHO) has recommended basic diagnostic criteria for HAM/TSP (**Table 1**).[10]

Table 1: World Health Organisation (WHO) basic diagnostic criteria for HAM/TSP.

Clinical criteria

- Age and sex – mostly adult, sometimes familial, mostly females
- Onset – usually insidious but may be sudden

Main neurological manifestations

- Chronic spastic paraparesis, progresses slowly, may remain static after progression
- Weakness of lower limbs, more marked proximally
- Bladder disturbance usually early, constipation later, impotence and decreased libido
- Sensory symptoms such as tingling, pins and needles, burning
- Low lumbar pain with radiation to legs
- Vibration sense is frequently impaired, proprioception less often affected
- Hyperreflexia of the lower limbs, often with clonus and Babinski's sign
- Hyperreflexia of the upper limbs, positive Hoffman's sign
- Weakness of upper extremities may be absent
- Exaggerated jaw jerk in some patients

Systemic non-neurological manifestations: pulmonary alveolitis; uveitis; Sjogren's syndrome; arthropathy; vasculitis; ichthyosis; cryoglobulinaemia; monoclonal gammopathy; adult T-cell leukaemia/lymphoma.

Laboratory diagnosis: HTLV-1 antibodies or antigens in blood or CSF. CSF mild lymphocyte pleocytosis and mild to moderate increase in protein, lobulated lymphocytes in blood or CSF.

Table 2: The clinical, aetiological, and radiological differences between progressive multiple sclerosis and tropical spastic paraparesis.

Multiple sclerosis	Tropical spastic paraparesis
Exacerbating remitting or chronic progressive	Slowly progressive
Postpartum exacerbation common	Possible postpartum exacerbation
Motor weakness, spasticity, impaired vision, ataxia, sensory symptoms, bowel and bladder dysfunction, upper motor neuron signs	Motor weakness and spasticity mostly in lower extremities, sensory symptoms, bladder dysfunction, upper motor neuron signs
Aetiology unclear. Possible exposure to viral agent triggers an immune response	Usually associated with HTLV1. Can be seronegative or HTLV2. Immune response
MRI shows white matter plaques	MRI may be normal or show sub-cortical white matter lesions or atrophy of cervical or thoracic spinal cord

TSP and progressive multiple sclerosis (MS) have very similar clinical pictures (**Table 2**); therefore, to aid in the differentiation between these two conditions, MRI of the spinal cord may give more specific insight.

Although both diseases may demonstrate atrophy of the cervical or thoracic spinal cord, it was observed that there were some differences in the pattern of white matter lesions where high signals are observed. In TSP patients the high signal is more diffuse and uniform, compared to a patchy high signal in MS patients.[11] MRI is not very specific for definitively diagnosing TSP, as other disease processes may mimic these MRI changes, or the MRI may appear normal. Additionally, parenchymal inflammation of spinal cord with memory CD4 cells has been reported in early TSP.[9,11,12]

There are no reports in the literature on the safety of epidural anaesthesia for labour in TSP; thus, it was felt that this case needed to be described, given the increasing prevalence of TSP, and the similarities with MS, which has known possible postpartum complications. Research Ethics Board approval was obtained and the patient gave consent for this case report.

A major concern in this case was that any worsening of neurological state could not definitively be determined aetiologically. There was also concern that added weakness from epidural-induced motor block would compromise pushing; conversely, epidural use could also actually ease painful spasms unrelated to labour and facilitate pushing.

Case report

A 36-year-old gravida 1 para 0 (G1P0) lady from Ethiopia was referred at 37 weeks' gestation for assessment by the Department of Anaesthesia at St Joseph's Health Centre. This was due to obstetrician query regarding whether epidural analgesia in labour would be contraindicated in her then-undiagnosed spastic syndrome affecting mainly the lower limbs. The patient voiced concerns about her ability to push effectively during labour due to her symptoms of spasms and weakness, and enquired about the possible need for a caesarean section. The obstetrician requested anaesthesia review regarding her condition and whether epidural anaesthesia would be an option.

Options for pain management in labour were discussed, and she was reassured that a trial of vaginal delivery would be reasonable based on previous case reports (in which no epidural was mentioned).

Her symptoms began when she was a teenager in Ethiopia, but she did not seek medical advice at that time. At 14, she reported several episodes of convulsions, and at 17 she began to experience progressive weakness and painful spasms in her limbs (primarily in the right upper leg), which consequently affected her ability to walk normally. She also experienced low back pain intermittently.[9]
Systems review was notably negative for urinary symptoms, which would be more common in MS, but positive for intermittent constipation.[9]
She was seen by a neurologist at 33 years old, and had genetic testing, which excluded hereditary spastic paraparesis. She was also seen at 37 weeks' gestation by a neurologist at St Joseph's in consultation. MRI of the brain and spinal cord was positive only for mild disc bulging at L4/L5 and L5/S1.
The neurology consultation queried possible TSP. HTLV-1 and 2 and HIV blood tests were negative; however, the patient met all of the clinical and neurological diagnostic markers for TSP.
After multidisciplinary discussion and comparison of TSP to differentials such as MS, it was decided that epidural anaesthesia was not contraindicated. The patient was informed that due to the progressive nature of her spasticity and weakness, there was concern that she could worsen functionally postpartum, and in that case it would be impossible to determine whether the deterioration were due to the epidural. Options for pain management in labour were discussed, and she was reassured that a trial of vaginal delivery would be reasonable based on previous case reports (in which no epidural was mentioned).[7] The patient was admitted two weeks later in labour and requested epidural analgesia. She experienced adequate analgesia with an epidural loading dose of 6ml of bupivacaine 0.25%, and maintenance of continuous epidural infusion of bupivacaine 0.125% with fentanyl 1mcg/ml at a rate of 6-12ml/h. She delivered the baby vaginally with vacuum assistance. There were no postpartum complications for mother or baby.
On follow-up with the neurologist two months postpartum, the rate of worsening of her spasticity had not increased. There were no significant changes in her neurological signs or symptoms, although postpartum MRI of the cervical thoracic spinal cord demonstrated mild atrophy of the cervical cord, supportive of the diagnosis of TSP.

Discussion

We report the first case of epidural analgesia for labour and delivery in a patient with a diagnosis of (seronegative) TSP. Previous letters to the editor describe safe use of thoracic epidural for a pulmonary bullectomy as well as spinal anaesthesia for urological surgery in patients with TSP.[13,14] A previous case report of HAM/TSP described improvement of neurological symptoms during the pregnancy but exacerbation postpartum, thought to be due to rebound phenomenon after immunosuppression of pregnancy. There was no mention of epidural use.[15]

These feared complications were due to the evidential similarities between TSP and MS, that although caesarean deliveries and infant mortality were similar to that of the general population, women who delivered vaginally had an increased incidence of lagging labour progression, resulting in intervention.

A major concern in this case was that any worsening of neurological state could not definitively be determined aetiologically. There was also concern that added weakness from epidural-induced motor block would compromise pushing; conversely, epidural use could also actually ease painful spasms unrelated to labour and facilitate pushing. The decision to proceed with epidural was made because of similarity in clinical picture between TSP and MS. Although TSP is slowly progressive rather than relapsing and remitting like most cases of MS, spasticity in both cases results from disturbance of corticospinal tract

pathways or myelopathy.[16] Additionally, both are thought to have immune-mediated pathophysiology.[8] There is some concern among anaesthetists regarding causing an exacerbation of MS by exposing demyelinated areas of the spinal cord to potentially neurotoxic local anaesthetics; therefore, there is some controversy around the safety of spinal anaesthesia in MS, but epidural is considered safe, especially when dilute solutions of local anaesthetic are used in labour.[17]

Conclusions

In this case of a patient with a diagnosis of seronegative TSP who received epidural anaesthesia during labour, there was no obvious change in neurological symptoms during the pregnancy or postpartum and the patient delivered vaginally with vacuum assistance and without postpartum complications or worsening of her symptoms. These feared complications were due to the evidential similarities between TSP and MS, that although caesarean deliveries and infant mortality were similar to that of the general population, women who delivered vaginally had an increased incidence of lagging labour progression, resulting in intervention.[17]

After multidisciplinary discussion about alternate differential diagnoses (such as MS), and with informed consent, TSP should not contraindicate neuraxial anaesthesia. Epidural labour anaesthesia appears to be an acceptable option for patients with TSP; however, the evidence base is small and future research is needed to confirm this finding.

Acknowledgements

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Shower power: a case report of cannabinoid hyperemesis syndrome

Abstract

Cannabis use is becoming more common globally, making it important for physicians to be aware of cannabinoid hyperemesis syndrome (CHS). CHS presents in chronic cannabis users, typically under the age of 50, and entails a severe cyclic nausea and vomiting pattern with abdominal pain but normal bowel habits. Symptoms typically predominate in the morning, are relieved by hot baths or showers, and resolve with discontinuation of cannabis use. This report details a case of a 32-year-old woman who presented to the emergency department at a large Canadian hospital with severe nausea, vomiting and a history of regular use of marijuana cigarettes. In an attempt to alleviate her symptoms she reported taking frequent hot baths and using as many as five marijuana cigarettes per day. The patient's clinical presentation, chronic daily use of marijuana and relief of symptoms with hot baths led to the diagnosis of CHS. The antiemetic properties of cannabis are widely known in the community, meaning patients may not associate marijuana use with their symptoms. Additionally, cyclic vomiting syndrome is present in many different conditions, making physician awareness of this syndrome crucial. Recognition and diagnosis of this condition can prevent unnecessary, costly diagnostic tests, and provide an opportunity to initiate counselling on cessation.

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Introduction

Cannabis is the most commonly used recreational drug in the US.[1] There is a global trend towards increased medicinal use of cannabis as well as a political trend towards decriminalisation or legalisation, which is likely to result in higher overall cannabis use. In Ireland between 2006 and 2011, lifetime use of cannabis increased from 21.9% to 25.3% and the proportion of young adults (15 to 34 years) who reported using cannabis increased from 28.6% to 33.4%.[2] There are reports of an association between chronic cannabis use and hyperemesis: cannabinoid hyperemesis syndrome (CHS).[3] As availability and social acceptance of cannabis use increases, patients may be more comfortable disclosing use to healthcare providers. Cannabis is viewed as an effective antiemetic and CHS is in contrast to this, possibly making it difficult for patients to accept the diagnosis. Physician awareness and knowledge of this syndrome can lead to a higher index of suspicion for CHS and potentially avoid unnecessary tests while providing an opportunity to initiate counselling on cessation. In this article we present a case of hyperemesis secondary to chronic cannabis use.

Pharmacology of cannabinoids

The principal active compound in cannabis is delta-9-tetrahydrocannabinol (THC). Most of the effects of THC are mediated through agonistic actions at cannabinoid receptors.[4] Two cannabinoid receptors have been identified: CB_1 and CB_2.[5] Activation of the CB_1 receptors by THC results in the psychoactive effects (euphoria, relaxation, perceptual disturbance, intensified sensory experiences and memory impairment) associated with marijuana use.[6] Selective CB_2 receptor agonists can have therapeutic use as analgesic and anti-inflammatory agents.[5,7] THC has antiemetic properties and has been used as a treatment for nausea. This effect is mediated through CB_1 receptor activation in the

Table 1: Laboratory investigations on admission.

Investigation	Result (normal values)
Haemoglobin	167g/L (130-180g/L)
White blood cell count	16.1 x 10^9/L (4.0-11.0 x 10^9/L)
Creatinine	197μmol/L (64-111μmol/L
Lactate	2.4mmol/L (0.5-2.2mmol/L)

brainstem in animal models.[6] Stimulation and blockade of CB_1 receptors can inhibit and induce vomiting in a dose-dependent manner.[8] This paradoxical effect whereby chronic cannabis use leads to hyperemesis is poorly understood, but it may be explained by downregulation of CB_1 receptors.[5,7] Hyperemesis with chronic cannabis use may also be related to the central effects on the hypothalamic-pituitary-adrenal axis.[5,7,8]

Case report

A 32-year-old female presented to the emergency department at a large urban hospital in Ontario, Canada, with severe nausea and occasional vomiting for seven days, which progressed to vomiting up to seven times daily for two days prior to presentation. Her nausea and vomiting were alleviated with frequent hot baths. Notably, she denied fever, anorexia, weight loss, dysphagia, changes in bowel habit, haematemesis or rectal bleeding. There were no recent lifestyle or dietary changes and she denied any new social stresses, significant family or past medical history, drug or food allergies, and tobacco use or alcohol misuse. She was not taking any medications. She was a regular user of two to three marijuana cigarettes daily but in an attempt to alleviate the nausea had been smoking up to five marijuana cigarettes daily for the past several days. Over the past year she had been admitted to hospital on three occasions with similar symptoms. During these admissions abdominal x-ray, ultrasound and CT scans, as well as blood and urine tests, were all normal. During each admission, treatment consisted of intravenous fluids and ondansetron resulting in symptom improvement. On examination she was afebrile but hypertensive (168/97) and tachycardic (118bpm). She was clinically dehydrated with a flat jugular venous pulse and a decrease in systolic blood pressure of 28 and diastolic blood pressure of 17 with standing. Her abdomen was non-distended and diffusely tender without any peritoneal findings. The cardiovascular, respiratory, neurological, musculoskeletal and skin examinations were normal. The laboratory investigations were consistent with dehydration (**Table 1**). Urine toxicology was positive for THC confirming marijuana use. Liver enzyme tests, serum glucose, and extended electrolytes and abdominal x-ray were normal. A pregnancy test was negative. As with previous admissions, the presentation was consistent with cyclic vomiting syndrome (CVS). The additional chronic daily use of marijuana and relief of symptoms with a hot bath raised suspicion for a diagnosis of CHS. The absence of a more probable alternate diagnosis and normal investigations supported this diagnosis.

Table 2: Causes of cyclic vomiting.

Factor	Example
Medications	Chemotherapy, non-steroidal anti-inflammatory drugs, antibiotics/antivirals, narcotics
Gastrointestinal	Bowel obstruction, gastroparesis, irritable bowel syndrome, malignancy, functional disorders, infection
Neurological	Raised intracranial pressure, seizures and labyrinthine disorders
Psychiatric	Anorexia nervosa, bulimia, psychogenic vomiting, anxiety, depression
Urologic/gynaecologic	Pregnancy, ovarian cysts/malignancy, urolithiasis
Metabolic	Uraemia, parathyroid disorders, hyperthyroidism, Addison's disease, acute intermittent porphyria

Discussion

CHS was first described in 2004.[3] This syndrome is typically seen in patients less than 50 years old who report normal bowel habits and a morning predominance of symptoms. Clinical features include chronic marijuana use, severe cyclic nausea and vomiting, abdominal pain, and resolution of symptoms within days of discontinuing use. The symptoms and signs usually return within weeks of resuming marijuana use. Characteristic of CHS are paroxysms of intense and persistent nausea and vomiting, often relieved by a hot shower or bath. The mechanism for this phenomenon is unclear, but hot showers may reset the hypothalamic thermoregulatory centre and transiently overcome the disequilibrium caused by chronic cannabis use.[3,9] It may be related to dose-dependent hypothermic effects of THC, or direct effects on CB_1 receptors in the hypothalamus.[9] The effect may also be due to the action of THC on cannabinoid receptors in the limbic system of the brain.[3,6] The "cutaneous steal syndrome" hypothesis is that hot showers cause peripheral vasodilation and preferential blood flow to the skin and away from the gut, providing temporary relief from nausea and vomiting.[9] CHS is often undiagnosed, and associated with recurrent emergency room visits and unnecessary diagnostic tests or even surgical intervention.[3,10] The diagnosis is often delayed or missed because patients may not readily disclose marijuana use and physicians may fail to obtain an adequate history of substance use. Finally, the symptoms often resolve with symptomatic treatment, resulting in discharge without a definitive diagnosis.

CHS is most often confused with cyclic vomiting syndrome (CVS). The

Rome III criteria for the diagnosis of CVS require a minimum of three discrete episodes in the preceding year of stereotypical acute-onset vomiting lasting less than one week, with absence of nausea and vomiting between episodes, and no metabolic, gastrointestinal, central nervous system, structural or biochemical disorders.[11] A personal or family history of migraine headaches is supportive of a diagnosis of CVS. The differential diagnosis of CVS is broad (**Table 2**), so the assessment of a patient with cyclical vomiting should include a detailed history, as it is imperative to exclude organic causes of CVS prior to making a diagnosis of CHS, irritable bowel syndrome or psychiatric disease.

The characteristic alleviation of symptoms with compulsive hot showering is unique and potentially pathognomonic of CHS. Focused investigations will depend on the history and examination, particularly when there is a high pretest probability for an organic cause of cyclic vomiting. Even when a diagnosis of CHS is most probable, it is imperative to undertake laboratory testing to assess the extent of dehydration and electrolyte and acid-base abnormalities caused by hyperemesis. A pregnancy test should be done in all women of childbearing age to exclude morning sickness or hyperemesis gravidarum. A urine toxicology screen can be helpful when the diagnosis is suspected but a history of marijuana use is not forthcoming. The management of CHS includes fluid resuscitation and correction of electrolyte and acid base abnormalities. Typical antiemetics (e.g., diphenhydramine, ondansetron, metoclopramide, or prochlorperazine), although commonly used for symptomatic relief, are often ineffective.[12] There are reports of successful symptom relief with intravenous haloperidol[12] and lorazepam.[13] Cessation of cannabis use is essential in the treatment of CHS, and long-term management should include counselling on the diagnosis and treatment options for abstinence. Resolution of CHS symptoms generally occurs within days of discontinuing marijuana use; however, symptoms may also persist for several weeks after last use.

Conclusion

The patient, despite multiple admissions and no alternate diagnosis, refused to acknowledge the association between her symptoms and cannabis use. She was a regular user of cannabis for over 15 years and had no interest in counselling or entering a rehabilitation programme. As the antiemetic properties of cannabis are a common stereotype, patients may not associate their marijuana use with their symptoms. Physician awareness of the diagnosis will result in more active search for the condition and can facilitate patient education. Additional research into treatments for CHS is required and the physicians prescribing medical marijuana should be fully aware of possible side effects. Ultimately, there is a growing need for evidence-based patient and healthcare provider education on this condition; it should include both the benefits and risks of medicinal and recreational cannabis use, and available community resources for cessation of use.

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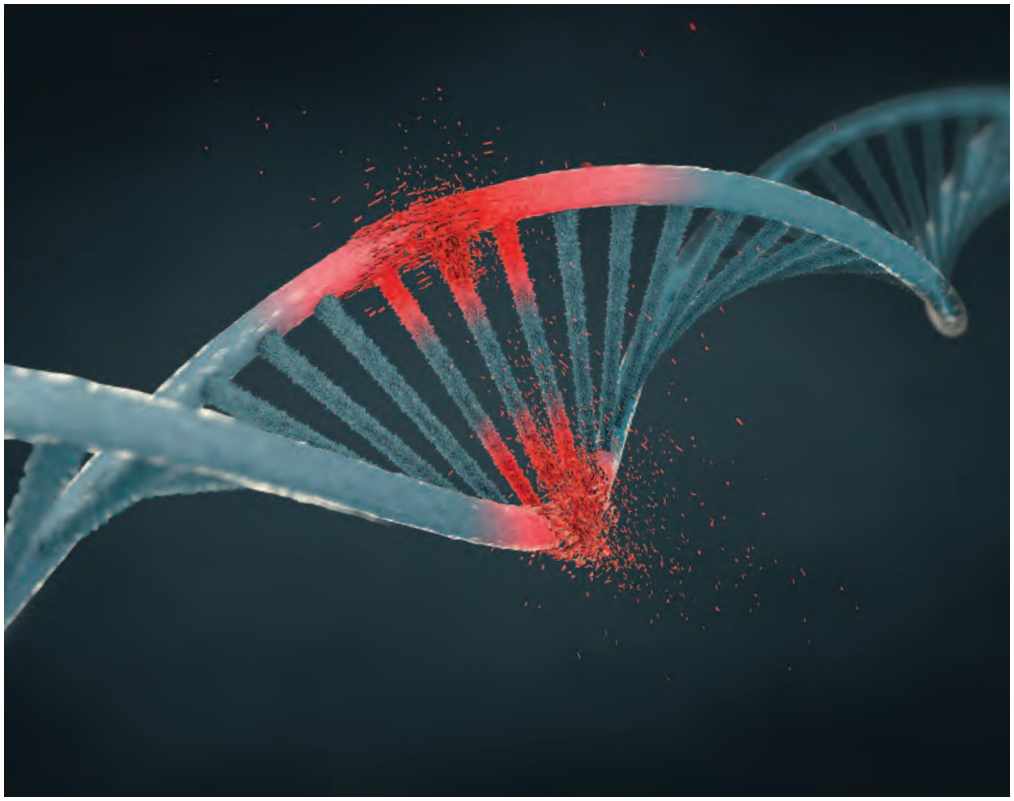
RCSI smj case report

Advancements in the diagnosis and management of Wolf-Hirschhorn syndrome



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Abstract

Introduction: Cooper and Hirschhorn first characterised Wolf-Hirschhorn syndrome (WHS) in 1961 as a condition described as a midline fusion defect with a partial chromosomal deletion.

Case: A 15-month-old female presented to the clinic with dysmorphic features, developmental delay, atrial septal defect (ASD) and pulmonary stenosis (PS). On physical examination, numerous craniofacial abnormalities were observed including a microcephaly with a head circumference of 42.5cm (<2nd centile), low-set ears, prominent glabella, down-slanting palpebral fissures, and a high nasal bridge with a characteristic 'Greek warrior' appearance seen in WHS patients.

Discussion: Modern innovations have demonstrated that the deletion size on chromosome 4 has a significant effect on long-term prognosis and management of WHS patients. As such, comparative genomic hybridisation array (CGH-array) has allowed for a more advanced diagnosis of complex phenotypes associated with microscopic deletions in WHS.

Conclusion: WHS is a rare condition that is often unnoticed or a neglected diagnosis by many doctors. Patients presenting with failure to thrive as an isolated finding and with characteristic facial features with other major deformities may be suggestive of WHS.

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Table 1: Presentation of Wolf-Hirschhorn syndrome by organ system.[5]

Cardiology	Congenital heart defects: atrial septal defect (ASD) or ventricular septal defect (VSD)
Ophthalmology	Ocular hypertelorism, extropia, blepharoptosis, colobomata of the iris, strabismus, microphthalmia
Gastroenterology	Dysphagia, gastro-oesophageal reflux, hepatic adenomas
Dermatology	Epicanthal folds
Neurology	Epilepsy, mental retardation, muscular hypotonia
Otolaryngology	Cochlear deafness, recurrent otitis media, respiratory tract infections, dysplastic ears
Nephrology	Renal agenesis, oligomeganephronia, obstructive uropathy, cystic dysplasia, bladder exstrophy
Orthopaedic	Scoliosis, retardation of skeletal development, growth retardation, 'sacral dimpling'

Introduction

In 1961, Cooper and Hirschhorn first described Wolf-Hirschhorn syndrome (WHS) as an extremely rare condition characterised by a midline fusion defect and partial chromosomal deletion.[1] Subsequently, in 1965, Wolf *et al.* and Hirschhorn *et al.* brought the condition to the attention of geneticists and, more importantly, the medical world.[2,3] WHS has an estimated minimum birth incidence of one in every 96,000 births with a 2:1 female-to-male ratio.[4] WHS has very characteristic cranio-facial features including: microcephaly; a cleft lip and/or palate; a high anterior hairline with prominent glabella; widely spaced eyes; epicanthus; a short philtrum; micrognathia; and, poorly formed ears.[5] It can also present with features in virtually every organ system (**Table 1**).[5] Some cases do not exhibit a clinical presentation consistent with WHS, whereas other conditions have features that overlap with some of the WHS phenotype.

On physical examination, several craniofacial abnormalities were observed including a microcephaly with a head circumference of 42.5cm (<2nd centile), low-set ears, prominent glabella, down-slanting palpebral fissures and a high nasal bridge with the characteristic 'Greek warrior' appearance.

In most cases WHS is not an inherited condition but occurs as a result of a random, *de novo* partial deletion of the short arm of chromosome 4 (4p-).[6] Certain genes have been localised as WHSC1 and WHSC2, which are proteins required to inhibit DNA damage through the methylation of histones.[6] In about 50% of patients, the deletion is *de novo* at the 4p16.3 region and in 40-45% of patients there is an unbalanced translocation with both a deletion of 4p and a partial trisomy from a different chromosome arm.[7] In a small minority, these translocations may be inherited from a parent so it is important to genetically screen both parents for chromosomal rearrangements.[7] Prenatal ultrasound may be able to detect the distinct physical characteristics of WHS, which should be followed up by karyotyping through amniocentesis or umbilical blood sampling for definitive diagnosis.[8]

Case report

The proband was a 15-month-old girl presenting with dysmorphic features, developmental delay, atrial septal defect (ASD) and pulmonary stenosis (PS). Initially, at four months of age, the mother became concerned that the patient was not gaining weight properly and not meeting the appropriate developmental milestones, so brought her into the multidisciplinary early intervention team for a consultation (paediatrician, physiotherapist, occupational therapist, dietician, and speech and language therapist).

The patient was born to healthy, non-consanguineous parents at term at 39 weeks following induction of labour due to intra-uterine growth retardation (IUGR). Birth weight was 2.24kg. She was put in the special care baby unit for monitoring and required a nasogastric tube for feeding. She has received all vaccinations for her age with the exception of the BCG and current medication only includes occasional oral lactulose 5ml for constipation. She has had no previous surgeries and currently

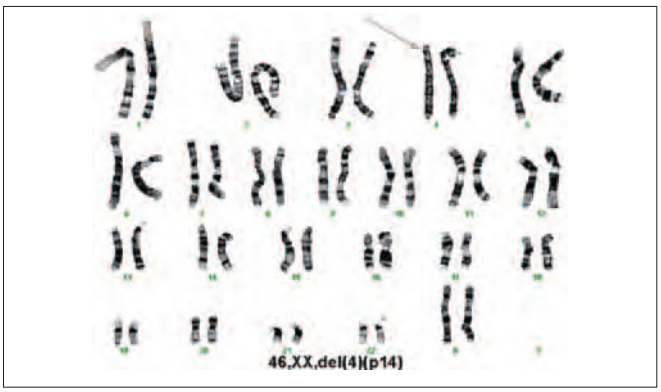

FIGURE 1: Karyotype analysis. This karyotype represents that of a typical patient with 46,XX and a chromosomal deletion on the short arm of chromosome (4p-) consistent with WHS.

lives at home with her mother, father, grandmother and sister. She is the second child in the family, with an older sibling (five years old) who was macrocephalic (>98th centile) but otherwise clinically normal. There is no family history of any genetic abnormality on either side.

The mother is reluctant to give solid foods and typically blends food prior to giving it, but the child has been introduced to meats, fish and vegetables.

On physical examination, several craniofacial abnormalities were observed including a microcephaly with a head circumference of 42.5cm (<2nd centile), low-set ears, prominent glabella, down-slanting palpebral fissures and a high nasal bridge with the characteristic 'Greek warrior' appearance. A cleft lip was also observed; however, an accompanying cleft palate was not present. There was also significant developmental delay present. In terms of gross motor, she had been rolling since four months of age, sitting without support and crawling, but not yet walking with or without support. Socially, she was affectionate, maintaining good eye contact and showing signs of stranger anxiety. Fine motor skills showed a pincer grip and mouthing, as well as pointing to objects and speaking few words. In contrast, at 15 months of age, a developmentally normal infant would be walking well and climbing stairs, drinking from a cup, speaking ten or more words and able to stack three cubes.[9]

Further clinical examination revealed marked growth retardation at a weight of 5.76kg (<0.4th centile) and short stature at a length of 59.5cm (<0.4th centile). A recent blood test revealed a concurrent antibody deficiency in both IgA and IgG2 subclasses, a finding common in WHS patients. An echocardiogram showed an ASD with a minor PS. There was also no recorded or observed history of seizures, a common neurological manifestation of WHS patients, and an MRI showed no focal deficits. With a clinical diagnosis of WHS, the patient's blood was karyotyped in Temple Street Children's University Hospital and revealed a 46,XX with a 4p deletion consistent with WHS (**Figure 1**).[10] The patient's parents were also genetically analysed and were found to have no chromosomal abnormalities.

Management

A dietician has met with the family on a monthly basis and has provided the patient with a Haberman feeder to improve feeding and prevent backflow. The mother is reluctant to give solid foods and typically blends food prior to giving it, but the child has been introduced to meats, fish and vegetables. The patient was scheduled in Temple Street for a cleft lip repair, pending confirmation from the cardiology department that she is fit for surgery. Cardiologists were also scheduled to meet with her in Our Lady's Children's Hospital Crumlin (OLCHC) every six months for check-ups. The child currently has not developed any seizures, which is atypical for a child with WHS. The current treatment of patients with WHS who develop epilepsy is sodium bromide, which may be considered at a later stage if seizures do subsequently occur.[11] The parents wanted to have another child and after the genetic analysis results showed no chromosomal deletion abnormalities, they were reassured that they were at no increased risk of having another child with WHS.

Discussion

The life expectancy of a person with WHS can vary from 18 to 34 years, with about 30% of patients dying in their first two years of life.[4] This is a definite improvement from decades prior, where the life expectancy was significantly lower.[4] Deletion size on chromosome 4 appears to have a considerable impact on life expectancies in *de novo* deletion patients,[3] and many studies have emphasised the importance of the strong genotype-phenotype correlation.[12,13] Three main phenotypes have been described in WHS:

- micro deletions under 3.5Mb are associated with typical facial appearance without microcephaly and growth retardation;
- deletions between 5 and 18Mb are associated with the classical WHS phenotype of severe psychomotor retardation; and,
- deletions larger than 22Mb are classified as severe and typically incompatible with life.[8,11]

The parents wanted to have another child and after the genetic analysis results showed no chromosomal deletion abnormalities, they were reassured that they were at no increased risk of having another child with WHS.

Advancements in the past decade, including improved genetic analysis and techniques, have allowed for further understanding of WHS.[10] In particular, comparative genomic hybridisation array (CGH-array) has allowed for a much more advanced diagnosis of complex phenotypes associated with microscopic deletions.[10] A study by Maas *et al.* of 21 subjects with the WHS phenotype found that only eight patients, or 38%, had a deletion detectable by conventional cytogenetic methods, while the remaining 62% had a sub-microscopic deletion, which could only be detected and diagnosed by microarray.[14]

Conclusion

WHS is an extremely rare condition and as such is often overlooked or a missed diagnosis by many clinicians. Any patient with a growth restriction as an isolated finding, or with facial dysmorphism and other major deformities, may be suggestive of WHS.[10] Genetic investigations must be done in these patients with not only traditional karyotyping but also molecular analysis of the (4p-) deletion for an accurate prognosis. Parents of patients should be cytogenetically analysed and genetic counselling should be provided. Ultimately, WHS is a complex condition, which requires a prompt diagnosis and a multidisciplinary early intervention team to provide these patients with the best prognosis.[15]

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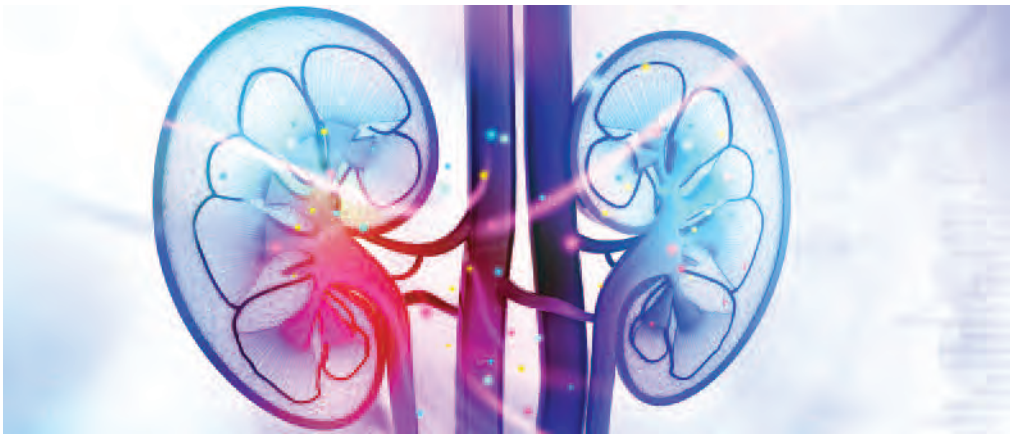
The development of renal cell carcinoma within the native kidneys of renal transplant recipients and the significance of annual screening



Abstract

Background and aims: The risk of developing renal cell carcinoma (RCC) is 50 times greater in renal transplant recipients than in the general population. Our study set out to determine the prevalence and prognosis of each subtype of native-kidney RCC, while making evidence-backed recommendations for screening.

Methods: We retrospectively examined the charts of 2,538 renal transplant recipients and identified 71 patients who developed RCC within their native kidneys post transplantation. Analysis of variance (ANOVA) was used to calculate means and standard deviations, while Fisher's test was used to compare groups. Kaplan-Meier estimates were used to determine patient survival rates. The Cox-Mantel test was used to determine significance, with $p<0.05$ described as significant. Pathological markers vimentin, CD10, cytokeratin, and CD58 characterised the four different subtypes of RCC.

Results: Four histopathological subtypes of RCC were detected: clear cell (n=41, 57.75%); papillary (n=24, 33.80%); sarcomatoid (n=4, 5.63%); and, chromophobe (n=2, 2.81%). Patient survival rates for the RCC subtypes varied: sarcomatoid = 34.1% one-year and 0.80% 10-year; clear cell = 65.2% one-year and 38.5% 10-year; papillary = 85.3% one-year and 62.0% 10-year; and, chromophobe = 99.4% one-year and 85.0% 10-year.

Conclusions: Due to our hospital's annual ultrasound screening protocol, our cumulative patient mortality rates were significantly lower in comparison to healthcare institutions with triennial or no screening protocols. We advocate for all transplant centre protocols to include annual ultrasound screening of all renal transplant recipients.

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Introduction

Renal transplantation is the first-line treatment for those living with end-stage renal disease (ESRD). Renal transplantation removes the numerous risks associated with dialysis, including increased susceptibility to myocardial infarction and strokes.[1] However, the lifelong immunosuppression after renal transplantation confers an increased risk for infectious diseases and malignancies.[1] Second to infectious diseases, malignant neoplasms account for the greatest mortality in renal transplant recipients worldwide.[2]

This study set out to determine the prevalence and the prognosis of each subtype of *de novo* native-kidney renal cell carcinoma (RCC) in renal transplant recipients at our institution, in order to inform an evidence-based recommendation for screening with an emphasis on early detection.

Methods

We retrospectively examined our database and identified 2,538 patients receiving a renal transplant between July 28, 1988 and December 1, 2015. Patient information and post-transplant complications were documented, including acute rejection, patient death, allograft loss, delayed graft function, and cystic dysplasias.

Means and standard deviations were calculated using analysis of variance (ANOVA) while groups were compared against one another with Fisher's test. Patient survival rates were calculated using Kaplan-Meier estimates. Significance was set at $p<0.05$, using the Cox-Mantel test to calculate p scores. Categorical data were evaluated with Chi-square tests, while continuous results were evaluated using logistic regression analysis. Staging of tumours was done according to the 7th Edition TNM RCC scale.[2] Due to the numerous immunosuppression regimens used over the 27 years of our data collection period, a comparative analysis between immunosuppression therapy and its effects on the development of different subtypes of native-kidney RCC could not be performed. Pathologically, RCC subtype was defined by the presence of four tumour markers: vimentin, CD10, cytokeratin and CD58. Vimentin positivity was indicative of clear cell RCC, with CD10 being indicative of papillary RCC. Sarcomatoid RCC was cytokeratin positive, with chromophobe RCC being CD58 positive.

This study set out to determine the prevalence and the prognosis of each subtype of de novo native-kidney RCC in renal transplant recipients at our institution, in order to inform an evidence-based recommendation for screening with an emphasis on early detection.

Results

Out of the total of 2,538 patients who underwent renal transplantation, 71 developed RCC of the native kidney post transplantation (2.80%). Fifty-three of the 71 recipients (74.65%) showed evidence of acquired cystic kidney diseases (ACKD) and/or multicystic dysplasia within their native kidney(s) prior to transplantation.

The mean interval between renal transplantation and biopsy confirmation of native-kidney RCC was 7.1±5.6 years (range 0.93-20.53 years).

Four histopathological subtypes of RCC were detected among the 71 recipients. The most common histological RCC subtypes were: clear cell RCC (n=41, 57.75%); papillary RCC (n=24, 33.80%);

Table 1: Histopathological subtypes of RCC.

Histological type	One-year survival rate	Two-year survival rate	Five-year survival rate	10-year survival rate
Clear cell	65.2%	58.7%	49.0%	38.5%
Papillary	85.3%	81.8%	76.5%	62.0%
Sarcomatoid[3]	34.1%	22.6%	3.5%	0.80%
Chromophobe[4]	99.4%	96.1%	90.9%	85.0%

Patient survival rates based on histopathological subtype. Data for sarcomatoid and chromophobe subtypes was not sufficient to calculate results in this study; rates included are from existing literature and for comparison purposes only.

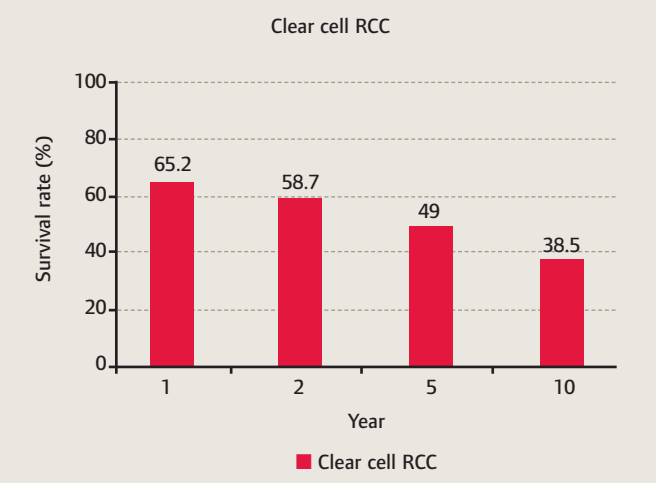

FIGURE 1: Patient survival rates for clear cell RCC.

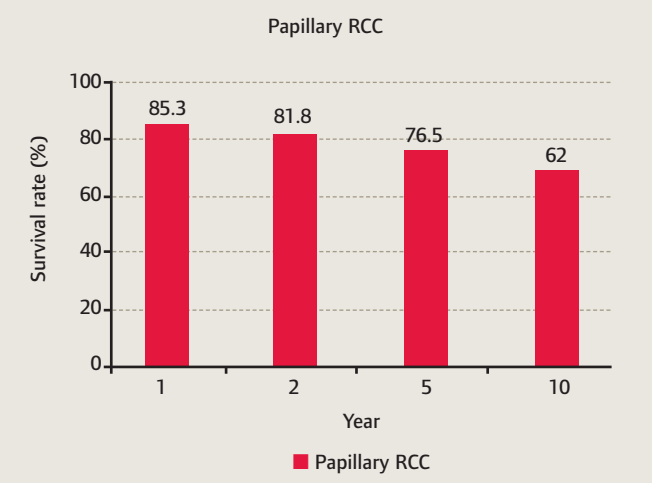

FIGURE 2: Patient survival rates for papillary RCC.

sarcomatoid RCC (n=4, 5.63%); and, chromophobe RCC (n=2, 2.81%). The survival rates of recipients with each type of RCC are shown in **Table 1**.

Due to the very small sample size of patients with either sarcomatoid or chromophobe RCC, mortality and patient survival rates could not be calculated to statistical significance from our results, so results from two large sample studies are documented in **Table 1** for comparison purposes.[3,4] Our data exhibited an increased incidence of papillary RCC (33.8%) within renal transplant recipients as opposed to the general rate of 12-14% seen in the general population.[5]

Fuhrman nuclear grade was able to be determined in 60 out of the 71 RCC cases: 42 tumours were grade I, 15 were grade II, and three were grade III. Using the TNM staging system for tumour size classification, 45 tumours were classified as pT1a (limited to kidney and <4cm), 21 were pT1b (limited to kidney, ≥4cm but <7cm), two were pT3 (vascular invasion, but not beyond perirenal fascia), and three were pT4 (invasion into ipsilateral adrenal gland, beyond perirenal fascia). Using the overall TNM staging groups, 66 tumours were Stage I (92.96%) and five were Stage IV (7.04%).

Categorical data were evaluated with Chi-square tests while continuous results were evaluated using logistic regression analysis. Staging of tumours was done according to the 7th Edition TNM RCC scale.

Patient survival

During our 27-year data collection period, 37 out of the 71 recipients died (52.11%). The mean age at death was 63.7±7.9 years (range 45-82). In those deceased, the mean survival period after RCC tumour diagnosis was 4.1±3.2 years (range 0.3-20.4 years). The most common causes of death were: pneumonia-related complications (n=21, 56.76%); tumour advancement (n=14, 37.84%); and, congestive heart failure (n=2, 5.41%). The cumulative Kaplan-Meier survival rates among the 71 recipients who developed native kidney RCC were: 75.65% at one year; 70.35% at two years; 62.75% at five years; and, 50.25% at 10 years. There was no statistically significant difference between the survival rates of men and women in our study. Male five-year survival was 60.45% and 10-year survival was 48.42%, versus female five-year survival of 65.05% and 10-year survival of 52.08% (p=0.451). Our patient survival rates for clear cell RCC and papillary RCC are shown in **Figures 1** and **2**, respectively.

Post-transplant neoplasms

Malignancies developed in 343 of the 2,538 recipients (13.5%) after transplantation. The most common malignancy was basal cell carcinoma of the skin (n=106, 30.90%). The second most common was RCC of the native kidney (n=71, 20.70%). Additional malignancies were lung carcinoma (n=27, 7.87%), hepatocellular carcinoma (n=25, 7.29%), breast carcinoma (n=22, 6.41%), colorectal carcinoma (n=19, 5.54%), Kaposi's sarcoma (n=18, 5.24%), and thyroid carcinoma (n=15, 4.37%).

Discussion

The United States Department of Health has stated that the risk

of developing RCC is 50 times greater in renal transplant recipients than in the general population.[6] Previous literature has found 4-21% of post-transplant malignancies to be RCC, and RCC has been known to occur in up to 5.4% of total renal transplant recipients.[7-9] In this study 20.7% of post-transplant malignancies were RCC and RCC occurred in 2.80% of total renal transplant recipients; our data is therefore consistent with peer-reviewed literature on this topic.

In the development of *de novo* native-kidney RCC within renal transplant recipients, immunosuppression has not been shown to play a role. The same study identified nearly identical incidence rates of RCC between cardiac transplant recipients and the general population at one year, two years, and five years post transplantation.[10] These figures suggest an alternative aetiology for the development of native-kidney RCC. ACKD and multicystic dysplasia have been shown to be the most significant risk factors for the development of native-kidney RCC within renal transplant recipients.[11-16] In our institution, retrospective examination of abdominal ultrasounds, conducted by two radiologists, revealed 53 out of the total 71 recipients (74.65%) to have evidence of cystic disease and/or multicystic dysplasia within their native kidney(s) prior to transplantation. As nearly three-quarters of this study's RCC patients showed evidence of pre-transplant cystic changes, there is great benefit to pre-transplant ultrasound in predicting which recipients are at a higher risk of developing post-transplant RCC and who therefore should be screened more frequently.

The United States Department of Health has stated that the risk of developing RCC is 50 times greater in renal transplant recipients than in the general population.

Immunosuppression did play a role in RCC pathogenesis in terms of increased tumour invasiveness. Our data exhibited five patients who developed invasive RCC (TNM staging score ≥3). This patient group represents 7.04% of our total RCC population. When compared to the general population, only 5.50% of diagnosed RCC are TNM stage ≥3, and this too despite irregular screening and often-symptomatic presentation at the time of diagnosis within the general population.[17,18] Despite consistent follow-up and regular ultrasounds within renal transplant recipients, this patient group is still at a higher risk of developing invasive RCC.[5,19-21] This elevated risk for developing invasive RCC is consistent regardless of the choice of immunosuppressive therapy.[5,21] Different histopathological subtypes of RCC were significantly predictive of patient survival and prognosis. Clear cell RCC was the most common subtype diagnosed and had the poorest prognosis within our patient sample, while papillary RCC was the second most common subtype diagnosed and had the best prognosis within our patient sample (**Table 1**). Within the general population, papillary RCC comprises only 12-14% of total RCC cases;[22] however, in accordance with other studies, this study's data exhibited an increased incidence of papillary RCC (33.8%) within renal transplant recipients.[22-24]

Although this study was unable to calculate patient survival rates for sarcomatoid and chromophobe RCC, two large studies have found sarcomatoid to have the poorest prognosis of the four RCC types, while chromophobe has been described in literature as a promising prognosis.[3,4]

With the exception of the five TNM stage IV patients, the remaining 66 patients were all treated via retroperitoneal laparoscopic (n=23) or open (n=43) radical nephrectomies. The five patients with stage IV tumours were managed palliatively due to severe metastasis.

In line with current research, nephrectomies conducted within this hospital are done using the retroperitoneal laparoscopic approach.[25] This has been shown to greatly reduce surgical complications while demonstrating an excellent ability in resecting and treating RCC of TNM stage ≤2.[25]

The phenomenon of native-kidney RCC developing within renal transplant recipients is globally significant. The United States Organ Procurement and Transplantation Network estimates that 118,000 renal transplant recipients are living with native-kidney RCC in the United States alone.[26] Numerous studies demonstrate a continuous trend towards increased RCC incidence and an increased incidence of highly-invasive disease (TNM stage ≥3) within this patient group globally.[27-29]

This project is one of the largest retrospective studies of its kind to date. As a primary kidney transplant centre, our institution kept meticulous patient notes on all renal transplant recipients. Patient records mentioned excellent oncologic diagnostic detail, allowing us to clearly demarcate between the subtypes of RCC. Included within the detailed patient records were the incidence of ACKD and multicystic dysplasia, which allowed us to reiterate a very strong correlation between the two risk factors and RCC. All 71 patients attended only our hospital, allowing us to manage and document all aspects of their medical care. No patients were lost to follow-up.

Abdominal ultrasound has been proven to be the most effective screening test in detecting RCC.[30,31] In 2010, the European Association of Urology updated its RCC screening guidelines to include annual ultrasound screening of the native kidneys in all renal transplant recipients. This report exhibited earlier detection and better patient prognosis with annual ultrasound screening when compared to biennial or triennial screening routines. Taking into consideration the increased cost of annual screening, the report still demonstrated a vast financial benefit in terms of reducing treatment cost associated with late tumour detection.[31] Ultrasound is the screening method of choice due to its relatively low cost, minimal invasiveness, minimal patient preparation, and accuracy in detecting nominal cystic changes and dysplastic parenchyma.[30-32] Transplant centres with no screening protocol have been shown to have a higher cumulative patient mortality rate attributable to native-kidney RCC than hospitals with an annual, biennial, or triennial screening protocol.[33] These findings illustrate the utility of regular ultrasound screening in reducing patient mortality.

Limitations

Although it has been shown that immunosuppression does not play a role in the development of native-kidney RCC, in an ideal research study design, it would be best practice to compare patients who have all received identical immunosuppressive therapy, in order to keep all variables consistent. Additionally, our institution started routine ultrasound imaging in 1995, which may have led to a relatively lower detection rate of RCC between 1988 and 1994, thereby giving us an underestimation of the true RCC prevalence. We do not feel that the implications of our findings are invalidated by these limitations.

Numerous studies demonstrate a continuous trend towards increased RCC incidence and an increased incidence of highly invasive disease (TNM stage ≥3) within this patient group globally.

Conclusion

Our results exhibited the most prevalent *de novo* RCC subtypes within renal transplant recipients to be clear cell, papillary, sarcomatoid, and chromophobe. The RCC subtype associated with the poorest prognosis in renal transplant recipients was clear cell, followed by papillary. Pre-transplant acquired cystic diseases/multicystic dysplasias are responsible for the development of RCC within this patient group. The greater proportion of invasive RCC reflects immunosuppression's role in increasing tumour aggressiveness. Largely due to our hospital's annual ultrasound screening protocol, our cumulative patient mortality rates attributable to native-kidney RCC were significantly lower in comparison to healthcare institutions with triennial or no screening protocols. With these results in mind, we would advocate that all transplant centres update their protocols to include annual ultrasound screening of all renal transplant recipients.

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All-trans retinoic acid solid lipid nanoparticle characterisation and assessment of anti-inflammatory activity in a human lung epithelial cell line

Abstract

Background: Chronic obstructive pulmonary disease (COPD) results from chronic inflammatory airway response resulting in destruction of lung tissue. There is currently no cure for COPD, with current treatments aiming for symptomatic relief. The lack of effective treatments has seen extensive research carried out into therapeutic approaches to target the underlying pathophysiology. Retinoids are important in regulating airway branching and maturation of epithelial cells in normal alveolar development and may be useful as a therapeutic modality.

Aims: This study investigated all-trans retinoic acid (ATRA) as an inflammatory mediator in a human lung epithelial cell line (A549). ATRA was formulated in solid lipid nanoparticle (SLN) vehicles for drug delivery.

Methods: ATRA SLNs were formulated using an emulsification-ultrasonication method and particles characterised for size and charge. Drug release was determined using a Franz cell apparatus; ATRA SLNs' immunomodulatory effects were determined by assessing IL-6 downregulation in an A549 human lung epithelial cell line.

Results: Average particles were approximately 300nm, of spherical, uniform size, with 78.34% encapsulation. ATRA release ranged from 19.7% to 31.7% over 96 hours dependent on release media used. After 72 hours, the high- and medium-dose ATRA elicited significant reduction in the IL-6 pro-inflammatory markers.

Key words: All-trans retinoic acid (ATRA); solid lipid nanoparticles; immunomodulation; A549.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease of the lungs in which inflammation of the epithelium has a detrimental effect on respiratory physiology and breathing patterns.[1] COPD encompasses both emphysema and chronic bronchitis,[2] and typically presents with elevated breathlessness, productive cough and wheezing.[3,4] Approximately 1.2 million people have been diagnosed with COPD globally,[5] with around 110,000 people affected in Ireland and approximately three million in the UK alone.[6,7] Alongside lung cancer and pneumonia, COPD is one of the three leading contributors to respiratory mortality in developed countries.[5] Current total mortality rate figures for the UK, USA and Ireland are 210.7, 248.2 and 191.7 per million population, respectively.[5] Ireland's average death rate for respiratory disease (including COPD) is over twice the European average,[8] and 20% of Ireland's deaths are due to respiratory disease.[9]

Current treatments mainly aim for symptomatic relief and include mucolytics, antibiotics, and anti-inflammatory agents, which help to reduce inflammation of the airways.[10-12] Many of these agents are commonly delivered through inhalers, similar to those of other lung diseases (e.g.,

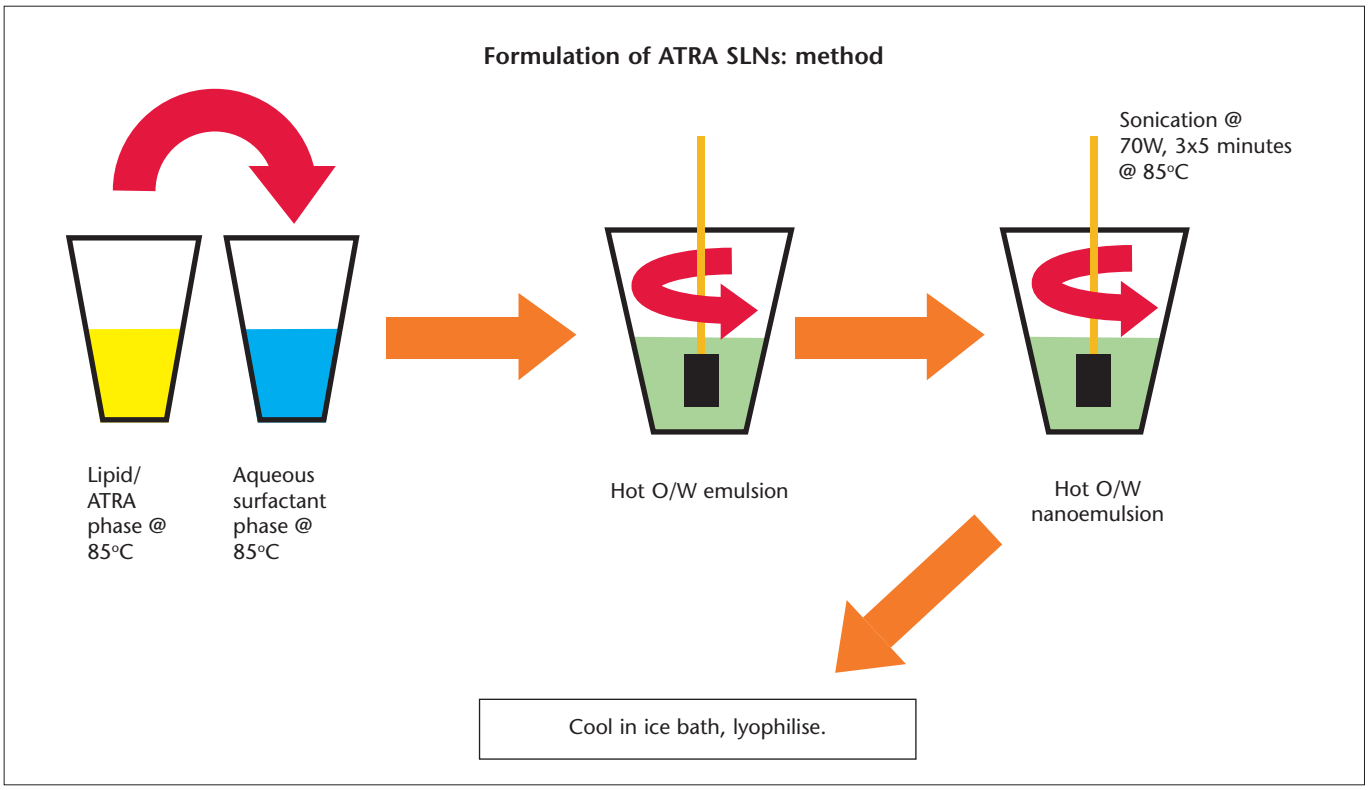


FIGURE 1: Formulation of ATRA SLNs. The lipid phase is melted and ATRA added. The aqueous phase is mixed with the surfactant and heated to the same temperature as the lipids. These phases are mixed to form an oil-in-water emulsion, trapping the ATRA in the oil particles, suspended in the aqueous phase. This is then sonicated to form the nanoemulsion, which is cooled and lyophilised to form the final SLN. However, 100% encapsulation efficiency was not achieved, likely due to heat-induced degradation as a result of both homogenisation and sonication steps in the SLN's formulation.

asthma). In end-stage disease, lung transplants have also been employed, although these are limited due to the scarcity of donor lungs and the invasiveness and complications associated with the procedure.[13,14] This has led to extensive investigation into other potential treatment approaches. Regenerative medicine aims to replace or regenerate human cells, tissue or organs to restore or establish 'normal' function.[15,16] Regenerative therapies often utilise small molecules such as growth factors or signalling molecules, which can alter the cell's specific microenvironment, leading to mediation of the inflammatory environment.

A reduction in pro-inflammatory signals can stimulate the recovery process, in which cells will regenerate in order to repair the damage caused during inflammation.[17]

Numerous studies have explored the potential use of retinoids in the regeneration of lung tissue due to retinol's regulation of airway branching and maturation of epithelial cells, which are both required for normal alveolar development. This makes all-trans retinoic acid (ATRA), the carbocyclic form of vitamin A, a potential regenerative medicine for COPD.[18-20] ATRA appears to work by promoting alveologenesis and modulation of elastin synthesis.[19]

As a hydrophobic drug, ATRA is challenging to formulate as it cannot be dissolved or suspended in aqueous solutions. It is also light and heat sensitive.[21]

However, there are formulation approaches to overcome these barriers and assist in protecting the drug from degradation.[22] One such formulation is solid lipid nanoparticles (SLNs), a mixture of hydrophobic and hydrophilic entities (lipids and surfactants), giving rise to a hydrophilic shell with a hydrophobic core, which allows ATRA to be encapsulated.[23] SLNs are micron-sized particles, which are biodegradable and biocompatible vectors for drug delivery, with little toxicity reported; they are often employed for prolonged- and controlled-release formulations, particularly for hydrophobic drug molecules.[24]

Aims

This project aimed to formulate and perform physicochemical characterisation of ATRA SLNs, assess the release profile of ATRA from SLNs, and determine the immunomodulatory effects of the drug on a lung epithelial cell line.

Table 1: Representative zeta size profile of ATRA SLNs.

Characterisation /particle type	Zetasizer (nm)	NanoSight (nm)	Zeta potential (mV)	Poly dispersity index	Encapsulation efficiency (%)
ATRA SLNs	299.71	180	-19.21	0.51	78.3
Blank SLNs	408.23	115	-18.35	0.45	0

The zeta potential provides the electric potential in the interfacing double layer (lipid and surfactant). The poly dispersity index denotes the distribution of particle size. Encapsulation efficiency (EE) denotes the amount of encapsulated ATRA in the SLNs after formulation. Each column gives an average value (n=3).

Methods

SLNs were prepared via an emulsification-ultrasonication method[25] using the process shown in **Figure 1**. SLNs were composed of Compritol 888 ATO (Gattefosse, France), poloxamer 188 (BASF, Germany), Tween 80 and ATRA (Sigma Aldrich, Ireland).

Numerous studies have explored the potential use of retinoids in the regeneration of lung tissue due to retinol's regulation of airway branching and maturation of epithelial cells, which are both required for normal alveolar development.

Characterisation of SLNs

Particle size, polydispersity index and zeta potential were measured using a Zetasizer Nano-ZS (NanoSeries; Malvern Instruments, UK). Particle size analysis was also determined using a Malvern NanoSight NS300 with nanoparticle tracking analysis software.

In vitro *drug release studies*

Drug release studies were performed using a six-cell Franz diffusion apparatus.[26] Two different receptor mediums were compared: an ethanol:Tween 80:PBS mix (80:10:10, pH 7.3) and simulated lung fluid (SLF; Gamble's solution, pH 7.4).[27]

SLF consists of a mixture of salts and bicarbonates to simulate the deep interstitial fluid within the lungs. Citrates are used in place of proteins to prevent foaming and acetates in place of any organic acids. Release samples were collected for the first eight hours and daily thereafter, and then were analysed for quantification of ATRA using high-performance liquid chromatography (HPLC; Agilent Technologies 1120 Compact LC).

High-performance liquid chromatography of ATRA

ATRA analysis was performed using high-performance liquid chromatography (HPLC), with a Kinetex 5µm C18 100 Å (250 x 4.6mm) column (Phenomenex, USA). The mobile phase consisted of methanol:acetonitrile:water:acetic acid in a ratio of 8:1:1:0.05. This was set to a flow rate of 1ml/min with UV detection at 356nm. The concentration of ATRA in each sample was determined using an ATRA calibration curve, ranging from 10µg/ml to 0.3125µg/ml.[28]

Immunomodulatory studies

IL-6 is often raised in COPD and other inflammatory conditions[29] and was selected as a marker in this study to ascertain ATRA's potential moderation of the inflammatory environment. To accomplish this, A549s, an ATCC human lung epithelial cell line,[30] were used as a 2D *in vitro* model of the alveolar region. Cells were cultured in T175 flasks (Sarstedt, Ireland) using DMEM/F12 nutrient media (Sigma Aldrich, Ireland) supplemented with 10% FBS (BioSera, France) and 1% penicillin/streptomycin (Sigma Aldrich). For this study, cells were seeded into 24-well plates at a seeding density of 20,000 cells/well in 0.5ml media.

After 24 hours (to allow cells to adhere) cells were activated using the pro-inflammatory cytokine interleukin 1b (IL-1b) (ImmunoTools, Germany), in order to simulate the inflammatory environment found in the lungs of a COPD patient. ATRA SLNs were suspended in media and then transferred to the wells. Low-dose (corresponding to 10µg/ml ATRA), medium-dose (50µg/ml ATRA) and high-dose (100µg/ml) ATRA SLNs were used, as well as blank SLNs and the cells alone as controls. Samples were taken at specific time points (4h, 24h, and 48h) and the concentrations of the chosen pro-inflammatory cytokine, IL-6, were quantified using ELISA.

Statistical analysis

Two-way ANOVA followed by Bonferroni *post hoc* analysis was performed to determine the statistical differences in immunomodulatory studies. All statistical tests were performed using GraphPad Prism v5 (GraphPad Software Inc., USA). Error was reported as standard error of the mean (SEM) and significance was determined using a cutoff of $p \leq 0.05$. A minimum of n=3 replicates was performed for all experiments.

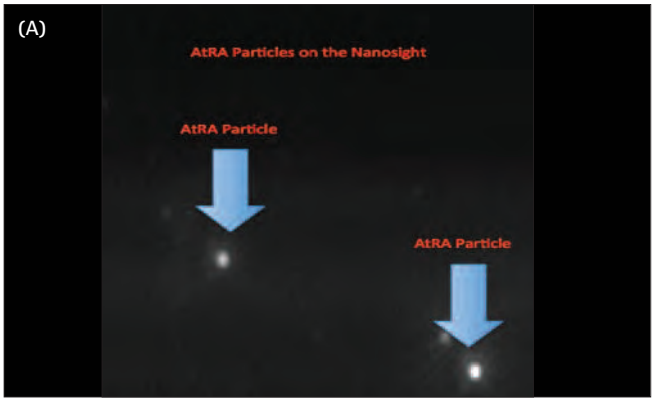


FIGURE 2: Physicochemical characterisation of ATRA SLNs. (A) Visualisation of ATRA particles on the NanoSight after being suspended in ethanol (10mg/ml).

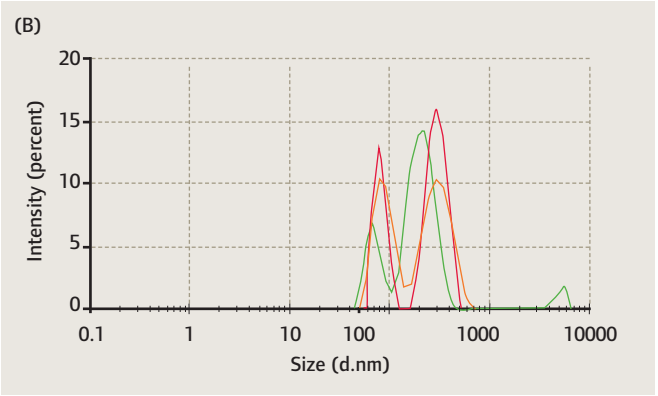
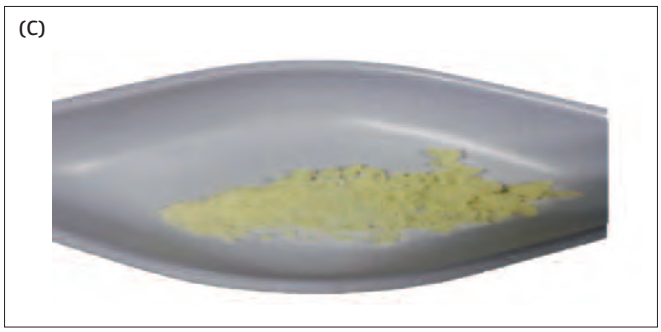


FIGURE 2: (B) Size profiling of ATRA particles on the Zetasizer, showing the size distribution (d.nm = diameter in nanometres), with red, blue and green peaks showing the results from each (n=3) trial performed.



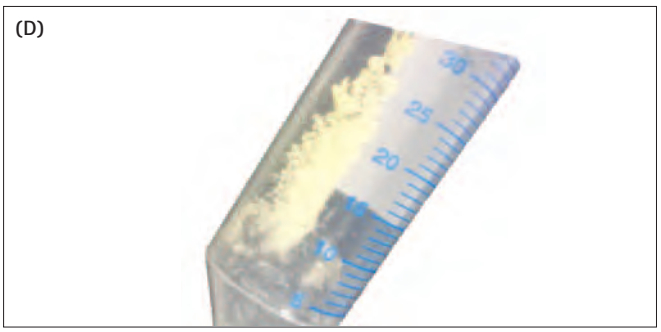


FIGURE 2: (C)(D) ATRA particles after lyophilisation: free-flowing yellow particulate powder.

Results

Characterisation results **(Figure 2** and **Table 1)** showed median particle sizes ranging from 115 to 408nm depending on measurement modality and formulation characteristics (blank vs. drug loaded). However, particle size distribution **(Figure 2B)** clearly shows a bimodal distribution with a peak at approximately 90nm and a second peak at approximately 850nm.

The zeta potential is negative and is similar for both types of particles. The poly-dispersity index (PDI) measures how particles are dispersed. The PDI is low (i.e., <0.5) for this sample; therefore, they are not aggregating and are within a small size distribution.[31]

Hence, the ATRA SLN particles formulated were distributed within a narrow size range, with an average size of 299.71nm. The encapsulation efficiency shows that, on average, 78.3% of ATRA is encapsulated.

Release studies

Release study results **(Figure 3)** demonstrate that both formulations gave a significant burst release in the first eight hours, with a slower sustained release thereafter. The SLF medium showed a higher release overall, with a total of 31.7% release after four days compared to the PBS:ethanol:Tween 80, which gave 19.7%.

Immunomodulatory studies

Immunomodulatory results **(Figure 4)** indicate that medium-dose and high-dose ATRA SLNs showed a significant decrease in inflammatory marker (IL1b) expression at 48 hours; however, no effect was seen with ATRA alone.

Discussion

This project aimed to perform physicochemical characterisation of ATRA SLNs, assess their release profile and stability, and determine the immunomodulatory effects of the ATRA SLN formulation on a lung epithelial cell line.

SLNs were chosen as a delivery system due to the low water solubility of ATRA. They are biocompatible vectors for pulmonary delivery, as their composition can include triglycerides and phospholipids found in physiological fluids in the deep tissues of the lungs.[32] SLNs have been widely assessed both for their biocompatibility and their ability to act as drug carriers across a range of pulmonary applications.[33]

The deposition of particles in the different regions of the lungs depends on the particle size of the formulation. Particles must be small enough to avoid deposition by inertial impaction on upper airways while large enough to avoid exhalation. The optimal particle size for achieving delivery deep into the alveolar region has been established to be an

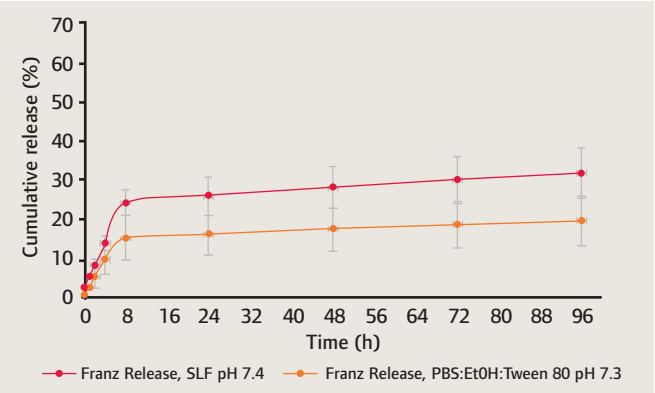


FIGURE 3: Release study for ATRA SLNs in SLF and PBS:EtOH:Tween 80. Cumulative % release of ATRA was calculated using the Franz cell apparatus (n=3). Both SLF and PBS:EtOH:Tween 80 release media are shown. Initial burst release for the first eight hours gave 24.2% and 16.4%, respectively, followed by a more prolonged, controlled release thereafter. Final release was 31.7% and 19.7% for SLF and PBS:EtOH:Tween 80, respectively. Error bars represent the standard error of the mean (SEM).

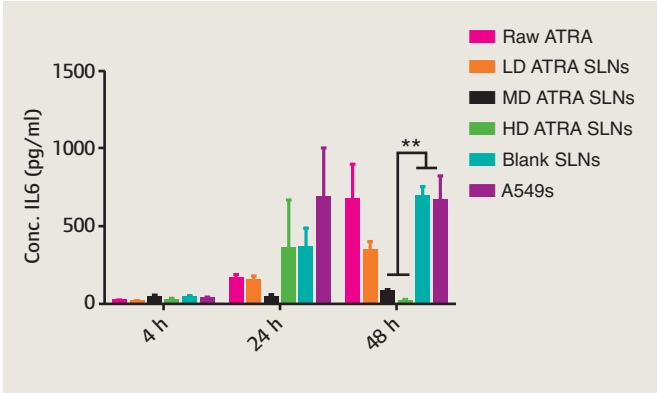


*FIGURE 4: Immunomodulatory studies for ATRA SLNs. Immunomodulatory effect of ATRA SLNs on IL6 concentration from A549 cells pre-treated with IL1B. Cells were treated with ATRA SLNs at three different doses, with untreated A549 as the control. Reductions in the inflammatory protein IL-6 were seen up to 48 hours, particularly in the medium-dose and high-dose particles. Two-way ANOVA followed by Bonferroni post-hoc analysis was carried out to determine statistical differences in immunomodulatory studies. Error is reported as SEM.**=p<0.001.*

aerodynamic diameter between 1 and 3μm.[34,35] The deposition of particles in the lung, however, is bimodal and ultrafine particles (less than 100nm) also appear to settle effectively in the alveolar regions, with a fractional deposition of around 50%.[33-35]

The median particle size for ATRA-loaded SLNs in this study was 299.71nm; however, distribution analysis indicated a bimodal distribution with a smaller particle size of approximately 90nm, and a secondary peak of approximately 850nm. This secondary peak is most likely due to aggregation of smaller nanoparticles due to the zeta potential of the SLN suspension (-19.21mV). Zeta potential is an indicator of the stability of nanoparticles, as the size of the charge indicates the level of electrostatic repulsion between the particles. Zeta potentials less than +/- 30mV are generally indicative of instability, and flocculation of the particles will occur,[36] supporting the bimodal particle size distribution observed for the SLNs. This aggregation will theoretically act to optimise delivery to the alveolar region of the lung to achieve optimal effect, as particles will lie within the optimal size range for alveolar delivery.[32,34,35]

An encapsulation efficiency of 78.34% was achieved for ATRA, which is significantly higher encapsulation than achieved for other ATRA SLN formulations.[37] Release studies indicated a biphasic release, with an initial burst in the first eight hours followed by a more controlled, sustained release. However, release of 100% of the ATRA from the particle is not achieved over the duration of the release study. This is most likely due to degradation of the ATRA over the involved time period and is supported by data from a study using Compritol SLNs, where 37.1% release over a period of five weeks was observed.[38] Our phosphate buffer release medium had reached 19.7% release after only 96 hours, compared to 37.1% release using SLF over 96 hours. This indicates that either the ATRA is more soluble or more stable in the SLF medium, which is a more suitable release medium as its composition is more physiologically representative of the *in vivo* environment than phosphate buffer, and so is a better predictor of *in vivo* release kinetics. However, the SLF medium does not include any surfactants, and as such is not entirely representative of the *in vivo* environment.

Therefore, studies evaluating other simulated lung fluids may add further insights into the release kinetics of the ATRA SLNs.[27] It would also be valuable to assess the release profile over a longer time period to evaluate total release and ATRA degradation. The sustained release of ATRA from the SLNs indicates that the use of ATRA SLNs could provide a prolonged anti-inflammatory effect on the tissue, enabling continuous cellular repair and regeneration of the alveolar region and synthesis of elastin over a prolonged duration.

The burst release could act as a 'loading' dose, followed by a continuous slow release of ATRA. Clinically, this would have the potential to minimise therapeutic troughs and peaks, and to reduce dosing regimens and improve adherence. The immunomodulatory study was key in showing that the bioactivity of ATRA is retained when formulated into SLNs. This was seen through statistically significant reductions in IL-6 (pro-inflammatory markers) levels after 48 hours. ATRA's anti-inflammatory effects are thought to be achieved by decreasing mRNA levels of helper T cell 2 (Th2) and helper T cell 17 (Th17), which are both thought to contribute to inflammation in the lungs. By reducing the amount of these through mRNA, ATRA stops the production of Th2 and Th17 cytokines (pro-inflammatory), hence allowing regeneration and repair of lung epithelium.[39]

Limitations

While these studies show the potential of ATRA SLNs in pulmonary regeneration, there were a number of limitations to the study. The *in vitro* release testing is not representative of the *in vivo* environment. The manner in which the particles are tested in the release study is not indicative of the manner in which particles would be distributed within the lung. The SLF fluid used for the release studies contained no surfactants, which are usually present within the lungs and which are likely to affect the dissolution profile of the SLNs. Additionally, only one inflammatory marker was studied, providing a limited view of the anti-inflammatory effect of ATRA. Further work should be carried out on inflammatory markers, such as TNF-α and IL-8, to study the full range of anti-inflammatory effects of ATRA within the lungs. Finally, while particles are theoretically in the correct size range for inhaled delivery, this has not been tested using technology for inhalation testing, such as cascade impactors.

Conclusions

In conclusion, this study has shown that ATRA SLNs can be consistently formulated within a suitable size range for pulmonary delivery. The SLNs showed a biphasic release profile, which can lead to optimal dosing regimens for patients, decreasing dosing frequency and resulting in a significant reduction in the anti-inflammatory marker IL-6.

Further work is required to evaluate how these particles could be delivered clinically in an optimal manner to the required sites of the lung in order to exert their effect and to fully assess the release kinetics of the ATRA from the SLNs.

Acknowledgments

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Idiopathic normal pressure hydrocephalus: pathological changes in cortical biopsies in relation to function and response to treatment. A preliminary study

Abstract

Introduction: Idiopathic normal pressure hydrocephalus (INPH) is a curable cause of dementia. There is a lack of research on pathology in relation to outcomes after shunt placement.

Objective: Our aim in this case series was to investigate pathological markers co-existing in INPH in patients, and the relation to improvement after shunt placement.

Methods: Cortical perioperative biopsies obtained from 11 INPH patients were immuno-stained for a variety of neurodegenerative disease biomarkers, and improvement in cognition, gait, and ventriculomegaly were compared prior to and after shunting.

Results: Five of 11 patients had beta-amyloid (AMYB) deposits; the amount of AMYB ranged from 0.08% to 12.8%. Plaque neurites were labelled for APP and AT8 in all three patients with cored plaques. The presence of AMYB was associated with age >75 (p=0.02). Improvements in Montreal Cognitive Assessment (MoCA) scores (6/8) were more common in patients without AMYB deposits (p=0.02). Cognitive improvement was associated with younger age and absence of amyloid deposits.

Conclusion: There was a tendency to improve in all patients, regardless of pathology. Pathological load was inversely correlated with improvement in cognition and younger patients improved to a greater degree. A study with a larger sample size would be required to confirm these findings.

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Introduction

Idiopathic normal pressure hydrocephalus (INPH) is a neurodegenerative condition that presents with an accumulation of cerebrospinal fluid in the ventricles alongside a counter-intuitively normal cerebrospinal fluid (CSF) pressure. INPH classically presents with a triad of frontal gait abnormality, cognitive decline, and urinary incontinence.[1] INPH is often misdiagnosed due to its presentation: both Parkinsonian-like gait and cognitive decline similar to that seen in Alzheimer's disease (AD) are common.[2] The 68% prevalence of concomitant AD and dementia pathology with INPH further complicates diagnosis.[3]

Treatment of INPH consists of surgical insertion of a ventriculo-peritoneal (VP) shunt to correct hydrocephalus and potentially reverse the

Table 1: Neurodegenerative disease stains and their associated pathology.[15,16]

Stained protein	Associated pathology
Amyloid precursor protein (APP)	Identifies the early stages of plaque formation in relation to AD
Beta-amyloid (AMYB)	Identifies the AD pathology
Tau	Indicates progressive supranuclear palsy, corticobasal degeneration, and tau-associated frontotemporal dementia
AT8	A more sensitive test for tau than APP, particularly for NFTs and neuropil threads
Alpha-Synuclein (aSyn)	Presence indicated Parkinson's disease and Lewy body dementia
TDP-43	Presence identified abnormally located neuronal cytoplasm displayed in frontotemporal dementia, amyotrophic lateral sclerosis, hippocampal sclerosis, and limbic encephalitis associated with AD
P62	To identify ubiquitination of proteins for degradation; excess P62 indicated neurodegeneration
Glial fibrillary acidic protein (GFAP)	Identify glial pathology

These stains were used to test for clinical query underlying pathology.

patient's symptoms. Despite VP shunting being an effective and widely-used treatment, there are high rates of complications, and causes and risk factors of poor response to a VP shunt are not well understood. It is hypothesised that this variance is due to the presence of concomitant neurodegenerative diseases such as AD.[3,4] While some studies have found that the presence of AD has no effect on post-shunting results, others have demonstrated that beta amyloid plaques and tau-immunoreactive neurofibrillary tangles (NFTs) have been related to a decreased response to shunting.[4,5] Other underlying neuropathologies, such as frontotemporal dementia and supranuclear palsy, which may also be associated with a decreased response to shunting, have not yet been explored. This case series aims to query underlying pathologies in INPH patients and their relationship to clinical outcomes pre and post shunting.

Objectives

This case series aims to investigate concomitant pathologies in INPH patients by staining for antibodies associated with the spectrum of neuropathological diseases. This is in hopes of attempting to understand which pathologies are simultaneously present, and to what extent they affect the results of shunting surgery.

Materials and methods

In this retrospective study, data was collected from 11 INPH patients (M=8, F=3) aged 67-88, admitted to St Michael's Hospital in Toronto, Canada, between 2012 and 2014. Inclusion criteria were patients undergoing standard ventriculo-peritoneal shunt surgery at St Michael's Hospital and who had cerebral cortical biopsies for clinical query of presence of pathology. Biopsy consent was implemented in 2012 for all patients undergoing ventriculo-peritoneal shunt surgery. All patients asked consented to the procedure. Diagnosis of INPH was confirmed with the classical triad of symptoms (dementia, urinary incontinence and gait disturbance), lumbar puncture test, and CT scan.[1]

Soarian Clinicals, the online patient database for St Michael's Hospital, Toronto, was used to obtain data for this study. The following clinical information was obtained: age, sex, intervention date, Evans ratio (ER), Montreal Cognitive Assessment (MoCA) scores, and walking test scores. The ER is the maximal frontal horn ventricular width divided by the transverse inner diameter of the skull. An ER greater than or equal to 0.3 signifies ventriculomegaly.[6] ER values were calculated from pre- and post-shunting MRI scans. MoCA is a 30-point form used to assess cognitive function.[7] For walking test scores, outcome values that indicated the number of steps taken to cover 10m were used. Biopsies for pathological analysis were obtained from the right frontal cerebral cortex, in order to minimise invasive procedures, as this is where the shunts were placed.

Immunohistochemistry

Tissue specimens underwent formalin fixation for a period of 24-48 hours. The specimens were then embedded within paraffin wax, sectioned to 5-20 micrometres and primarily stained with haematoxylin and eosin, amyloid precursor protein (APP), beta amyloid (AMYB), tau, AT8, alpha-synuclein (aSyn), TAR DNA-binding protein of 43kDa (TDP-43), P62, and glial fibrillary acidic protein (GFAP).[8-16] The associated pathologies are shown in **Table 1**. The BenchMark ULTRA IHC/ISH (Ventana Optimax, USA)

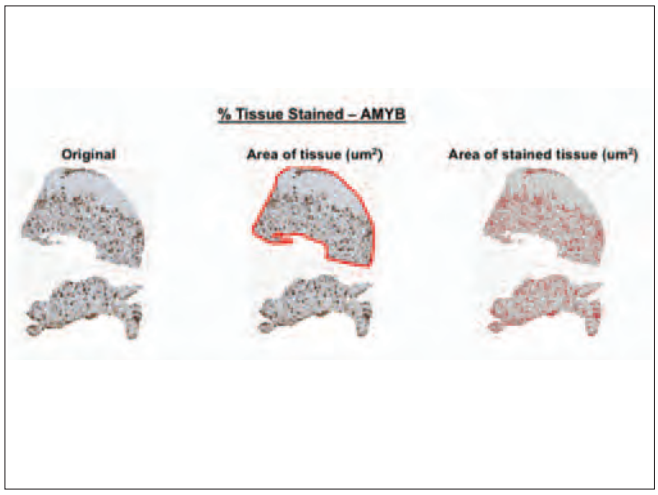

FIGURE 1: Quantification of percentage tissue stained. This figure demonstrates one patient's biopsy. The original is the untouched picture. The middle image demonstrates how the area of the tissue was determined via the selection tool in Image J. The third image demonstrates how the stained areas (AMYB) were selected in order to quantify percent area tissue stained.

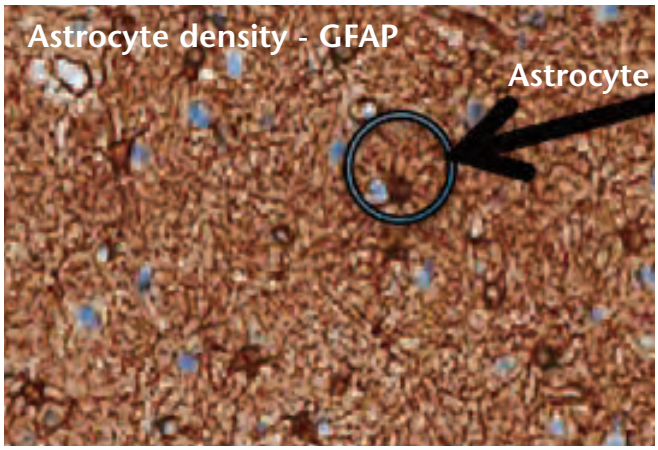

FIGURE 2: Cortical neural tissue stained with GFAP. The scans were first cleaned using Adobe Photoshop, after which astrocyte density was determined by cell counting. Image J was then used to quantify AMYB, using the selection tool to determine the area in μm² of the parts of the tissue. The "threshold" function was used (values were set and used for all AMYB slides) to determine area of stained tissue.

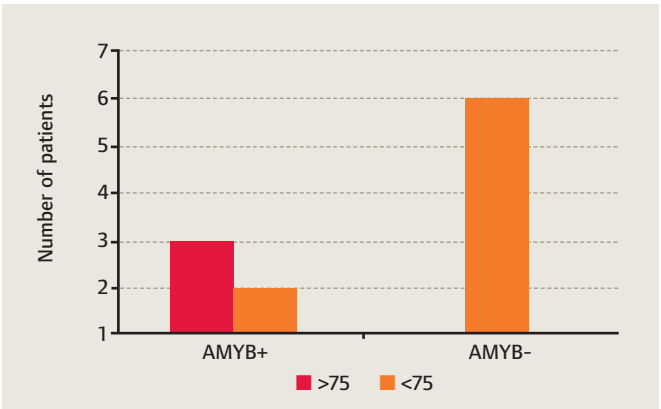

FIGURE 3: Age (≥75 vs. <75) and presence of AMYB (χ^2=4.95, p=0.02). Patients were grouped by age and staining for AMYB (+ vs. -) and the number of these patients were stratified based on these criteria.

staining module was used and the samples were prepared using a Ventana Optimax kit machine. An Aperio ScanScope AT Turbo (Leica Biosystems, Germany) was used to scan the slides. The snapshots were then isolated using Adobe Photoshop (Adobe Systems, USA). Image J, a Java-based image-processing program developed at the National Institutes of Health, was used to quantify AMYB using the selection tool to determine the area of cortical tissue in μm², as well as the area of stained tissue in μm². The percent tissue staining for AMYB was calculated from these values (**Figure 1**). GFAP was quantified using Adobe Photoshop to select grey matter, and astrocytes per μm² were determined (**Figure 2**). Statistical analyses of the data, particularly one-tailed Student's t-test, Pearson correlation, and chi-squared analysis, were performed using Graph Pad (GraphPad software, USA).

Results

Although case records were reviewed extensively, they did not all provide information for the MoCA and walking test to the same degree. Eight of the 11 cases had at least one pre-shunting and post-shunting MoCA score. Patient 6 did not have a pre-op MoCA score, and patient 7 did not have a post-op MoCA score; therefore, they were excluded from cognitive improvement analysis.

All patients had CT scans pre shunting and post shunting. All biopsied samples were of adequate size for accurate pathological assessment (1.25-3.62cm³).

Out of the 11 patients, five were AMYB+. Two had diffuse plaques only, and three had both cored and diffuse plaques; one had additional cerebral amyloid angiopathy (CAA). The quantification of AMYB ranged from 0.08% to 12.77% in the five patients.

All those who were AMYB+ stained for APP in plaques. The patient with diffuse plaques only, did not show APP-positive neurites in plaques. Two of three patients that had cored plaques and APP in plaques were AT8+; the third was not stained for AT8 due to exhaustion of available tissue. One patient that was positive for AMYB, APP, and AT8 additionally stained for tau in plaque neurites, neuropil threads, and NFTs. This patient alone showed decline in cognitive assessment post shunting. This patient also had no improvement in the post-intervention ER score but displayed improvement in the walking test.

All of the biopsies that were stained for GFAP in the cortex were positive; notably, one patient did not have an adequate amount of tissue to stain for GFAP; therefore, they were excluded from GFAP analysis. All patients in this study, except one, improved

cognitively based on their post-shunting MoCA score.

When stratified into groups of ≥75 and <75 years of age, there was a positive correlation with presence of AMYB (**Figure 3**; χ^2=4.95, p=0.02). When analysed for covariance, age was significantly associated with presence of AMYB (p=0.031) but not with amount of AMYB (r=0.57, p=0.31).

The presence of amyloid was not associated with average pre-shunting ER (t=0.22, p=0.41). There was no difference in ER improvement between patients with or without AMYB pathologies (t=0.16, p=0.43) or relation between degree of anatomical improvement (ventriculomegaly) and presence of pathology (t=0.52, p=0.31). There was not enough data to sufficiently power a calculation of the relationship between amount or presence of AMYB and pre-shunting MoCA scores. Amounts of APP, GFAP, or P62 did not correlate with pre-shunting values.

Cognitive improvements in MoCA were stratified by clinically noticeable improvements, using >5 and <5 score improvements in MoCa as an objective cut-off (**Figure 4**). Significant improvements in MoCA were more common in patients without AMYB deposits. Average change in MoCA scores was greater in AMYB- patients (mean improvement = 14) than AMYB+ (mean improvement = 5) patients (t=2.08, p=0.02). There was no correlation, however, between amount of AMYB and degree of cognitive improvement (r=-0.28, p=0.053).

As expected, younger age was associated with increased improvement in cognitive function (**Figure 5**; r=-0.5, p=0.019). There was also a correlation between increased age and presence of AMYB (χ^2=4.95, p=0.016).

The trend displayed no association of ventriculomegaly with age (r=0.23, p=0.30). MoCA improvement was inversely correlated with age (r=-0.5, p=0.019; **Figure 5**).

The density of cortical GFAP+ astrocytes showed a trend towards an inverse correlation with age (**Figure 6**); however, it did not reach significance (r=-0.58, p=0.06).

Discussion

This case series is the first of its kind to investigate pathological substrates in addition to those associated with AD, and their effect on shunting in INPH patients; however, only AD-associated pathology was found in our samples. The prevalence of the AD pathology in our study was 45%. This is in comparison to the 33% prevalence of AD in the normal elderly (>65) population, suggesting that AD pathology may be more common in INPH patients. In contrast, a study by Bech *et al.* suggests that there is a lesser

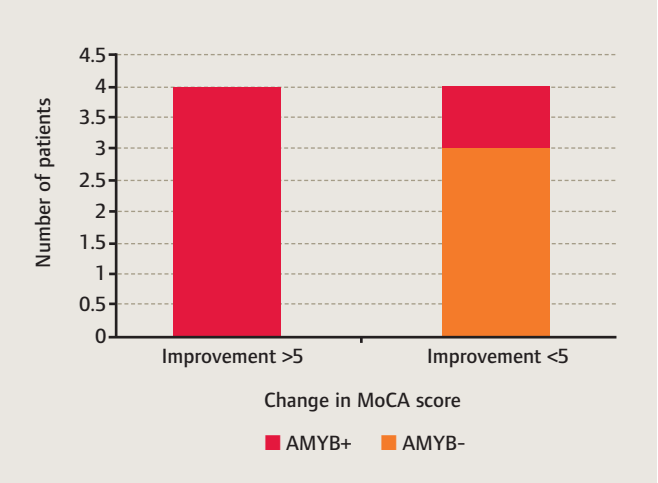

FIGURE 4: Number of patients (AMYB+ vs. AMYB-) and degree of cognitive improvement (χ^2=4.8, p=0.028). Patients were grouped in terms of degree of improvement in MoCA score (pre and post intervention) by five points and also displayed as either AMYB+ staining or non-AMYB staining.

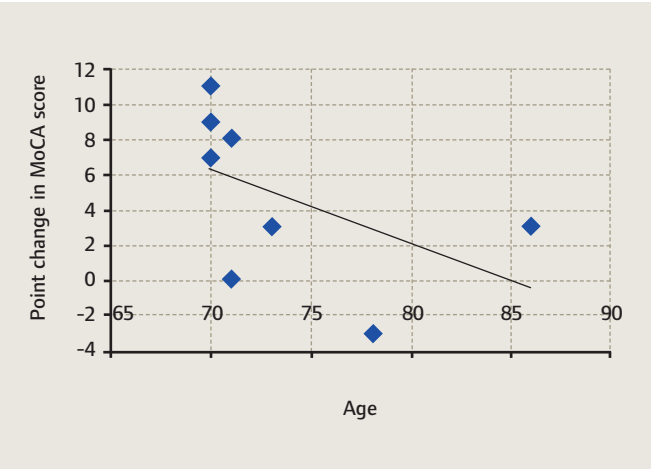

FIGURE 5: Age vs. point change in MoCA scores. Points are plotted for all patients who had both pre- and post-procedure MoCA assessments completed (n=8). (r=-0.5, p=0.019).

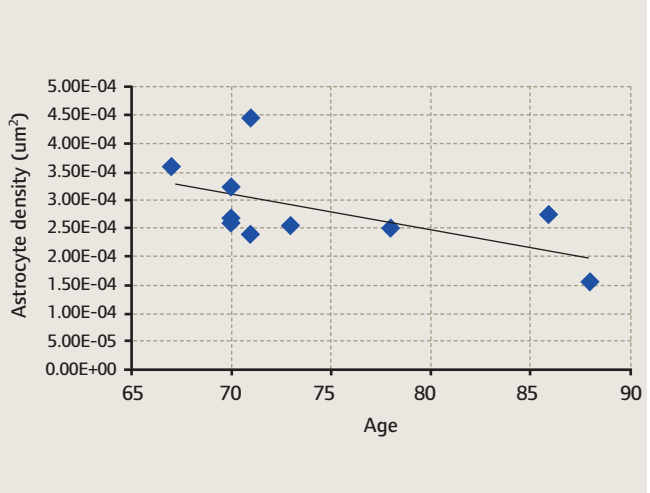

FIGURE 6: Age vs. astrocyte density (μm²). Points are plotted for all patients whose biopsies could be stained for GFAP (n=10). (r=-0.58, p=0.06).

prevalence of AD in INPH patients.[17] The majority of our patients, 75%, demonstrated a cognitive improvement after shunting regardless of AMYB presence. Our findings are consistent with another study demonstrating post-shunting improvement despite staining for AD markers.[5] However, this degree of improvement was smaller in the patient that stained for tau. In general terms, patients with less pathology improved; this finding is consistent with the findings of Hamilton *et al.* in that patients with mild pathologies responded well to shunting.[3] With reference to our study, the "mild pathology" group are the patients staining for AMYB, APP, and AT8. Neuropathologically, all patients with AT8+ were AMYB+, suggesting that the pathologies are associated; this also confirmed that the INPH patients that stained for biomarkers were for AD pathology only. The average length of time between shunt placement and assessment for ER was 76 days, and for MoCA was 142 days; our data are therefore indicative of long-term improvement following ventriculo-peritoneal shunt placement.

Furthermore, Hamilton *et al.* found that patients with moderate-to-severe tau and AMYB pathology displayed poor shunt outcome with respect to cognition and mobility.[3] This is consistent with our study, although the patient with CAA improved to the same degree as other AMYB-staining patients, and that only mobility in addition to cognition improved in patient 1. Patient 1 was the most pathologically affected, and yet still displayed an improvement in gait (+15 from 28 pre shunting).

It is important to note that the patient with the greatest amount of AMYB-stained tissue is the only one who also stained for tau pathology, which suggests that this patient had an independent development of AD due to how extensively affected the tissue was. Unexpectedly, the amount of surface area covered by AMYB was not associated with shunt outcome. Additionally, it is important to note that none of the patients in our study stained for aSyn or TDP-43, indicating that Lewy body and frontotemporal dementia (FTD) pathologies are not associated with INPH (although this could be a result of our small study size).

Our results demonstrate that although other factors could potentially contribute to the effects of ventriculo-peritoneal shunt surgery, the procedure ultimately has positive effects on patient response, regardless of presence of concomitant neurodegenerative diseases. This is in contrast with a study by Tudor *et al.* that demonstrated only 30-50% of INPH patients improving post shunting procedure, whereas our shunt improvement values in cognitive function (75%) are far higher.[18] It was also found that younger age was associated with increased improvement in cognitive function (r=-0.5, p=0.019). However, there was a positive trend between age and presence of AMYB (χ^2=4.95, p=0.016) so the increased improvement is likely due to lack of pathology. Furthermore, the presence of AMYB was associated with increasing age, which may be a contributing factor in the improvement seen in younger patients. Pre-shunting ER scores did not associate with age or AMYB presence. Improvement in ventriculomegaly did not differ between patients with or without AMYB pathologies and neither did age with ventriculomegaly. This is an interesting finding, as it would be expected that older patients have greater AD pathology and therefore greater ventriculomegaly. The majority of patients improved cognitively even with presence of AMYB, but the degree of their improvement was based on their age and presence of AMYB, not the amount of AMYB, meaning that age is a more reliable predictor of improvement than amount of AMYB. An interesting non-significant finding that merits further investigation was the apparent association between density of cortical GFAP+ astrocytes and age; there was a non-significant trend towards an inverse correlation with age (r= -0.58, p= 0.06) but not with AMYB or AT8 pathologies.

It is important to note that the patient with the greatest amount of AMYB-stained tissue is the only one who also stained for tau pathology, which suggests that this patient had an independent development of AD due to how extensively affected the tissue was.

Limitations

The size of our study reduced the power of our findings, and preliminary statistics were used in processing our collected data. Therefore, our study can only serve to identify trends in INPH patients, and can solely function as a preliminary experiment to guide subsequent research. It is important to note that not all patients had pre- and post-intervention MoCA or ER scores. This impact was most pronounced, however, in the walking test scores as only two patients in the study had both pre- and post-intervention scores available. There was also a lack in data with tissue available as one patient did not have enough tissue to be assessed for GFAP staining. Furthermore, when interpreting our findings, it should be noted that our cutoff for grouping of data for cognitive improvement (categorisation by ≥5 point changes in MoCA scores) was chosen retrospectively, as differences became statistically significant at this value, rather than having a preset cutoff value.

Conclusion

Overall this research functioned as a preliminary study where it was found that patients without significant AMYB deposits related to better cognitive and mobility outcomes. This study concluded that AD-related pathology was the only neurodegenerative process associated with INPH, and that there is a general tendency to improve in cognitive and mobility aspects post shunting procedure in INPH patients, regardless of pathological marker status. Cognitive improvement was associated with younger age and absence of amyloid deposits (with younger age also being a predictor of absence of amyloid deposits). Patients with small amounts of tau still improved in terms of cognition and mobility, in comparison with patients with large amounts of AMYB and additional tauopathy, who only improved in mobility. The decreased density of cortical astrocytes with age was an unexpected finding, and worth investigating in future studies. A larger number of patients, an investigation over a longer time period and across multiple hospitals, would increase the enrolment in future studies and therefore improve power to detect significant findings.

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Gaming to rehabilitate: comparing rigid and flexible handgrip devices in visuomotor tracking tasks

Abstract

Background/aims: The use of robotic handgrip devices for neurorehabilitation has great potential to supplement conventional physiotherapy. A novel, flexible handgrip has been developed as an alternative to currently used rigid handgrips, and is potentially better suited for repetitive functional grip training. This study aims to compare the performance and user preferences of flexible vs. rigid handgrips in visuomotor tracking-task 'games'.

Methods: This was a randomised, controlled crossover study comparing ease of use and functionality between rigid and flexible handgrips. Mean tracking error during play of visuomotor tracking games was assessed in 18 cognitively and physically unimpaired adult subjects using flexible vs. rigid handgrips. Psychometric data regarding user experiences and preferences were also collected.

Results: The median difference in tracking error made between flexible and rigid handgrip use was -0.51% (p=0.043) in the regularly patterned (S2C) game trajectory and -2.23% (p=0.003) in the more randomly patterned (HS) game trajectory (less error with flexible handgrip). Furthermore, 55.6% of subjects preferred the flexible handgrip (22.2% preferred rigid), although the difference was not statistically significant.

Conclusion: The flexible handgrip is more ergonomic and easier to use than its rigid equivalent, resulting in better accuracy in gaming tasks and potentially making it more suitable for use in hand rehabilitation therapy.

Keywords: Neurorehabilitation; neuroscience; rehabilitation; handgrip; technology; gaming.

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Introduction

Upper limb impairment is present in approximately 75% of stroke survivors in the UK,[1] with paresis as the most common motor symptom experienced after a stroke.[2] The upper limb is often more severely affected than the lower limb,[3] and due to the complex and fine nature of many essential hand movements, rehabilitation of the upper limb has proven to be particularly challenging. Poor recovery outcomes are often reported for such patients, with only 20% gaining functional improvement within the first six months.[4] In cases where neurological deficits (e.g., due to stroke) cause motor impairment, repetitive goal-oriented training – such as gripping and moving objects – provides functional benefit for patients as they involve complex neural circuits.[5] Conventional rehabilitation therapy, given by physiotherapists and other health professionals, is time and labour intensive. The use of robotic devices in rehabilitation has significant potential for use in long-term stroke recovery as an adjunctive therapy during and beyond hospital treatment. When used as gaming devices, they encourage independent use and self-motivated performance of therapy. This prevents decline in hand function from disuse, which may occur when physiotherapy stops.[6]

However, the use of robotic devices for therapy is

limited by a number of factors, including the need for supervised use and for relatively high baseline functioning in patients.[5] A novel, flexible handgrip neurorehabilitation device, designed by researchers at Imperial College London, utilises commercial gaming principles of challenges and rewards to increase motivation for therapy and provide a high number of exercise repetitions. Its design as an isokinetic grip device provides passive assistance to finger movement through a spring-based mechanism.[5] This improves joint control and muscle training of finger flexion and extension, with the potential to not only improve functional outcomes of grip retraining, but also to increase patient compliance due to a more ergonomic and user-friendly design. The device is highly sensitive, capable of capturing even 'flicker' movements from severely impaired patients.[5] These are novel features not present in currently available devices such as Tyromotion's Pablo isometric (fixed) handgrip.[7] Currently, a number of studies are being carried out to test the flexible handgrip's effectiveness and utility in clinical care.

Aims

This study aimed to compare differences in user performance at a computer-based game using a flexible and rigid version of the same handgrip, as well as to compare participants' subjective experiences with each device and determine their preferences. This tested the hypothesis that patients would prefer using the flexible handgrip over the rigid control, and that use of the flexible handgrip would result in a lower mean tracking error when performing tasks. A better technical performance at the cognitive tasks would suggest an increased ease of use that is expected of the flexible handgrip – a result of its supportive design – and support its use over a rigid/isometric design in hand rehabilitation.

Materials and methods

Participants

Healthy adults aged 20-80 years with no obvious upper limb deformity or neurological disease were recruited. The participants also had no signs of significant cognitive impairment, as they needed to be able to comprehend the tracking game. Both left- and right-handed participants were included in the study.

Procedure

After performance of the Edinburgh Handedness Inventory,[8] participants were given either the flexible or rigid device **(Figure 1)** and asked to play the game 'Star-Shooter', a visuomotor tracking task performed on a tablet computer, requiring participants to keep a cursor on a moving star. Each participant was asked to play the same game with both devices, holding the device in their dominant hand. The order in which

FIGURE 1: Flexible vs. rigid handgrips – the rigid handgrip (left, red) and flexible handgrip (right, blue) used in the study.

a participant used the rigid and compliant devices was counter-balanced via C-R or R-C blocks (where C-R means flexible or 'compliant' device first, before rigid device, and R-C vice versa) to eliminate order effects and learning bias. The path of the star was determined by two waveforms: S2C, a sinusoidal curve in which the star moved up and down across the screen with increasing frequency towards the end of the session; and, a HS (harmonic series) waveform, which gave the appearance of a more random movement of the star across the screen. None of the participants had previous experience with the devices or tracking task. Participants completed questionnaires on their experiences with each device after it was used, and noted their preference after using both. All questions were rated on a discrete five-point Likert scale (rated 0-4), and there was a section for additional comments from participants. Additionally, device and game data were recorded on the tablet computer, including each participant's grip force, and the position of the participant's cursor in relation to the moving target throughout the task.

Tracking performance analysis

Participant performance on the tracking task was saved as text code, and this was converted into visual representations of their cursor trajectories using MATLAB (MATLAB and Statistics Toolbox, The MathWorks, Inc.; Natick, Massachusetts, United States), a programming and analysis software. To quantitatively represent a participant's performance, the percentage error $\hat{E}$ was represented as the difference between the trajectory of the moving object (the star) and that of the participant's cursor, at various points over the course of the task. The difference in tracking error occurring with each device was calculated by subtracting the mean error for the rigid device from the mean error for the flexible device: $\hat{E}_{flex} - \hat{E}_{rigid}$ (%).

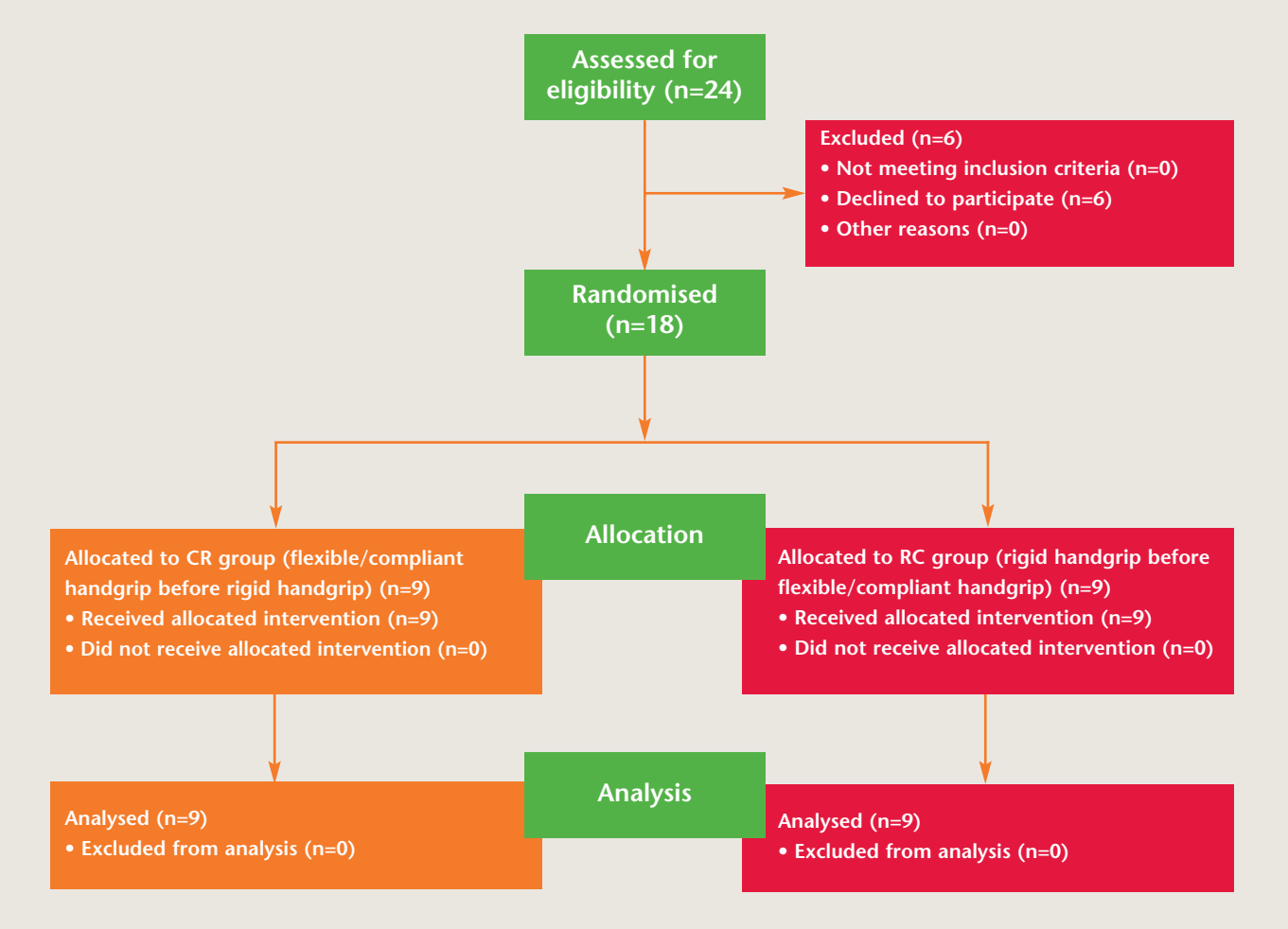

FIGURE 2: Study recruitment – flow diagram illustrating recruitment, randomisation and analysis for participation in this study.[10]

To reduce the effect of random errors due to distractions or other external factors at the time, the mean tracking for each device was calculated using a 30s segment of data of minimum tracking error (representing the segment of the participants' best and most consistent performance). The mean tracking error for the group with each handgrip was calculated and compared. A box plot comparing the difference in tracking error between the two handgrips for each trajectory waveform was made. Statistical significance was determined using Wilcoxon signed-rank test, where $p \leq 0.05$ was considered significant.

Psychometric data analysis

Answers from the questionnaire were collated into individual five-point bar charts to show their distribution among the group studied. The mean rating given by the group and for each device per question was also calculated. Statistical significance for the ordinal data was set at $p \leq 0.05$ using Wilcoxon signed-rank test.

Results

Eighteen individuals participated in the study **(Figure 2)**, and 14 of the participants were right-handed. The age range of the group was 22-67 years, and the mean age was 40.7. The gender distribution of the group was eight males and 10 females, and 33.3% (n=6) of participants reported that they had never played computer/smartphone/tablet games (QG).

Tracking performance results

Figure 3 shows a box plot comparing the difference in tracking error for each trajectory waveform. Results illustrate that the median difference in error for the S2C waveform was -0.51% ($p=0.043$), and that for the HS series was -2.23% ($p=0.003$), and this was statistically significant for both tasks (S2C and HS) using Wilcoxon signed-rank test, where $p \leq 0.05$.

Psychometric data results

The results for the participants' preferences for a handgrip device (QP

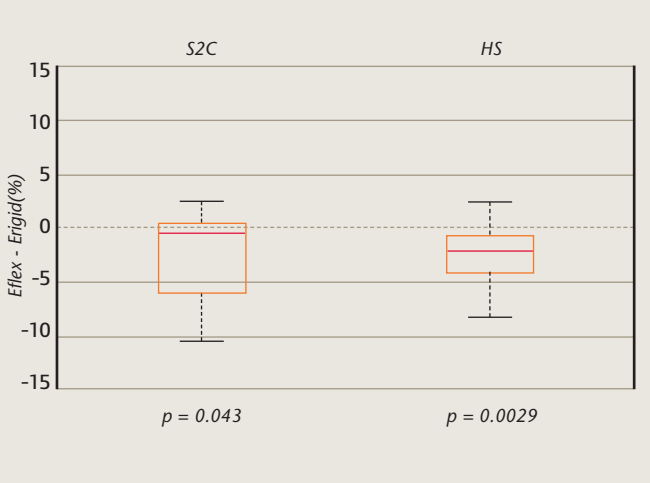

FIGURE 3: Mean tracking error difference – box plot comparing the mean difference in tracking error between a flexible and rigid device ($\hat{E}_{flex}$ - $\hat{E}_{rigid}$), when performing two visuomotor tracking tasks (S2C [left] and HS [right] waveforms).

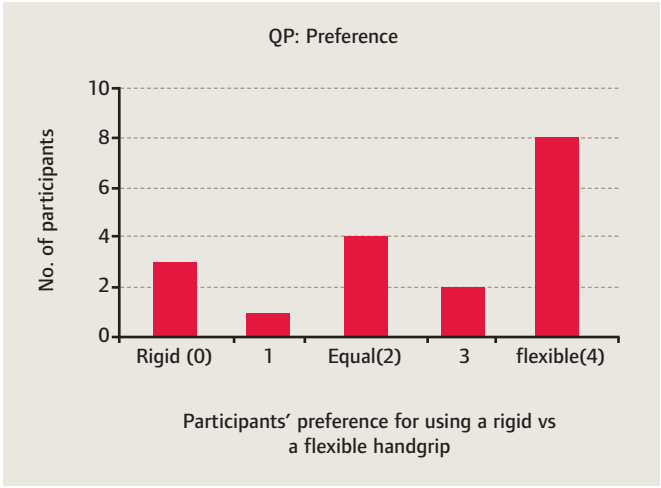

FIGURE 4: Participant preference – bar chart showing participants' preferences, arranged categorically, for using a rigid vs. a flexible handgrip during visuomotor tracking task game 'Star Shooter'.

question) are shown in **Figure 4**. Overall, 55.6% (n=10) preferred the flexible handgrip to the rigid device. The rigid device was preferred by 22.2% (n=4), and the other 22.2% had no preference. A two-tailed Wilcoxon signed-rank test comparing the distributions indicated that this difference was not significant (p=0.139).

The mean and standard deviations of the Likert ratings for each question are shown in **Table 1**.

Results showed that, on average, participants rated the flexible device higher in terms of their performance (Q1), enjoyment (Q2), improvement (Q4), control (Q6), and hand fatigue (Q5). The flexible device was rated lower than the rigid in terms of discomfort (Q3). Statistical analysis showed that there were no significant differences between the two devices in terms of participants' rankings of their performance, enjoyment, comfort, improvement, or fatigue while using the two devices. The only exception was Q6: the level of control participants felt while using the handgrips. On average, participants felt that they had more control when using the flexible device, and this difference was statistically significant (p=0.019).

Table 1: Psychometric data.

Question	Mean Likert scale grade(/4) Flexible	Rigid
Q1: Performance (0 – very bad; 4 – very good)	2.4±1.0	2.1±1.2
Q2: Enjoyment (0 – none; 4 – a lot)	3.1±1.2	2.7±1.3
Q3: Discomfort (0 – none; 4 – uncomfortable)	0.8±1.2	1.2±1.2
Q4: Improvement (0 – none, 4 – a lot)	3.2±0.7	2.7±1.2
Q5: Fatigue (0 – none, 4 – tired)	1.2±1.3	1.1±1.5
Q6: Control (0 – none, 4 – a lot)	2.8±0.8	2.0±1.0

Comparing the mean Likert ratings for each device in a psychometric questionnaire about user experience with the handgrips. Mean and standard deviations are shown for each question.

Discussion

The median difference in error for the S2C waveform was -0.51% (p=0.043), favouring the flexible handgrip, and that for the HS series was -2.23% (p=0.003), favouring the flexible handgrip, and this was statistically significant for both tasks (S2C and HS). The negative value of the error difference shows that use of the flexible device produced less error than use of the rigid device for both trajectory-tracking tasks. In the HS task, where the star followed a more random path and was thus more difficult to do, the mean tracking error difference is greater, and shows a more significant error reduction with the flexible device. Thus, the flexible handgrip resulted in significantly greater tracking accuracy when compared to the rigid handgrip. Its isokinetic spring mechanism is more supportive of hand gripping movements, and increases ease of use, as demonstrated by participants' greater accuracy in playing the computer games. Additionally, participants' preference showed a strong trend in favour of the flexible device – more than twice that of the rigid device – and reported significantly better control with the flexible handgrip. These results further support the hypothesis that the flexible handgrip is a more ergonomic design, better suited for repetitive functional grip training. Nevertheless, it is worth noting that both devices were well received in terms of their user experience. Both devices

generally received higher ratings for the 'enjoyment' and 'improvement' questions, and lower ratings for questions on discomfort and hand fatigue, which are important for their use as rehabilitative devices. Use of the flexible design may thus maximise the benefits and performance of the handgrip training device. Findings from this study are in line with that of a previous study comparing the same handgrips' performance in a different cognitive game setting – a visual feed-forward tracking task – which showed a high and statistically significant preference for the flexible handgrip (62% of participants, p=0.004). The study also found a better performance in the mean tracking error of the flexible handgrip, though it was not significant in that study.[5]

Limitations

A limitation of this study involved the recruitment of participants. The inclusion/exclusion criteria for participants with visual impairment were not outlined in the study protocol. While it can be assumed that none of the participants had severe vision impairment to be able to complete the tracking task and questionnaire, this was not actively screened for or tested. Visual impairment can affect an individual's tracking accuracy and influence results.

In this study, results from the questionnaires were analysed quantitatively through their Likert ratings by calculating the mean rating for the group per question. This works under the assumption that the ordinal data of the Likert scale can be treated as interval data through the assignment of arbitrary numerical values. There is some debate over whether the use of median or mode values might be more accurate in assessing such data.[9]

Conclusion

The incorporation of gaming tools in the area of rehabilitation provides an incentive to physiotherapy through its entertaining and interactive approach. This increases the likelihood of continued exercise repetitions, leading to improved functional outcomes of physiotherapy. Improving the quality of these rehabilitative devices and studying user engagement with these tools can further maximise these benefits. This study's results, in the context of existing literature, indicate that the difference in performance and user preference between the two handgrips holds true irrespective of the gaming context in which it is used. The flexible (isokinetic) handgrip appears to be more ergonomic and preferable to the rigid (isometric) design. Future research will involve clinical studies to see whether the benefits of the flexible design hold true for patient populations with hand weakness, and to determine whether this will ultimately translate to clinically-improved hand rehabilitation.

Ethics

The study was approved by the Imperial College London Research Ethics Committee, with all participants giving written and signed informed consent prior to participation.

Acknowledgments

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RCSI smj review

The surgical treatment of carotid artery disease: carotid endarterectomy vs. carotid artery stenting

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Abstract

Carotid artery stenosis from atherosclerotic plaque remains one of the leading causes of stroke. Therapy for this condition includes carotid endarterectomy (CEA) and carotid artery stenting (CAS). Achieving appropriate care for patients with carotid stenosis demands an understanding of these two revascularisation procedures. While early research has shown that CEA represents a safer alternative to CAS, recent research reflects a more nuanced comparison between the two revascularisation procedures. Up to one year after revascularisation, several randomised controlled studies (including EVA-3S, the ICSS, and CREST) have shown that CAS represents a higher risk of stroke than CEA. However, it is unclear if there is a difference in the severity and complications of stroke that may occur after either procedure. Beyond one year post revascularisation, the differences between the two procedures appear to be far less pronounced, if present at all. Considering this data, physicians should focus on age and other risk factors for stroke or myocardial infarction when deciding on the most appropriate revascularisation procedure for their patients.

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Introduction

Carotid artery disease in the form of advanced atherosclerotic plaque poses a significantly increased risk of stroke,[1] either through progressive stenosis with eventual complete occlusion of the artery or, more commonly, through plaque rupture and distal embolisation of the thrombus, both of which result in cerebral hypoperfusion, ischaemia, and potentially irreversible damage to brain tissue.[2] Stroke is the fourth leading cause of death in Western countries[3] and carotid artery disease is implicated in 10-15% of all ischaemic strokes.[4] Several medical and surgical approaches may be used in the management of atherosclerotic carotid artery disease. Medical treatment involving the use of dual antiplatelet therapy, high-dose statins, and antihypertensive medication has been shown to lower the incidence of recurrent events in symptomatic patients awaiting carotid revascularisation surgery.[5] Surgical options include carotid endarterectomy (CEA) or carotid artery stenting (CAS).

Carotid endarterectomy

CEA (**Figure 1**) can be done under local or general anaesthetic and usually involves an oblique incision along the anterior border of the sternocleidomastoid muscle to expose the carotid vasculature. The common, internal and external carotid are then clamped and a bypass device is used to reduce ischaemic time before another longitudinal incision is made along the area of the plaque to remove it from the vessel wall. A patch is then used to repair the defect.[6]

Carotid artery stenting

More recently, CAS (**Figure 2**) has emerged as a less invasive alternative to CEA.[7,8] CAS is typically performed by cardiologists or interventional radiologists and is achieved by threading a catheter under the guidance of real-time digital subtraction angiography, either trans-femorally or trans-radially, to the site of the lesion in the carotid artery.[8] Using the catheter as a guide, an embolisation protection device (EPD) is usually placed distal to the lesion. After the EPD is in place, a balloon predilation may be performed at the site of the lesion to allow for smooth entry of the stent. A self-expanding stent is then applied across the diseased portion of the artery, followed by post-dilatation ballooning.[7]

Revascularisation for carotid artery disease is generally recommended for symptomatic patients with over 70% carotid stenosis.[9] However, the choice between CEA and CAS has been the subject of debate, and multiple randomised controlled trials (RCTs) over the past two decades have attempted to answer the question of which is preferable (**Table 1**).[10-15] Understanding the risks and benefits of both revascularisation procedures is of critical importance for practitioners to better manage the healthcare needs of this patient population. This review will discuss the evidence from RCTs and meta-analyses to compare and contrast the two approaches in the short term and long term, followed by a discussion of the reasons why differences between the two revascularisation procedures exist.

Comparison of CEA and CAS less than a year after surgery

The differences in patient outcomes for CEA and CAS are greatest within the first year post revascularisation. Older studies show that in the short term CEA represents a lower risk to the patient compared to CAS. In 2006, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, a multi-centre European RCT enrolling 1,183 patients with severe symptomatic carotid stenosis, failed to prove the non-inferiority of CAS compared to CEA with respect to the peri-procedural complication rate. Recurrent carotid stenosis of over 70% was significantly more frequent in patients undergoing CAS (10.7%) compared to patients undergoing CEA (4.6%).[16] These results were supported by the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which randomly assigned 413 patients to CEA or CAS and found that restenosis was three times more likely in CAS than in CEA.[17]

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was an RCT that proved the non-inferiority of CAS with the use of an EPD in patients with severe stenosis at 30 days, and one and three years after revascularisation.[18,19] This data suggested that, under a specific protocol where an EPD was used, CAS may be as safe as CEA.

The Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was an RCT that enrolled 527 symptomatic patients with over 60% carotid artery stenosis. EVA-3S found that at 30 days post procedure, CEA patients had a lower (3.9%) risk of stroke or death compared to CAS patients (9.6%). This difference was not observed, however, after 30 days and up to six months post revascularisation.[13]

The results from the EVA-3S study have been corroborated by other trials including the International Carotid Stenting Study (ICSS). The ICSS enrolled 1,710 symptomatic patients in an RCT to compare outcomes in CEA vs. CAS. This study had an intention-to-treat (ITT) and per-protocol (PP) cohort. In the ITT and PP cohorts, fatal/debilitating strokes were equally likely if patients underwent CAS or CEA up to one year after revascularisation (absolute risk difference 0.7%; 95% CI [-1.0-2.5]).[11] However, in only the ITT

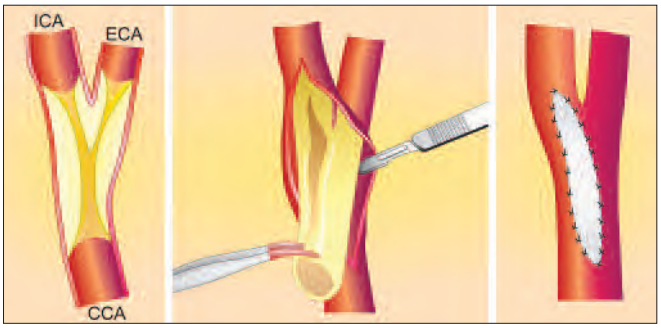


FIGURE 1: Schematic representation of carotid endarterectomy (CEA). Atherosclerotic lesions usually occur at the bifurcation point of the common carotid artery (CCA) into the internal carotid artery (ICA) and the external carotid artery (ECA). The plaque is removed and the defect is repaired with a patch. Adapted from Roffi et al.*, 2009.*

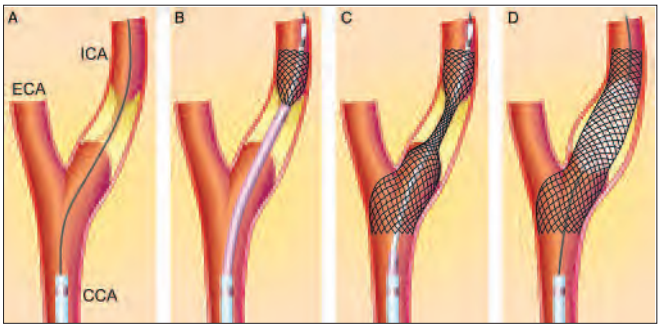


FIGURE 2: Schematic representation of carotid artery stenting (CAS). A catheter or guide wire is inserted through the common carotid artery (CCA) to the external carotid artery (ECA) or the internal carotid artery (ICA) (A). A stent is then deployed across the atherosclerotic lesion (B-C) followed by balloon dilatation (D) to expand the stent. Adapted from Roffi et al.*, 2009.*

Table 1: Randomised controlled trials comparing CAS and CEA.

Trial	Year	Number of patients enrolled	Devices used	Follow-up duration	Conclusion (outcomes)
ACT 1	2016	1,453	Emboshield/PRO, Emboshield NAV6, Abbott Vascular	30 days, one year, and five years	Non-inferiority was established between CAS and CEA for the rate of any stroke or death up to 30 days after revascularisation
CREST	2010, 2016	2,502	RX Acculink EPD used when appropriate	30 days, four years, and 10 years	Within 30 days risk of minor stroke was higher in CAS. Risk of myocardial infarction was higher in CEA. After four years, risk of minor stroke was still higher in CAS. Both procedures were equally safe after 10-year follow-up
ICSS	2015	1,713	Cerebral protection devices used at the discretion of operator	30 days, one year, five years, and end of follow-up (less than 10 years)	Any stroke or death was more likely in CAS within 30 days; however, both procedures were equally safe after 30 days
CSTC meta-analysis	2010	3,433	EPDs were used in all trials	30 days and 120 days	At 30 days mild or disabling stroke or death was more common in CAS patients. At 120 days only non-disabling stroke was observed more often in CAS
SPACE	2008	1,214	EPDs were used at the discretion of the operator	30 days and two years	Risk of stroke or death at 30 days and two years were the same in both procedures
EVA-3S	2006	527	EPDs were used but models not specified	30 days and six months	From 30 days to six months, risk of any stroke and death were higher in CAS
SAPPHIRE	2004	334	Angioguard or Angioguard XP, Cordis	30 days, six months, one year, two years, and three years	CAS with the use of EPD is not inferior to CEA

EPD: Embolisation protection device.

Table 2: Short-term risks of CEA and CAS in terms of stroke, death and myocardial infarction within 30 days of revascularisation.

Trial	Year	Hazard ratio	Confidence interval (-ve)	Confidence interval (+ve)	End points
ICSS up to follow-up	2015	1.06	0.72	1.57	Fatal or disabling stroke (follow-up was up to 10 years)
ICSS (up to 30 days)	2015	1.72	1.24	2.39	Any stroke or death
CREST (up to 30 days)	2010	1.90	1.21	2.98	Any stroke or death
CREST (up to four years)	2010	1.50	1.05	2.15	Any stroke or death
CREST (up to 10 years)	2016	1.37	1.01	1.86	Any stroke or death
EVA-3S* (up to 30 days)	2006	2.50	1.2	5.1	Any stroke or death
CSTC (up to 120 days)	2010	1.57	1.22	2.02	Any stroke or death
SPACE (up to two years)	2008	1.10	0.67	1.85	Ischaemic stroke or death

**Data is in relative risk*

	CAS		CEA			Peto odds ratio	Peto odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	Peto, fixed, 95% CI	Peto, fixed, 95% CI
CREST 10-year	98	1,262	71	1,240	16.5%	1.38 [1.01, 1.89]	
CREST 30-day	55	1,262	29	1,240	8.5%	1.86 [1.21, 2.88]	
CREST four-year	75	1,262	50	1,240	12.4%	1.50 [1.04, 2.14]	
CSTC	153	1,725	99	1,708	24.5%	1.57 [1.22, 2.03]	
EVA-3S	25	261	10	259	3.4%	2.48 [1.25, 4.93]	
ICSS 30-day	95	853	57	857	14.5%	1.74 [1.25, 2.43]	
ICSS to follow-up	52	853	49	857	10.0%	1.07 [0.72, 1.60]	
SPACE	56	613	50	601	10.1%	1.11 [0.74, 1.65]	
Total (95% CI)		8,091		8,002	100.0%	1.49 [1.31, 1.69]	
Total events	609		415				
Heterogeneity: χ^2 = 9.08; degrees of freedom (df) = 7 (p=0.25); I^2 = 23%							
Test for overall effect: Z = 6.11 (p<0.00001)							

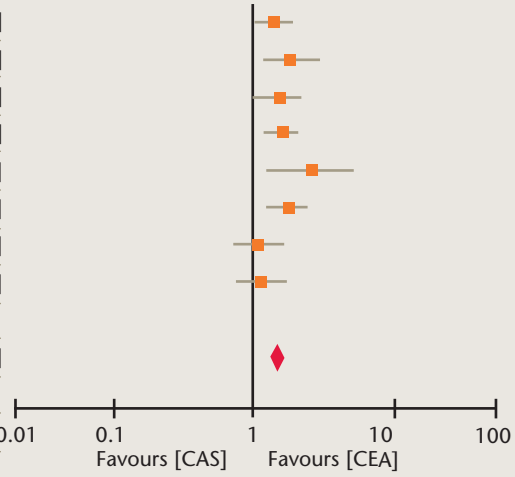
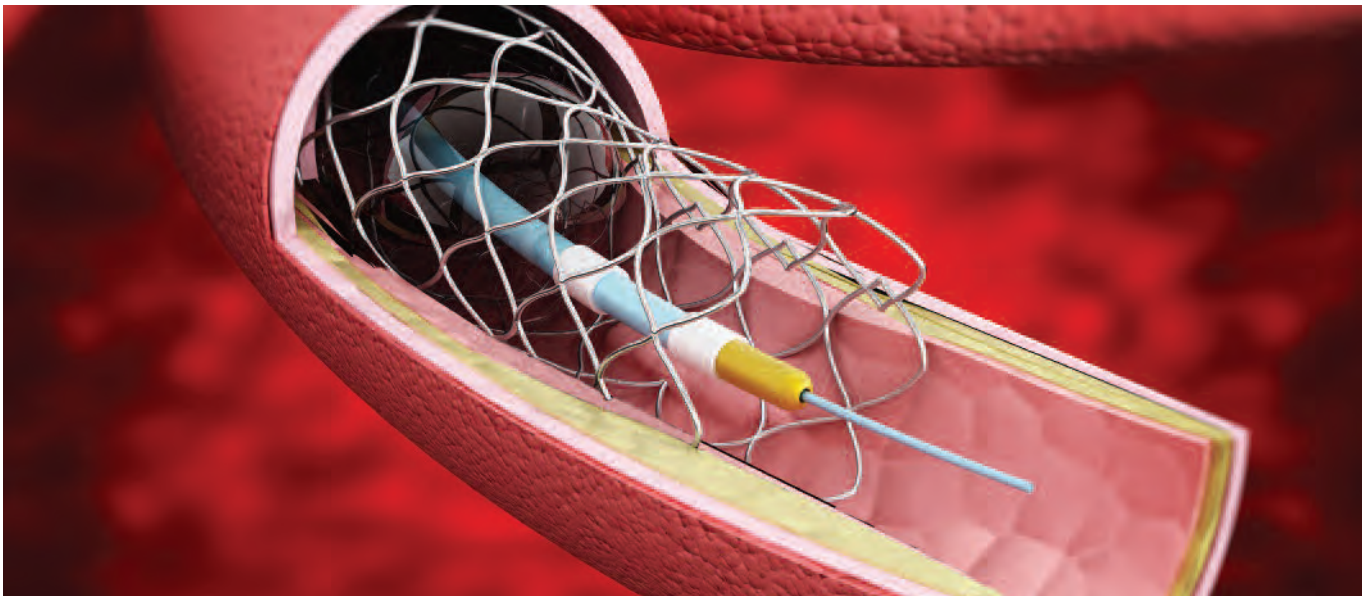


FIGURE 3: Risk of stroke or death in randomised controlled trials comparing carotid endarterectomy (CEA) with carotid artery stenting (CAS). Data analysis and graphical representation performed using Review Manager 5.3 from Cochrane Informatics and Knowledge Management Department.

cohort, CAS patients were more likely to suffer any stroke in the 30 days following revascularisation (absolute risk difference 4.4%; 95% CI [1.9-6.9]), and up to one year after the procedure (absolute risk difference 4.2%; 95% CI [1.9-6.6]). These strokes proved to be mostly non-debilitating. The discrepancy between the PP and ITT cohorts suggests that operator variability can have important consequences on the outcome of CAS. A separate analysis of patients who received stent treatment in the ICSS found that age was an independent predictor of risk of stroke, myocardial infarction, or death within 30 days of stenting.[12] The idea of age affecting stenting efficacy will be further discussed in long-term outcomes of CEA and CAS. The Carotid Revascularisation Endarterectomy vs. Stenting Trial (CREST) was a large RCT enrolling 2,502 symptomatic and asymptomatic patients from across North



America. The primary endpoints of stroke, myocardial infarction, and death were observed.[8] CREST found no difference in the incidence of the endpoints within 30 days after either procedure was performed (hazard ratio [HR] 1.18; 95% CI [0.82-1.68]; p=0.38).[20] However, if each individual component of the endpoint was observed independently, a difference between CEA and CAS emerged. Myocardial infarction occurred more often in CEA patients (2.3% vs. 1.1%; p=0.03) while, like in the ICSS and EVA-3S, non-debilitating stroke occurred more often in CAS patients (4.1% vs. 2.3%; p=0.01). These results were not affected by symptomatic status or sex.[20] One of the shortcomings of CREST was that it was underpowered in its asymptomatic cohort. This is important because historically CEA was considered safer for asymptomatic patients.[9]

The Asymptomatic Carotid Trial (ACT 1) was a prospective multi-centre analysis of asymptomatic patients, intended as a complementary study to CREST. Follow-ups occurred at one and six months, and then every 12 months for five years. Primary endpoints included stroke, myocardial infarction, and death. Analysis of the results showed that within 30 days post revascularisation, the event rate of the primary endpoints was the same in both groups, and even the incidences of stroke or myocardial infarction alone were not significantly different.[15]

In the short term, CEA and CAS represent different risks in terms of stroke, death (**Table 2**), and myocardial infarction within 30 days of revascularisation. However, these measures do not provide a complete picture of the patient's quality of life and other factors should also be investigated. Notably, CREST and ACT 1 found an increased risk of cranial nerve palsies, vascular injury and non-cerebral bleeds following CEA.[10,15]

Comparison of CEA and CAS more than a year after surgery

While differences in risk exist in the short term after revascularisation, recent data show that after one year post revascularisation, CEA and CAS are equally safe. CREST showed that the four-year rate of stroke or death was higher in the CAS patients compared to the CEA patients (HR 1.50; 95% CI [1.05-2.15]; p=0.03); however, this result was due to the high rates of stroke in asymptomatic patients.[10] ACT 1 found that CAS patients were more free of lesions associated with carotid stenosis one year after the procedure than their CEA counterparts (CAS: 99.4% vs. CEA: 97.4%; p=0.005).[15] Furthermore, five years after revascularisation, death and stroke were equally likely in both CEA and CAS, and 10-year follow-up results show that any difference in patient outcomes disappears after this time, with primary endpoints occurring as often in both CEA and CAS (HR 1.10; 95% CI [0.83-1.44]), regardless of symptoms or sex.[15] Long-term safety of CEA and CAS is further supported by other data including the ICSS, which found that the risk of any stroke in the PP cohort was the same in both procedures (absolute risk difference 3.1%; 95% CI [0.0-6.2]) up to five years post revascularisation.[12]

Finally, CREST and the ICSS agree that age may play a factor in CAS safety and success.[11,20] Both studies found increased efficacy in CAS patients younger than 70 years in terms of myocardial infarction, stroke, and death. These findings are further supported by other studies performed by teams such as the Carotid Stenting Trialists' Collaboration (CSTC). The CSTC analysed pooled data from EVA-3S, SPACE, and the ICSS and found that while CAS did have higher rates of any stroke or death within 30 days, which persisted until

120 days after revascularisation, this difference was only in patients that were older than 70 years.[21] CREST investigators suggest that this age dependence could be explained by increased vascular calcification or vessel tortuosity.[20]

Discussion

Amalgamated evidence (**Figure 3**) shows that CEA in the days to weeks following revascularisation represents a lower risk for any kind of stroke and a higher risk of myocardial infarction (**Table 1**).[12,20] The nature of the stroke appears to be non-disabling and certainly non-fatal; however, the studies performed do not offer a clear effect if any on the quality of life experienced by the patients.

The studies performed, while informative, do have some shortcomings. Firstly, the use of EPDs in these trials was variable; in most cases, the decision to use an EPD was deferred to the operators or depended on the current practice at the treatment centre.[14] Only SAPPHIRE and CREST controlled for the type of EPD used.[10,18,20] However, the ICSS, CREST, EVA-3S, and SAPPHIRE each had a committee that monitored the indications for use of EPDs.[10,13,18,20] Secondly, the data does not include the medical management of carotid stenosis. Data comparing medical and surgical treatments for carotid stenosis is sparse, as medical treatment has been historically reserved for asymptomatic patients, younger than 75, and with less than 70% stenosis.[22] The upcoming CREST II trial represents the first large RCT to compare endarterectomy with stenting and intensive medical therapy. Thirdly, operator experience varied among trials and centres, and the minimum experience required for operators was sometimes minimal.[23,24] One systematic review examined large administrative data-set registries. It demonstrated that nine of 21 registries that performed CAS reported rates of death and stroke in excess of the 3% risk threshold as specified by the American Heart Association (AHA) in asymptomatic patients. This can be compared to the one out of 21 registries that performed CEA that had rates of death and stroke above the AHA threshold.[25] The ICSS found that, regardless of the procedure performed, centres that enrolled more than 50 patients were less likely to have any outcome of their primary endpoint compared to centres that enrolled fewer patients. In these centres, CEA was safer in comparison to CAS.[12] Findings from the CSTC also found a decreased risk of procedure-related stroke or death in high-volume centres. This suggests that centres that have the most exposure to CAS cases are routinely safer than those with fewer cases regardless of the operator experience.[26]

Conclusion

In conclusion, within 30 days after CEA or CAS, both procedures bring with them their own specific risks. In this period, CAS represents a greater risk for stroke[14,20] (**Table 2**) and death,[14] while CEA represents a greater risk of myocardial infarction.[20] However, both procedures are equally safe for patients after one year.[10,14,20] When deciding which procedure should be performed, each patient and their particular needs must be taken into account. One factor that may be important is age, as patients under 70 years old may benefit more from CAS, while patients older than 70 may suffer fewer negative outcomes with CEA.[20] Operator skill and experience with CAS is also important, with the European Society of Vascular Surgery recommending CAS only being performed in high-volume centres with documented low rates of perioperative stroke and death.[24,27] While CEA was the preferred treatment for most symptomatic patients, CAS is becoming increasingly available,[28] and with increased operator expertise, is becoming an attractive, less-invasive option for patients who are at high risk for surgery.

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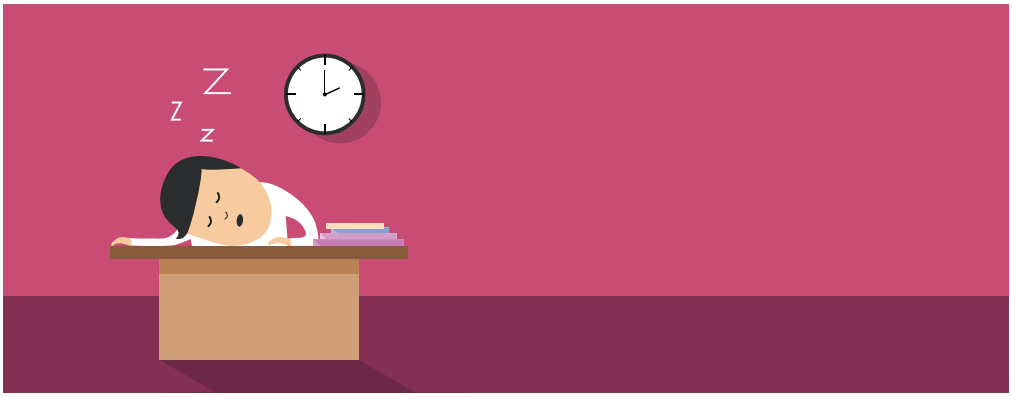
Methods of jet lag mitigation for the international student



Abstract

During international travel, a common conundrum is the mitigation of the phenomenon known as "jet lag". Medically termed "desynchronosis", jet lag is a physiological condition characterised by severe tiredness and other classically-associated symptoms resulting from travel across time zones. Methods of adaptation that have been tried and proven are discussed with regards to pre-, intra- and post-flight format. These techniques include modification of the classic light/dark and sleep/wake cycles, which act to dictate the body's internal clock. By changing light exposure and overall sleeping patterns prior to and during the flight, the body is phase-shifted to the destination time zone at an accelerated rate. Furthermore, both pharmacological interventions and specific diets can aid in the phase shift to the destination time zone, thus minimising adaptation time of the circadian rhythm. This review outlines current methods which have been shown to result in prompt internal body clock modification to the destination time zone, successfully mitigating jet lag.

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Introduction

Those who frequently travel abroad, including many international students, must constantly travel back and forth, often over long distances, and must quickly adjust to the different time zones to maximise productivity. This phenomenon of feeling perpetually tired after a journey over many time zones is estimated to be experienced by up to two-thirds of travellers, and is referred to as "jet lag".[1] Jet lag is associated with fatigue, impaired concentration, daytime sleepiness, headaches and gastrointestinal problems as a result of crossing three or more time zones rapidly.[2] The symptoms stem from disruption of the normal circadian rhythm, which is regulated by external stimuli called "zeitgebers".[3,4] Zeitgebers include stimuli such as light, meal times, exercise, sleeping patterns and daily activities.[5] Classically, jet lag has been regarded as an unavoidable component of travelling; however, elite athletes who continuously travel have initiated a trend of creating "anti-jet lag" regimens.[6-8] Due to the polymorphic nature of the gene PER3, which acts to control the circadian rhythm, individuals react differently to varying levels of sleep deprivation. Therefore, establishing universal methods of jet lag treatment can be difficult. This paper outlines a variety of approaches that have proven beneficial in modification of the internal body clock and adjustment to destination time zones in the majority of people.[9]

How is the internal body clock programmed?

Evolution has caused the body to naturally programme itself to be awake when there is light and to sleep when there is a lack of light.[3] Therefore, light is the most effective zeitgeber at resetting our internal body clock.[10,11] The body responds to light as a stimulus via the suprachiasmatic nuclei within the base of the hypothalamus; these are essentially the body's internal clock.[12] The suprachiasmatic nuclei receive information about light from the retinohypothalamic tract, which in turn receives stimuli from light-sensitive receptors in the retina, via retinal ganglion cells.[12,13] Information about general excitement and physical activity is also relayed to the suprachiasmatic nuclei via the retinal input centre, known as the intergeniculate leaflet. The response, or output, from the suprachiasmatic nuclei is to control the release of cortisol and melatonin from their respective glands, which have an impact on sleepiness and mental alertness.[14] When these hormones are released unnecessarily with increased or decreased stimulation, circadian desynchrony results.[3]

There are several methods of preventing drastic changes to the internal body clock, which decrease the impacts of jet lag. These include regulating the light/dark cycle, sleep scheduling, pharmacological intervention and meal preparation.[15-20] These methods can be implemented prior to, during, and after travelling.

Pre-flight methods

Prior to the flight, adapting to the time zone of the intended destination plays a large role in both adjusting the internal clock and mitigating jet lag.[15-17] Some proven methods include adapting to the light/dark cycle of the destination, modifying daily sleep schedules, and exogenous doses of melatonin. The most effective methods for phase-shifting to destination time revolve around the light/dark cycle.[3,11,21]

Light exposure dictates the circadian rhythm due to the photic neural input pathway known as the retinohypothalamic tract.[13,22,23] This pathway directly communicates with the body clock sending signals about light in the external environment to the suprachiasmatic nuclei.[13] Burgess *et al.* conducted a study wherein healthy individuals were divided into three groups: continuous dim light, continuous bright light, and intermittent light exposure, in an attempt to phase-shift their circadian rhythms to the destination time zone prior to the flight.[21] Those exposed to continuous bright light had a gradual advance in their sleep schedule in comparison to the other groups, suggesting that changes to light exposure prior to flying can phase-shift circadian rhythm.[21] The suprachiasmatic nuclei also communicate with the pineal gland, secreting melatonin, which is released in response to darkness, acting to regulate the sleep/wake cycle.[13,19] Melatonin causes peripheral vasodilation and decreases core body temperature via receptors in the suprachiasmatic nuclei, pituitary gland and elsewhere in the brain to promote night-time physiology.[19] When administered properly, it aids in entrainment to a new time zone; it is more beneficial to take low doses, around 0.5-1.5mg, for two to three days prior to a flight, allowing for slower phase changes.[17-19]

Shifting both sleep patterns and meal schedules up an hour, three to four days prior to the flight, can also act to adjust the internal 24-hour cycle.[15-17] Emphasis should also be placed on maximising sleep prior to departure, as it has been shown to be important to prevent accumulation of sleep debt before flying.[16,17] The accumulation of sleep debt can result in an increased level of tiredness at the beginning of a trip, thereby elongating the amount of time to adjust to the destination time zone.[24] In summary, pre-flight adaptations including adjusting light exposure, taking low dose melatonin, and changing sleeping patterns can mitigate the effects of jet lag.

On the flight

During the flight, adjustments of the internal clock to the destination time zone via sleeping patterns and food intake adaptation are crucial.[16,17] Firstly, it has been shown that most people fare better with a "phase advance", in westward travel, as opposed to a "phase delay", which occurs during eastward travel.[2] Eastward flights, upwards of six hours, are often scheduled between 5.00pm and 11.00pm, making sleep crucial to adapt to the destination time zones.[3,25] One method to maximise sleep is wearing eyeshades, as light is one of the main zeitgebers dictating the circadian rhythm. The body becomes more awake in response to light, hence the utilisation of eyeshades that block light can prevent the activation of the retinohypothalamic tract and eventual waking of the body.[13,26] Additionally, earplugs or noise-cancelling headphones can act to block out noise and maximise sleep. During eastward travel, meals are commonly served an hour into the flight, which is often not conducive to destination time zones; in-flight meals should be eaten on destination time to adjust the internal clock.[16,27] Additionally, with the current standard of airplane food, prepacking meals permitted through security or purchasing meals at the airport can act as an alternative. Eating foods containing familiar and healthy ingredients can prevent any gastrointestinal and bowel irregularities that are common with a lack of sleep and increased travel.[17,19,28,29] For example, the Argonne anti-jet lag diet and the Harvard anti-jet lag fast are two diets that follow the postulation that the circadian rhythm can be reset via gastrointestinal zeitgebers.[19,30] This 'reset' is accomplished by fasting both prior to and during the flight. Upon arrival at the destination, the consumption of a large meal is recommended to fuel the body with nutrients required to stay awake throughout the day.[30]

Table 1: Summary of recommendations for eastward and westward travel.

The types of effective intervention in mitigating jet lag vary by direction of travel and can be broken down into three time frames.

	Travelling through six+ time zones	Pre-flight	In-flight	Post-flight
Six+ hours eastward travel	Light	Morning: bright light Evening: avoidance of light	Dependant on flight time, but normally no light exposure	Morning: bright light Evening: avoidance of light
	Sleep	Wake up: early Go to sleep: early	Maximise sleep	Follow sleep patterns of destination
	Diet	Match diet to light/ sleep schedule	Minimal food consumption Stay hydrated	Consumption of a full meal upon arrival
	Drugs	Melatonin: 0.5-1.5mg (two to three days prior to flying)	Melatonin or ramelteon to aid sleep	Morning: caffeine 50-200mg or armodafinil 150mg/d Evening: melatonin 3-5mg
	Other	Maximise sleep	Eyeshades, noise-cancelling headphones, change watch to destination time zone Avoid: alcohol and caffeine	Increase physical activity
Six+ hours westward travel	Light	Morning: avoidance of light Evening: bright light	Maintain light exposure	Morning: avoidance of light Evening: bright light
	Sleep	Wake up: late Go to sleep: late	Maximise wakefulness	Follow sleep patterns of destination
	Diet	Match diet to light/ sleep schedule	Consume food following patterns of destination Stay hydrated	Consumption of a full meal upon arrival
	Drugs	Melatonin: 0.5-1.5mg (two to three days prior to flying)	No drugs	Morning: caffeine 50-200mg or armodafinil 150mg/d Evening: melatonin 3-5mg
	Other	Maximise sleep	Change watch to destination time zone	Increase physical activity

Staying hydrated should also be a priority due to both dry air on board (10% relative humidity) and an observed lack of water intake while in transit.[15-17] Avoidance of alcohol and caffeine is recommended, as they increase dehydration and can have unwanted effects on the body while phase-shifting forward.[15,31] One negative effect includes the inhibition of endogenous melatonin by both alcohol and caffeine, as melatonin plays a large role in the regulation of the sleep/wake cycle.[19] Moreover, psychologically, by changing the time on watches and phones one can rapidly become accustomed to the destination time.[17]

Pharmacologically, melatonin or ultra-short-acting and short half-life hypnotic sedatives, such as ramelteon or agomelatine, may be used to aid sleep while in transit.[17,32] Endogenous melatonin, however, is inhibited by aspirin, ibuprofen and prescribed drugs like beta blockers.[19] Therefore, unless medically required, these drugs should be avoided during travel. In summary, during the flight it is important to both mentally and physically shift to the destination time zone by changing mealtimes and scheduling sleep appropriately.

Post-flight methods

Upon arrival at the destination, adjusting the zeitgebers via sleep schedule, light exposure, meal consumption and pharmacological aids is crucial. In terms of adapting the light/dark cycle, natural light is the most effective form of light as it is of the greatest intensity.[16,33] After eastward travel, morning exposure to bright light, around 30-60 minutes, and evening avoidance of bright light is recommended. Conversely, after westward travel evening exposure to bright light and morning avoidance of bright light is recommended.[16,17] Additionally, napping may have negative implications for the circadian rhythm, so should be avoided.[17,19]

Adaptation most easily occurs if meals are eaten in small amounts more frequently and at time zone-appropriate periods.[17] Certain foods can promote different characteristics; carbohydrates promote sleepiness, whereas high protein induces alertness.[19] Additionally, by consuming a full meal upon arrival to the destination (as advised in the Argonne diet mentioned above) the body is more appropriately fueled throughout the day.[30] Maintaining a high level of physical activity upon arrival at the intended destination can phase-shift the body forward, thereby resolving jet lag at a faster rate.[34]

Other methods of sustaining alertness and preventing tiredness, which should be taken in the morning, are caffeine (taken in doses between 50 and 200mg) or armodafinil, a wakefulness-promoting agent.[16,19,31] A phase 3, double-blind, randomised, placebo-controlled study of

armodafinil for excessive sleepiness associated with jet lag disorder showed that 150mg per day increased wakefulness after eastward travel through six time zones. Therefore, this drug can be recommended to phase-shift to the destination time zone after a long eastward flight.[1]

Taking melatonin supplements has been regarded as an effective method of jet lag treatment. This is further proven by a meta-analysis that examined ten trials in which melatonin was taken at bedtime of the destination time zone. It was concluded that melatonin is effective in treating jet lag disorder in eastward travel, as it allows for a forward phase-shift in the 24-hour clock.[16,35] Post-flight melatonin is recommended around 30 minutes prior to bedtime and should be taken in doses of 3-5mg.[17,35-37] Another study suggested that to both promote sleep and facilitate forward phase-shifting, melatonin should be taken one hour prior to sleeping and three to four hours before bed, respectively.[19,38] Drugs that act as melatonin receptor agonists include ramelteon and agomelatine; they both have a greater affinity and half-life than melatonin, and could therefore be further clinically developed for jet lag.[19,32,39]

Furthermore, melatonin is found naturally in oats, sweetcorn, barley, rice, ginger, tomatoes, and bananas, which could be incorporated into meals before, during, and after travel as appropriate.[19]

The combination of evening melatonin, morning bright light, and afternoon decrease in light increases the circadian phase-progressing capacity for eastward travel.[16,19,38] Recommendations for using melatonin and light therapy can also be found in the American Academy of Sleep Medicine practice parameters on circadian rhythm sleep disorders.[16,40] A summary of recommendations for mitigating jet lag can be found in **Table 1**.

Conclusion

Determining methods of mitigating jet lag are becoming more relevant as travelling is becoming increasingly more prevalent through work, school and leisure.

Further development in the pharmaceutical treatment of jet lag is currently underway through the use of melatonin receptor agonists such as ramelteon and agomelatine. These drugs have proven to be more efficient than melatonin as they have a greater affinity for melatonin receptors and a greater half-life. Both drugs are currently licensed as hypnotics, and further clinical trials are underway to assess their efficiency as jet lag treatment.[41]

Upon rapidly travelling through three or more time zones the internal body clock, which normally dictates the sleep/wake cycle, is dysregulated. For now, evidence suggests that a multifaceted method, including light exposure and sleep adaptation, along with pharmaceutical intervention, implemented pre, intra and post flight, can act to successfully minimise the effects of jet lag.

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Systematic review of the impact of depression on subsequent smoking cessation during pregnancy

Abstract

Objective: Smoking during pregnancy is the most significant modifiable risk factor for adverse pregnancy outcomes. Tobacco use has a long-standing relationship with depression, but has not been critically investigated in pregnancy. We systematically reviewed studies of the association between depression and subsequent smoking cessation during pregnancy.

Methods: A systematic literature search was conducted in electronic databases including all dates up to April 2016 (PubMed, Cochrane, Psychinfo, CINAHL) for prospective studies of pregnant women, which measured depression at baseline (e.g., pre-pregnancy or during pregnancy) and smoking status at follow-up.

Results: A total of 1,526 articles were retrieved after removing duplicates. Of the 1,526 articles, 193 were then selected to be reviewed and evaluated in full. After the final review, 20 articles were selected for this systematic review. These papers included two repeat datasets, leaving 18 datasets for review. Of these, 12 papers showed the significance of the effect of depression on smoking cessation during pregnancy and the remaining eight papers reported a null hypothesis.

Conclusions: Depression is associated with poor smoking cessation rates in pregnancy. Future research is needed to focus on depression and smoking status as an outcome of interest in pregnancy with repeatable and objective measures used for data collection.

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Table 1: Comprehensive keyword and subject heading search, February 2016.

Database	Search terms	Total hits
PubMed	((("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Adjustment Disorders"[Mesh] OR depress*))) AND ("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR pregnan* OR antenatal OR ante-natal OR perinatal OR peri-natal) AND (("Smoking"[Mesh] OR "Smoking Cessation"[Mesh]) OR ("Tobacco"[Mesh] OR "Tobacco Use Cessation"[Mesh] OR smok* OR tobacco))	725
Cochrane	depress* AND smok* AND pregnan* depression (word variations have been searched) AND smoking:ti,ab,kw (word variations have been searched) AND pregnancy (word variations have been searched)	35 177
PsycInfo	(depress*.mp. OR exp Reactive Depression/ or exp "Depression (Emotion)"/ OR depressive disorder.mp. OR adjustment disorder.mp. or exp Adjustment Disorders/) AND (exp Pregnancy/ or pregnancy.mp OR pregnan*.mp. OR exp Pregnancy/ or pregnant women.mp. or exp Perinatal Period/ OR antenatal.mp. OR ante-natal.mp. OR perinatal.mp. OR peri-natal.mp.) AND (exp Smoking Cessation/ or smoking.mp. or exp Tobacco Smoking/ OR smok*.mp. OR exp Tobacco Smoking/ or tobacco.mp.)	478
CINAHL	(MH "Depression") OR "depression" OR (MH "Depression, Reactive") OR (MH "Adjustment Disorders") AND (MH "Pregnancy") OR "pregnancy" OR (MH "Perinatology") OR "antenatal" OR "anti-natal" OR "perinatal" OR "peri-natal" OR (MH "Expectant Mothers") OR "pregnant women" AND (MH "Smoking") OR "smoking" OR (MH "Smoking Cessation") OR (MH "Smoke") OR (MH "Tobacco") OR "tobacco"	273

Introduction

Tobacco is the single greatest cause of preventable death worldwide.[1] In Ireland, it is estimated that 5,200 people die annually from smoking-related diseases.[2] Tobacco use during pregnancy not only presents risk factors to the mother's health, but also to foetal health outcomes.[3] The overall prevalence of cigarette smoking up to June 2016 in Ireland was 18.6%. Smoking rates are highest among young adults (18-44 years), reaching 25.9% in the 25-34 age group, with 49.5% being female.[2] As this is the same timeframe as the reproductive period for females, an understanding of the barriers to smoking cessation during pregnancy is crucial.

Smoking during pregnancy is the most significant modifiable risk factor for adverse pregnancy outcomes.[3] However, reported quit rates and population estimates in the United States suggest that only 11.3% of smoking women aged between 18 and 49 years stop smoking for the duration of their pregnancy.[3] The harm associated with intrauterine exposure to nicotine substantially increases the risk of infant morbidity and mortality.[4] It is associated with preterm birth, perinatal mortality, low birth weight, subsequent development of neurodisruptive disorders[5,6] and direct teratogenic effects on foetal brain development.[7]

Tobacco use has been associated with depression in several studies.[8-11] Smokers have a higher incidence of depressive symptoms; those with depressive symptoms and coronary heart disease or respiratory conditions are less likely to quit smoking and are more likely to relapse if they do quit.[8,9] This co-dependent relationship between smoking and depression suggests an association that is complex, pernicious, and potentially lifelong.[10] Hence, during pregnancy, when a woman is at particular risk of altered mood or depressive symptoms, smoking cessation may be inhibited by mood.[10] Risk factors for antenatal depression include a history of previous depression,[10] lack of social support from family or friends, lack of partner support, lack of education, low income[9] and negative life events.[11] Pre- and antenatal depression have also been associated with adverse foetal outcomes including pre-eclampsia, spontaneous abortion, preterm birth, placental abruption, sudden infant death, respiratory problems, hearing loss and low birth weight infants.[12,13]

The association between depression and smoking cessation during pregnancy has not been subject to systematic review. Several studies have reported the relationship between smoking behaviours and depressive symptoms, but a compilation of all those relevant articles will provide a more comprehensive and precise estimate of the effect of depression on smoking cessation in pregnant women than single studies alone.

Methods

Search strategy

A systematic literature search of PubMed, Cochrane, PsychInfo and CINAHL was performed in February 2016. Keywords and agreed subject headings (Medical Subject Hadings [MeSH] terms) were combined to enable a comprehensive search, as shown in **Table 1**.

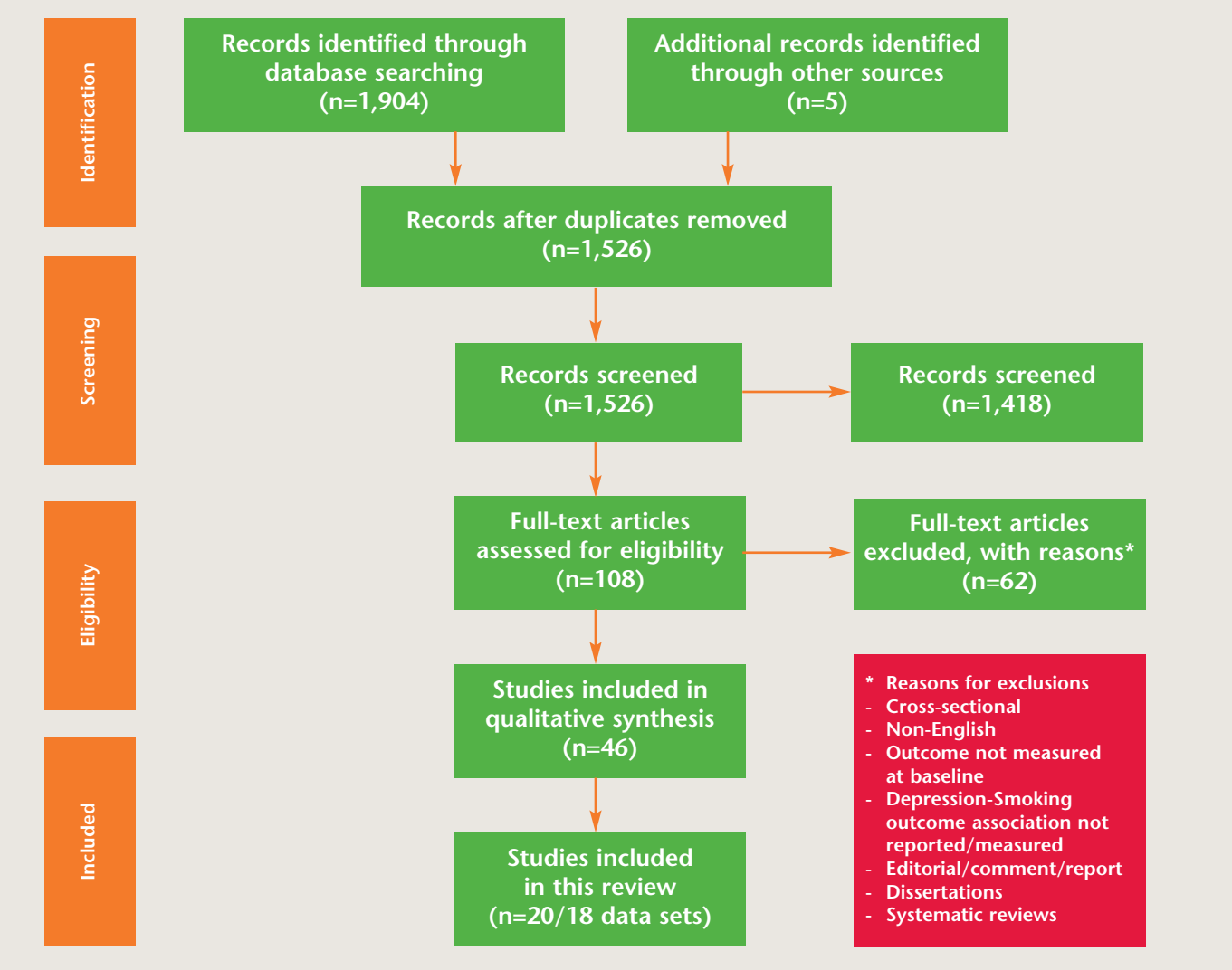

FIGURE 1: Prisma flow diagram.

The reference lists of retrieved articles were also searched to identify any additional relevant studies. All searches were uploaded to EndNote and duplicates were removed. This resulted in 1,526 studies.

Study selection and data extraction

Studies were included if they met the following eligibility criteria:

- assessed pregnant women in at least two time points (baseline and follow-up);
- had a measure of depression at baseline; and,
- had a measure of smoking at follow-up.

We excluded articles with the following: cross-sectional studies (as they only measure variables at one specific point in time); dissertations; other systematic reviews; and, articles not written in English. At the first screening, two reviewers read titles and abstracts. Studies that have met the eligibility criteria were read in full text and suitability for inclusion was independently determined by two different reviewers. Authors were contacted if insufficient data was available. Disagreements made about specific articles were managed by consensus or discussion with a third reviewer. Data was extracted to a Microsoft Excel spreadsheet for analysis.

Quality assessment

Once data had been extracted from all 46 studies, quality of the studies was assessed using the Crowe Critical Appraisal Tool (CCAT),[14-16] a standardised tool that has been used in several recent systematic reviews to assess the quality of evidence available.[8,9,17] This tool provides a more specific way of scoring the research using a checklist. The CCAT consists of eight category items that correspond to each aspect of the study, including: preamble (text, title and abstract); introduction; design; sampling; data collection; ethical matters; results; and, discussion. Each category contains a

Table 2: Included studies and qualitative data.

Author	Sample	Sample Size: B, FU
Eiden *et al.*(2011)	Pregnant women	270
El-Mohandes *et al.* (2011)	Pregnant African Americans	500, 396
Dornelas *et al.* (2013)	LSES ethnically-diverse pregnant smokers	194, 177
Hauge *et al.* (2013) Hauge *et al.* (2011)	Norwegian mother and child study	73,579, 45,369 (2013); 73,418-71,757 (2011); 10,890 participated twice
De Wilde *et al.* (2013)	Flemish pregnant women	627, 523
Forray *et al.* (2014)	Efficacy of substance abuse among pregnant women	176, 129
Newport *et al.* (2012)	Pregnant women	195
Eiden *et al.* (2013)	Pregnant women	215
Blalock *et al.* (2006)	Smoker pregnant women	82,81
Bottomley *et al.* (2008)	Pregnant adolescents	94,81
Spears *et al.* (2010)	Ethnic minority adolescents	305, 305
Patterson *et al.* (2012)	Mainly black American pregnant women	1,521, 465
Munafo *et al.* (2008)	Mixed-race English pregnant women	7,089, 4,286
Ludman *et al.* (2000)/Soloman *et al.* (2006) – SAME DATA SET	Pregnant smoking women less than 18 weeks' gestation	151, 151
Lopez *et al.* (2015)	Pregnant young, LSES	289, 289
Pritchard (1994)	Pregnant women	395, 395
Sidebottom *et al.* (2014)	Mixed-race young pregnant females	594, 594
Pottinger *et al.* (2009)	Newly-registered antenatal clients	452, 312

B = baseline; FU = follow-up; SR = self-report; SalCot = salivary cotinine; Mec = infant meconium results; FTND = Fagerstrom Test for Nicotine Dependence (FTND) score; LSES = low socioeconomic status; BDI = Beck Depression Inventory (please contact author for full dataset results).

number of items that are marked as present, absent or not applicable, with only those items applicable to a specific research design being included in the appraiser's score. Each category is also scored on a scale from 0 (no evidence) to 5 (highest evidence). Therefore, scoring allows for both subjective (scoring) and objective (tick boxes) marking of each category. Total scores for each study, ranging from 0 to 40, are presented as a percentage, which allows for comparison of quality between studies.

Results

Study identification

A flow diagram of the search strategy is presented in **Figure 1**. The initial search yielded 1,526 articles, of which 1,480 were excluded. Data extraction and quality assessment were performed on the remaining articles and 20 were eventually deemed eligible for inclusion in the systematic analysis. A summary of all included articles for final review is presented in **Table 2**.[18]

Of the 46 papers initially chosen for full text review, 20 were included in the systematic review. The 26 papers that were excluded measured depression at baseline and smoking status at follow-up but did not report an association between these variables. One paper was excluded as it reported the cross-sectional data only,[19] and a further two reported insufficient data so the authors were emailed requesting further data.[20,21] Of the 20 papers reviewed,[22-41] two repeat datasets were included.[30,31,35,36] In total, 18 datasets provide an estimate of the association between depression and smoking. Length of follow-up varied from seven weeks to three years. Sample sizes also differed between studies (82 to 73,418 [CI: 0.73, 0.88] participants). Various methods were used to measure depression; however, smoking was always measured by self-report along with

Follow-up duration	Depression measure (FU)	Smoking outcome measure	Quality score
Nine months	BDI	SR, SalCot and Mec	85%
Three years	HADS	SR, SalCot	90%
> or = 26 weeks until 32-34 weeks' gestation	DSM-IV	SR, FTND	67.5%
Up to 30 weeks' gestation (2013); 17 weeks' gestation – six months postpartum (2011)	SCL-5	SR	75% 80%
Up to six months postpartum	BDI	SR and SalCot	80.0%
Before 26 weeks' gestation until three months postpartum	IDS-SR > or = 24 MINI Interview	SR	62.5%
Nine months	DSM	SR	47.5%
11 months	BDI	SR and SalCot	57.5%
One month postpartum	Center for Epidemiologic Studies – Depression Scale	SR and SalCot	62.5%
Five months	Edinburgh Postnatal Depression Scale	SR	67.5%
12 months	20-item Center for Epidemiological Studies Depression Scale (CES-D)	SR	82.50%
Seven weeks	The Center for Epidemiological Studies – Depression Scale	SR	87.5%
Up to 33 weeks' postpartum	Edinburgh Postnatal Depression Scale	SR	85%
Nine months	Beck Depression Inventory (BDI)	SR	80%
Up to 24 weeks' postpartum	BDI	SR and SalCot	80%
10 weeks	Hospital Anxiety and Depression Scale	SR	72.5%
Prenatal to 12 weeks' postpartum	PHQ-9	SR	90%
Nine months	Edinburgh Postnatal Depression Scale	SR	87.5%

other methods such as salivary cotinine levels. Eleven prospective, longitudinal papers and one randomised controlled trial (11 data sets) reported a significant association between depression and subsequent smoking cessation during follow-up.[22-33]

Six prospective longitudinal studies and two randomised controlled trials (seven data sets) supported the null hypothesis that depression levels at baseline had no impact on subsequent smoking cessation.[34-41] The average quality rating scores for the studies that reported a positive correlation was 76%, and 75% for those studies that reported a null hypothesis.

Discussion

Despite the large amount of studies found, few of the studies reported the association between depression and subsequent smoking status in a prospective longitudinal design. This review recruited 20 papers (18 datasets), which revealed mixed findings on the association between depression and smoking cessation. Of the 20 papers, 12 showed a significant effect of depression on smoking cessation in pregnant women, and the remaining seven datasets reported a null hypothesis.

The 46 studies were appraised by individual reviewers and the scores were averaged. It has exhibited a good degree of reliability[15] and construct validity[9] and is simple to implement and suitable for all research designs in healthcare. The quality ratings between the studies that showed a significant correlation versus those with a null hypothesis did not differ discernibly (76% v 75%, respectively). However, they did differ significantly on the amount of women recruited into the studies. The 11 datasets reporting a significant result totalled 79,024 women. The seven datasets reporting a null hypothesis had totalled 1,597 women; thus, approximately 2% of

the women belonged to the null hypothesis cohort. Those smaller studies might have been underpowered to show a significant difference and this may have impacted the conclusions reached. The majority of the cohort that demonstrated a significant result is part of the Hauge study,[30,31] a large population-based Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health. They conclude that women who experience a relative increase in symptoms of psychological distress during pregnancy are at higher risk of maintaining smoking. Also, women reporting increasing levels of psychological distress across pregnancies had a lower likelihood of quitting smoking prior to their second pregnancy (OR, 0.79; 95% CI [0.66, 0.94]) (2011). Living with a smoking partner, low educational attainment, symptoms of psychological distress, and increasing number of years between pregnancies were all associated with smoking during the second pregnancy.[30,31] These findings were consistent with the other studies that reported a significant correlation between depression at baseline and subsequent smoking cessation during pregnancy.

Estimated rates of antenatal depression vary between countries and socioeconomic groups.[42] Pregnancy smokers are typically less educated, poorer, less likely to be married, and have more smokers in their social network.[31,43]

A previous study by Massey *et al.* aimed to distinguish the psychological differences between smokers who spontaneously quit during pregnancy and those who did not.[44] Pregnant smokers with conduct disorder had an increased tendency to behave in ways that maximise short-term benefit over long-term consequences. When they reviewed psychological stress as a predictor of smoking cessation they found that both very high and very low levels of stress and anxiety were predictive of lower levels of smoking cessation.[45] Therefore, short-term benefit was seemingly more important to these women than the long-term benefits of smoking cessation. Similar to our study, they found a lack of consistency in the literature in the quality of reporting of the data. Smoking levels were mainly self-reported with very few objective levels considered. Furthermore, many studies did not account for the level of nicotine dependence among the women. Women were generally considered smokers based on the fact that they had more than one cigarette a day – not by the actual amount of cigarettes they had.[45] This review suggested no independent relationship between smoking cessation during pregnancy and depression after nicotine dependence is controlled for. The consistent association of smoking with depression raises the difficult question of causality. Doyle reported an association between depression and decreased levels of smoking cessation in patients with CHD.[9] Our review also found a lack of published data in studies, which means that this systematic review may be skewed and thus may limit the results. Similarly, due to time constraints, a meta-analysis has not yet been completed and so this report remains qualitative in nature. However, a review of the reported data from all studies in this review points to more evidence of an association between depression and subsequent smoking cessation. Even the studies with a null hypothesis reported a cross-sectional association at baseline, suggesting some association does exist at different time points across pregnancy.

Limitations

As stated, there were several limitations to this review. Firstly, although the majority of the studies supported our hypothesis that depression has an impact on subsequent smoking cessation during pregnancy, the results of this review could have been enhanced had all studies included the relevant data. There are 44 articles that have depression measures at baseline and measure of smoking status at follow-up, but not all report the association between the variables. Secondly, depression in all 20 studies included in this review was measured using questionnaires (i.e., Beck Depression Inventory score, Hospital Anxiety and Depression Scale, and Center for Epidemiologic Studies Depression Scale) instead of diagnostic interviews. It could be argued that diagnostic interviews would be a more accurate measure of depression compared to self-reported questionnaires, as depression is diagnosed and reported by psychiatrists, who are considered more accustomed to their field of expertise. It is suspected that this adjustment would result in a more accurate sample for future reviews. Thirdly, the measure of smoking, as stated above, is based on self-report rather than objective measures such as biochemical verification. This can lead to bias due to human error and inaccuracies in recall.

Finally, the follow-up duration period for a majority of the studies included ranges from early gestation to months postpartum. As depression is a chronic mental illness with phases of relapse,[46] studies with longer follow-up duration and over numerous pregnancies would be better able to truly measure the effect of depression on smoking cessation and, consequently, produce better results in terms of accuracy.

Conclusion

The majority of studies included in this review report an association between depression levels and subsequent smoking cessation during pregnancy. Further conclusions can be drawn from the literature once a quantitative meta-analysis is conducted. However, based on the qualitative findings of this review, diagnosis of depression is associated

with poorer smoking cessation rates during pregnancy. More studies, particularly higher quality studies with longer follow-up periods, objective outcome measures (e.g., diagnostic interviews) and objective smoking status (e.g., biochemical confirmation) are needed to further enhance this review. It is clear from the literature that there are serious risk factors associated with perinatal smoking, both for the mother and the offspring; thus, the importance of smoking cessation in this cohort should not be underestimated. It is imperative to determine the impact of depression on subsequent smoking cessation in this patient group. In summary, a future meta-analysis would strengthen the results of this review, which suggests an association between depression and smoking cessation.

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What's cool in neonatal hypoxic-ischaemic encephalopathy?

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Abstract

The field of neonatology has come a long way in the care of newborn infants, from the development of the first neonatal incubator and the Apgar scoring system to the modern day neonatology intensive care unit (NICU), which is fully equipped with temperature-controlled incubators, mechanical ventilators and other life-sustaining interventions for premature and term infants alike. Hypoxic-ischaemic encephalopathy (HIE) is a condition whereby the brain is deprived of adequate oxygen, therefore resulting in delayed cell death and devastating consequences for the developing neonatal brain. Through animal models, the pathophysiology of HIE is now increasingly being understood as an evolving process rather than a singular event. HIE is a major cause of neonatal morbidity and mortality, with only supportive treatment available until the development of therapeutic hypothermia in the early 21st century. Even with the implementation of therapeutic hypothermia as the standard of care, there are still major limitations with the treatment, most notably its partial efficacy. This review discusses what steps are currently being taken in the field to improve HIE outcomes, particularly adjuvant neuroprotective strategies such as erythropoietin (EPO) and stem cell therapy to be used in combination with therapeutic hypothermia, and the limitations facing HIE therapeutic development.

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Background

The incidence of hypoxic-ischaemic encephalopathy (HIE) is estimated to be approximately one to three per 1,000 live births in the United States; however, in developing countries it is reportedly up to 26 per 1,000 live births.[1-3] During the perinatal period, hypoxaemia, ischaemia and other impairments to the exchange of respiratory gases can lead to neonatal asphyxia. These injuries can result due to the dysfunction of one or a combination of maternal, placental or foetal factors; common examples include impaired maternal oxygenation due to respiratory diseases, inadequate perfusion of the maternal placenta due to hypotension or pre-eclampsia, placental abruption, nuchal cord, cord prolapse or uterine rupture. Additionally, foetomaternal haemorrhage and foetal thrombosis can also affect foetal oxygenation and perfusion.[4] HIE is a disease that develops in the immediate perinatal period, causing injury in the developing brain as a result of hypoxia/ischaemia, and carries a high risk of mortality or devastating lifelong morbidities including intellectual disability, cerebral palsy, epilepsy and various other neurological handicaps.[5,6]

These acute intrapartum events can cause moderate to severe neonatal encephalopathy, metabolic acidosis, and spastic or dyskinetic quadraparesis.[7] HIE typically presents in the early days of life, in a term infant; features include depression of tone and reflexes, difficulty initiating and regulating respiration, subnormal levels of consciousness and numerous seizures.[3] It is crucial to rule out other causes of neonatal encephalopathy in order to facilitate the diagnosis of HIE and timely implementation of neuroprotective intervention.[8]

Pathophysiology

The success of hypothermia is a reflection of progress in the understanding of the complex pathophysiological mechanisms of HIE itself. In HIE, the injury afflicting the immature brain results in cell death via excitotoxicity, inflammation and oxidative stress.[9] In recent years, there has been a major shift in the understanding of HIE from that of a single event to more of an evolving process that results in delayed cell death.[6,10] This new understanding has identified novel strategies for intervention, such as targeting the impaired blood-brain barrier (BBB), attempting to inhibit apoptosis and inflammation, or promoting neurogenesis and angiogenesis.

The first phase of HIE (zero to six hours) is a change in vasculature when the placental blood flow is disrupted and asphyxia occurs, causing a loss of auto-regulation of cerebral blood flow. Any decrease in the systemic arterial blood pressure then increases the risk of tissue acidosis and ischaemic brain injury.[3,11] The second phase is primary energy failure due to the loss of oxygen availability to the brain, with shifts towards anaerobic metabolism, which results in the accumulation of lactic acid and depletion of phosphate.[12] The loss of cellular homeostasis further results in an 'excitotoxic-oxidative cascade' due to intracellular collection of sodium, calcium, water and excitatory neurotransmitter. The influx of calcium elicits free radical production and mitochondrial dysfunction that subsequently signals cell death.[11-13] A secondary energy failure phase (six to 48 hours) also occurs whereby there is a release of excitatory neurotransmitters and free radicals and depletion of phosphate stores, but differs from the primary phase as it is independent of cerebral acidosis.[14,15] The third and final phase (>48 hours) involves a mechanism of chronic inflammation and epigenetic changes that impairs or alters axonal growth, neurogenesis and synaptogenesis, thereby causing further damage and worsening outcomes.[13]

In HIE, the injury afflicting the immature brain results in cell death via excitotoxicity, inflammation and oxidative stress. In recent years, there has been a major shift in the understanding of HIE from that of a single event to more of an evolving process that results in delayed cell death.

Evolving management of HIE

Prior to therapeutic hypothermia, the only treatments available to patients with HIE were symptomatic or palliative in nature.[3] During the late 1990s, therapeutic hypothermia was found to protect neurons in numerous preclinical models of HIE, including newborn swine and near-term foetal sheep.[16-18] Therapeutic cooling was then developed for clinical treatment and demonstrated to reduce the severity of brain injury and improve neurological outcomes in HIE.[19,20] Currently, therapeutic hypothermia is well established as the gold standard treatment for HIE, in combination with comprehensive clinical care including mechanical ventilation, close physiologic and biochemical monitoring, neuroimaging and seizure detection, with a focus on improving outcomes by optimising cooling protocols.[21] Evidence recommends commencing treatment within six hours of birth with either whole-body cooling to a temperature of 33.5°C or head cooling to a temperature of 34.5°C, which is maintained for 48-72 hours. Rewarming is then recommended at a rate of 0.5°C per hour.[21]

The incidence of hypoxic-ischaemic encephalopathy (HIE) is estimated to be approximately one to three per 1,000 live births in the United States; however, in developing countries it is reportedly up to 26 per 1,000 live births.

The modified Sarnat scoring system grades HIE based on the clinical assessment of the neonate's consciousness, spontaneous activity, tone, suck, Moro reflex and respiration pattern. The scoring system, in combination with the electroencelphalogram results, then determines the severity of HIE,[22] which in turn determines management – only infants with moderate to severe HIE have been found to benefit from therapeutic hypothermia.[20] Even so, it is only partially effective, with data suggesting that only one in six infants benefits.[23] Additionally, clinical trial reports estimate that infants with HIE suffer a high rate (greater than 40%) of death or moderate to severe disability even after therapeutic hypothermia.[24-27]

Current HIE neuroprotective clinical trials

In an effort to further improve outcomes after HIE, many groups have undertaken investigations into potential adjuvant neuroprotective therapies. Prospective therapeutic moieties currently being explored in clinical trial studies include xenon, topiramate, allopurinol, erythropoietin (EPO) and even stem cell transplantation.[6]

Xenon

Xenon is a potent anaesthetic that crosses the BBB easily and was found to have an additive neuroprotective effect when given in combination with hypothermia in animal models of HIE.[28-30] A recent phase II trial showed that xenon was safe for use despite early concerns of triggering neurodegeneration in the developing brain.[31,32] However, the limited natural availability of xenon (and its prohibitive cost) would require the usage of a recirculating ventilator, therefore limiting its availability to tertiary units.[33]

Topiramate

HIE is the leading cause of seizures in term infants, which have been associated with poor outcomes, but it remains unclear whether the seizures are the cause of injury or simply reflect the evolution of pre-existing injury.[1,2] There is considerable interest in anticonvulsant therapy and whether it is capable of augmenting hypothermic neuroprotection. For example, topiramate is an anticonvulsant with multiple mechanisms of action and neuroprotective qualities related to AMPA and kainate receptor inhibition, blockade of sodium channels, high voltage-activated calcium currents, carbonic anhydrase isoenzymes and mitochondrial permeability transition pore.[34-39] Topiramate in combination with melatonin was shown to decrease infarcted brain volume and apoptosis, and demonstrated dose-dependent and long-lasting neuroprotection in animal models of HIE.[34,40] The recently completed NeoNATI trial (NCT01241019) was designed to evaluate whether topiramate may potentiate the neuroprotective effect of therapeutic hypothermia in newborns with HIE.[41-43]

Allopurinol

Allopurinol is classically known as a gout medication that works by inhibiting xanthine oxidase. Additionally, it also functions as a chelator of non-protein-bound iron and a direct scavenger of hydroxyl radicals, which is indicative of its neuroprotective potential.[44] In a recent follow-up study in human neonates with allopurinol used on term, asphyxiated neonates showed benefits on mortality and severe disabilities at four to eight years of age.[45] It has been demonstrated that allopurinol administered

intravenously to the mother rapidly crosses the placenta with satisfactory concentrations reaching the neonate at birth.[45] It is also safe for both mother and neonate, thereby making it a feasible treatment option for early foetal neuroprotective therapy during labour.[45] There are ongoing trials to investigate whether allopurinol does reduce free-radical-induced post-asphyxia brain damage (NCT00189007) and what outcomes are at two years of life (the European ALBINO trial).[46]

Evidence recommends commencing treatment within six hours of birth with either whole-body cooling to a temperature of 33.5°C or head cooling to a temperature of 34.5°C, which is maintained for 48-72 hours.

Erythropoietin

EPO is a cytokine well known for its role in erythropoiesis, but it has also been found to have neuroprotective and neuroregenerative effects in the brain.[47-49] EPO receptors are expressed in numerous brain cell types including neuronal progenitors, mature neurons, astrocytes, oligodendrocytes and microglia.[50-52] EPO exhibits anti-apoptotic and anti-inflammatory effects acutely after brain injury, and promotes neurogenesis and tissue remodelling after hypoxia-ischaemia in animal models of HIE.[53-56] A phase II multicentre trial run by a group at Stanford University recently published encouraging data that multiple high doses of EPO given to infants undergoing therapeutic hypothermia appeared safe, resulted in reduced brain injury on imaging and led to improved short-term motor outcomes at one year. The study also found that the treatment combination was safe with no increase in adverse events, which makes the treatment combination feasible.[57] These positive outcomes warrant testing on a much larger scale with plans for a phase III trial underway to assess the combination of EPO and hypothermia, and its impact on long-term neurologic outcomes in HIE.[57]

Stem cells

Stem cell transplantation has also gained importance as an adjunct to hypothermia treatment based on recent clinical trials that have shown the combination to improve mortality and morbidity.[58] There are numerous sources for stem cells including neural stem/progenitor cells derived from foetal tissue, mesenchymal stem cells or embryonic stem-induced pluripotent stem cells.[59,60] Cord blood represents a rich source of stem cells and autologous transplantation of cord blood has the advantages of minimal manipulation, no need for immunosuppression, and easy access and storage requirements.[58] Current clinical trials are underway to assess autologous cord blood infusion in term infants with HIE.[58,61] Further investigation into optimising the best therapy plan will be needed to optimise transplantation timing, cell dosage, *ex vivo* modulation, method of administration and choice of stem cells.

Limitations of HIE therapeutic development

Even with the field's enthusiasm for new interventional targets for HIE, there are some limitations to their development. Due to HIE's inherent heterogeneous aetiology and presentation, discovering the ideal method to study the disease has always been a challenge.[62]

The majority of established animal models of HIE utilise rodents, with the main issue being that rodents to some extent lack neurological responses to sensorimotor cortex lesions compared to humans.[63-65] Hence, there remains an ongoing challenge to develop a disease model that sufficiently mimics human pathophysiology, which may require a non-human primate model.[63-66]

The well-known challenge of treatment strategies for central nervous system (CNS) disease is the drug delivery mechanisms for crossing the BBB.[67] In the absence of specific solutions to this problem, HIE drug treatments are restricted to lipid-soluble and low molecular weight agents. Progress in the field of neuroscience in the understanding of the BBB and chemical pharmacology may pave the way to greater availability of effective CNS therapies. Promising research avenues to circumvent the BBB currently under investigation include the chemical modification of drugs to increase their affinity for carrier proteins on the BBB and the use of high-intensity focused ultrasound, which allows for more localised exposure to the therapeutic agent.[68]

Neonatal HIE also incurs another layer of complexity in the clinical translation of new therapeutics: the population it affects. Most pharmacological developments are approved only for adults, and the regulations for paediatric and neonatal use are highly restricted, often limited to off-label usage.[69-71] Therefore, research is required in the appropriate patient group – neonates – in order to properly optimise the dosage and safety of new treatment.

Conclusions

There have been impressive strides in understanding the multi-phasic pathophysiology of HIE in order to develop new neuroprotective therapies. The advent of the current standard of care – therapeutic hypothermia – represented a significant achievement in the treatment of HIE, although with limited efficacy. The complex pathophysiology of HIE requires treatment combinations that act on multiple levels, including targeting the impaired BBB, attempting to inhibit apoptosis and inflammation, or promoting neurogenesis and angiogenesis.

There are some practical challenges to therapeutic development that need to be addressed – particularly developing disease models that adequately mimic human physiology, drug design for delivery to the CNS, and testing in a limited and protected patient population (neonates) – in order to optimise dosage and safety. In order to further improve outcomes of neonatal HIE, new neuroprotective strategies need to work through mechanisms complementary to the gold standard of therapeutic hypothermia. Nonetheless, it is encouraging that currently both stem cell and EPO investigations are in tertiary phase testing, which suggests that they are promising candidates for adjuvant treatment to early therapeutic hypothermia in neonatal HIE.

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Bots in the brain: advances in robotic keyhole neurosurgery

Abstract

Advancements in robotics have facilitated the progression of patient outcomes and procedural proficiency in modern healthcare systems. However, keyhole transcranial endoscopic neurosurgery is a field where there are currently no full robotic systems in widespread clinical use. The mechanical requirements of neurosurgery and keyhole approach pathways must be considered for robotic development, with an emphasis on systems that embody simplicity, cost-effectiveness and efficacy. Mechanical force requirements for surgical instruments, ranging from <0.01N to 1.68N, emphasise the delicate quality of neurosurgery, and the consequently meticulous and careful instrument control that must be offered by robotic platforms. Current major keyhole approaches were investigated for cranial entry diameter, access to key anatomical corridors/spaces, pathologies treated, and limitations. The transparenchymal approach, as used with the Neuroendoport tubular retraction system, emerged as a potential candidate for robotic augmentation. After reviewing current systems and their pitfalls, prototypes in development – namely the NeuroCYCLOPS – were explored. Prototype testing with a peg transfer task, compared against rigid endoscopic instruments, revealed fewer instrument clashes and lower NASA-TLX scores. Although further research and development is warranted to develop this technology, these prototypes offer promise and lend encouragement for the future of robotics in endoscopic transcranial neurosurgery.

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Introduction

Advancements in medical technology have been integral in shaping modern healthcare systems. In particular, the recent surge in medical robotics has, in select operations, allowed attainment of a new height of beneficial patient outcomes and procedural proficiency. However, such innovation must be balanced with a consideration of healthcare economics; that is, designing technology with cost in mind so that its widespread use in clinical practice is viable. The most recent trend in surgical innovation development has reflected this outlook, with a change in emphasis from the complex, extremely expensive, multifunctional platforms such as the da Vinci platform to simpler, lower-cost systems, which are effective in a specific function or procedure.[1] However, one field that has yet to see the benefits of robotic augmentation is that of keyhole transcranial endoscopic neurosurgery.[2] Indeed, this represents a field where there are currently no robotic operating systems that fulfil its technical demands and procedural limitations with a cost feasible for common clinical practice.[2]

Such limitations include general challenges of keyhole surgery: the combination of single port access and long rigid instruments results in restricted range of instrument movement and the "fulcrum effect" (instrument endpoints move in the opposite direction to the user's hand due to the pivot point at the access port).[3] There are also limitations associated with specific approach pathways (**Table 1**). This article will explore the mechanical requirements of neurosurgery and keyhole approach pathways, which must be considered for robotic development. The emphasis of the discussion will be on systems that fulfil the modern criteria for new robotics including simplicity, cost-effectiveness and efficacy in addressing current limitations faced in the field.

Table 1: Analysis of keyhole surgical approaches used in minimally invasive neurosurgery.

Approach	Space access	Selected examples of uses	Specific limitations
Supraorbital	• Anterior cranial fossa (ACF) • Middle cranial fossa • Includes suprasellar space: 25x18x20mm (APxSIxL) =6,255mm^3[10]	Vascular (~70%):[11] • Ant. CoW aneurysms • AVMs Tumours (~30%):[12] • ACF (e.g., olfactory groove meningiomas) • Parasellar (e.g., pituitary adenoma) • Sphenoid ridge (e.g., meningioma)	• A prominent orbital rim = impeding of the surgical degree of freedom[9] • Sub-arachnoid haemorrhage[11] • Giant aneurysms[11] • Pos. CoW circulation pathology[11] • Large tumours, infiltrating tumours[13]
Intraventricular	• Access to the ventricular system (normally around 25,000mm^3) and selected surrounding structures, e.g., pineal gland[14] is gained via entry through the lateral ventricle	CSF flow:[14] • Non-communicating hydrocephalus Tumours:[13,14] • Pineal tumours • Intraventricular tumours (e.g., meningiomas, ependyomas, subependyomas)	• Large tumours, infiltrating tumours[13]
Transsphenoidal	• Endonasal/ extended endonasal space depends on the amount of surgical exploration done[15]	Tumours:[15] • Pituitary adenoma • Craniopharyngioma	• Large tumours, infiltrating tumours[15] • High rate of high-grade CSF leak[15]
Retrosigmoid	• Cerebellopontine: 20x19x15mm= 3,428mm^3[10]	Cerebellopontine angle pathology:[17] • Vestibular schwannomas • Meningiomas	• Large tumours, infiltrating tumours[16]
Transparenchymal, NEP technique	• Flexible depending on target pathology and pre-operative functional scanning[19] • The NEP allows effective tubular retraction of tissue while creating a surgical corridor[19]	Deep-seated parenchymal and intraventricular brain lesions, e.g.;[18] • Gliomas • Cavernous haemangioma • Intracerebral haemorrhage • Intraventricular tumours	• Extensively infiltrating tumours[19] • Superficial cortical tumours[19]

Abbreviations: AP = anterior to posterior; SI = superior to inferior; L = lateral; ant. = anterior; Sup. = superior; Pos. = posterior; CoW = circle of Willis; AVM = arteriovenous malformations.

Table 2: Forces used in neurosurgical procedures at the distal end of instrument effectors.

Study	Force measurement method	Results
In-vivo brain, neuroarm robotic system study[6]	Sensors attached to the end-effector; suction in the left ram, bipolar forceps in the right. Recorded over the course of four operations: one oligodendrocytoma; two meningiomas; and, one cavernous angioma.	Max forces for suction and coagulation by axis: • X-axis: 1.67N • Y-axis: 1.65N • Z-axis: 1.68N
Cadaveric brain, neuroarm robotic system study[7]	Using a force-sensing bipolar forceps, coagulation (closing) and dissection (opening) forces were measured on three cadaveric brains.	Max (and mean) forces for coagulation and dissection: • Coagulation forceps: 1.16N (mean: 0.1-0.41N) • Dissection: 1.35N (mean: 0.16-0.65N)
Cadaveric brain, DENSO robotic system[8]	Sensor located between DENSO robot's tool holder and end-effectors; Beaver Mini-Blade (stab, carrying, sharp dissection) and Rhoton No 6 Spatula Dissector	Median by action: Stab: 0.01N; carrying incision: 0.05N; retraction: 0.08N; sharp dissection: 0.02N (injury at 0.28N); blunt dissection: 0.11N (injury at 0.6N). Median by area of brain: brainstem: 0.05N; cerebrum: 0.03N; cerebellum: 0.02N; corpus callosum: 0.01N; third ventricle floor: <0.01N.

Mechanical requirements in neurosurgery

With respect to the mechanical requirements of neurosurgery it is imperative to understand the instrument forces used intraoperatively. Evidently, the range of forces required when manipulating brain tissue is quite low (<0.01N to 1.68N; see **Table 2**), whereas forces recorded during operations on other organs, such as laparoscopic cholecystectomies, are in the region of 17N.[4] This highlights the intricate nature of neurosurgery, and hence, the delicate and precise intraoperative instrument control robotic systems must allow. Suction, bipolar forceps and dissectors are among the most commonly used instruments in neurosurgery, with suction often used exclusively by the left hand and other instruments used by the right hand.[5] Configuration of instrument effectors must take this into account during development by implementing technologies to address these specifications, such as multifunctional instrument arms or interchangeable instrument effectors.[6-8]

Major neurosurgical keyhole approaches

The current major keyhole approaches were investigated for cranial entry diameter, access to key anatomical corridors/spaces, pathologies treated, and limitations, to further highlight the potential for robotic augmentation (**Table 1**). From this analysis the decisions made by robotic development teams in their process of innovation can be better appreciated.[9-18]

Current technologies used in endoscopic neurosurgery

Despite the extensive knowledge of the requirements and limitations of keyhole endoscopic transcranial neurosurgery, there are not currently any fully robotic systems in regular clinical use. There are, however, technologies in clinical use that are effective for specific roles during surgery, such as brain tissue retractors.

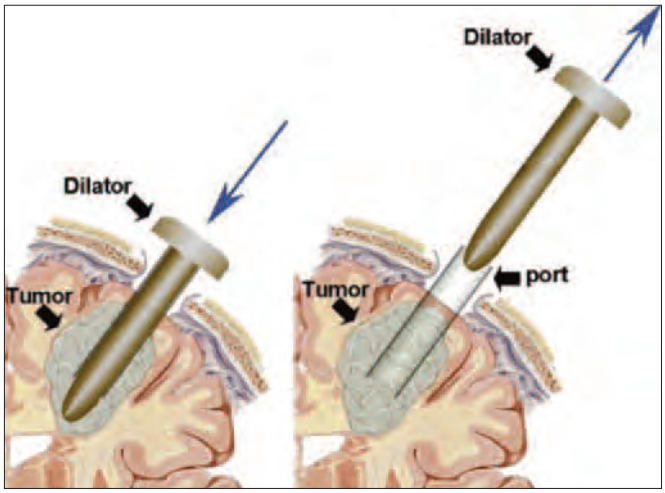

FIGURE 1: Schematic of intra-parenchymal lesion removal using the NEP system. Left: initial tubular retraction of the tissue with the advancement of the NEP conduit and bullet shaped dilator. Right: removal of the dilator allows lesion removal via the now in-position conduit.[19]

These specific technologies can potentially be integrated into a full robotic system for a synergystic effect. The Neuroendoport (NEP) is one such example; its tubular retraction system is aimed at minimising the retraction-associated injuries to the brain tissue while allowing access to deep-seated brain lesions (**Figure 1**).[19] Tubular retraction uniformly distributes pressure to surrounding healthy tissue and thus reduces retraction-associated injury (oedema, focal neurological deficits, ischaemia and seizures).[19-22] Although a variable amount of fascicular transection is often required, the use of natural anatomical passageways (e.g., sulci) when possible minimises damage to eloquent areas.[19,22] The bullet-shaped tubular retractor is advanced to allow intraparenchymal placement of a tubular conduit, through which bimanual dissection using two suctions can be performed (via endoscopic visualisation). The conduit's position is often adjusted multiple times to facilitate resection of lesions larger than the conduit's diameter. For firmer tumours, use of instruments (e.g., grasping forceps) may be indicated. This technique may be used to access a multitude of pathologies (**Table 1**) and is not limited to a specific approach pathway or entry point,[19] making the NEP technology a prime candidate for integration into a robotic system.

Proposed integrated robotic platforms

Many platforms are currently in development for endoscopic neurosurgery. An example of such a system is the neuroArm, with two arms, each with eight degrees of freedom (DOF), which provide visual, auditory and tactile feedback to the surgeon. It is also MRI compatible, therefore allowing real-time intraoperative image guidance. Although early case series have shown positive performances, the robot's design is orientated towards microneurosurgery rather than endoscopic neurosurgery.[23]

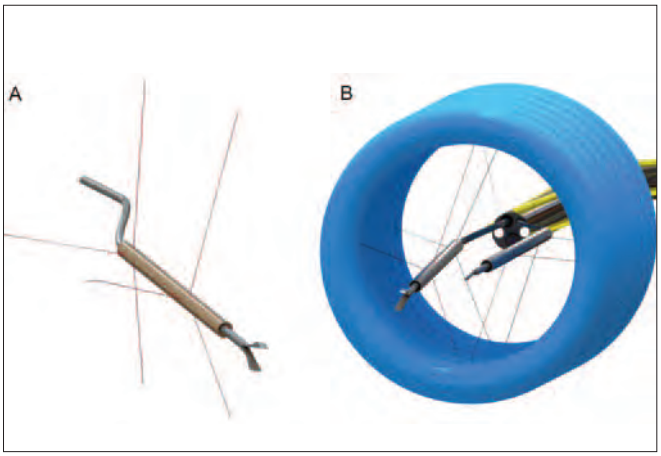

FIGURE 2: Schematics of previous CYCLOPS models showing tendon attachment to overtubes holding flexible endoscopic instruments (A and B), and a deployable scaffold with openings through which lateral tendons are passed and attached to two overtubes within the scaffold (B). Courtesy of Dr George Mylonas, Imperial College London.

In contrast, the da Vinci surgical system is designed specifically for endoscopic keyhole surgery. The two to three arms feature articulated endowrists, which carry the instruments and allow a great amount of dexterity to the surgeon while eliminating natural tremor.[24] Although the system has been used with great success in other fields, particularly urology, cadaveric studies using the da Vinci have highlighted the lack of required miniaturisation of the robot's arms for use in endoscopic neurosurgery, leading to arm collisions and therefore safety concerns.[24,25] Furthermore, the system's high cost poses an additional barrier to its use in a field where its benefits are currently questionable.[2] Another example is the NeuRobot, which was the first telesurgical robot designed specifically for keyhole neurosurgery. The system is designed as a 10mm single shaft, containing a 3D endoscope, and three sets of micromanipulators, each with three DOF. Although promising in simple procedures, the system's clinical limitation was seen in its lack of manoeuverability in the restricted work spaces present in endoscopic neurosurgery.[26]

As current systems have found little success in this technically demanding field, a glimpse into the potential future of robotic endoscopic neurosurgery can be seen by reviewing prototypes of systems in development. For example, the NeuroCYCLOPS is being developed by Mylonas *et al.*[27] and is based on the CYCLOPS system (**Figure 2**), a parallel tendon manipulator previously developed by the same group for minimally invasive general surgery.[28] Its unique design offers superior force exertion, haptic feedback and tissue triangulation capabilities when compared to the more common continuum mechanical manipulators,[29] characteristics that aim to mitigate the aforementioned limitations of endoscopic neurosurgery. Flexible endoscopic instruments are passed through overtubes and controlled in five DOF by the changing of tendon lengths.[28] The current NeuroCYCLOPS has been developed for NEP conduit adaptation and is manually controlled.[27] As the NEP has been optimised through extensive clinical use and study,[19,22,30,31] development of an adaptable NeuroCYCLOPS was considerably simplified. With this combination, the NEP conduit would act as a scaffold upon which the NeuroCYCLOPS system could be supported to perform bimanual dissection of targeted

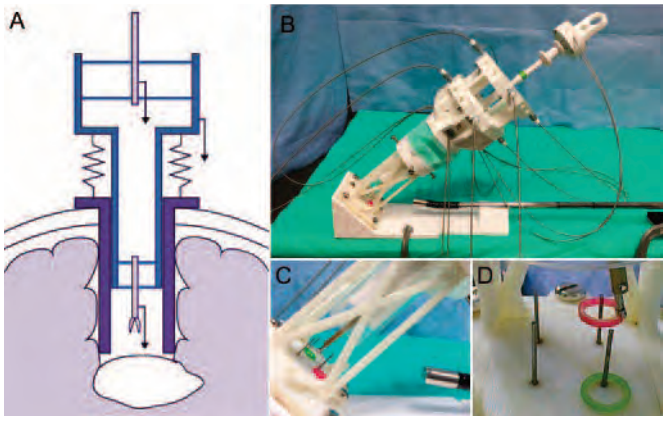

FIGURE 3: (A) Schematic of the NeuroCYCLOPS (blue) adapted to the NEP (purple) for intraparenchymal lesion removal. (B) Experimental set up of the NeuroCYCLOPS prototype. (C) Close-up lateral view. (D) 2D endoscopic view.[27]

intraparenchymal lesions (**Figure 3a**).[27] Furthermore, for optimum intraoperative visualisation and depth perception,[32] a 3D-HD neuroendoscope could be used within the system.

Ideally, the instruments used in this NEP-NeuroCYCLOPS system would be multifunctional, endoscopic and flexible with appropriate torsional rigidity to transfer rotational forces down the instruments (e.g., by using the "steerable tube" flexible joint described by Dewaele *et al.*).[33] Indeed, the NeuroCYCLOPS represents an exciting prototype that has combined concepts from previous models and other available technology in the field. Early prototype testing (**Figure 3**) included a peg transfer experiment (testing a basic surgical skill)[34] compared against rigid endoscopic instruments used through a tubular conduit.[27] There were significantly fewer instrument clashes with the NeuroCYCLOPS compared to the standard rigid instrument, achieved without significant difference in completion times. Furthermore, use of the NeuroCYCLOPS also resulted in lower NASA-TLX scores (assessing the mental, physical and temporal demand as well as performance, effort and frustration). These preclinical results suggest that the NeuroCYCLOPS platform may allow for more intuitive instrument control during endoscopic neurosurgery.[27] Thus, future research and development are warranted to further develop the technology.

Conclusion

Keyhole endoscopic transcranial neurosurgery is a field in which there is a huge opportunity for robotic augmentation. As with the innovation process of robotic development in other fields, knowledge regarding current procedural mechanics and limitations is of paramount importance, with simplicity, efficacy and cost-effectiveness as the core principles of subsequent prototype development. Such principles will prove vital in clinical uptake of these systems, a hurdle that has yet to be crossed in this field. Prototypes in development, such as the NeuroCYCLOPS, offer promise and lend encouragement to future development in the field of robotic neurosurgery.

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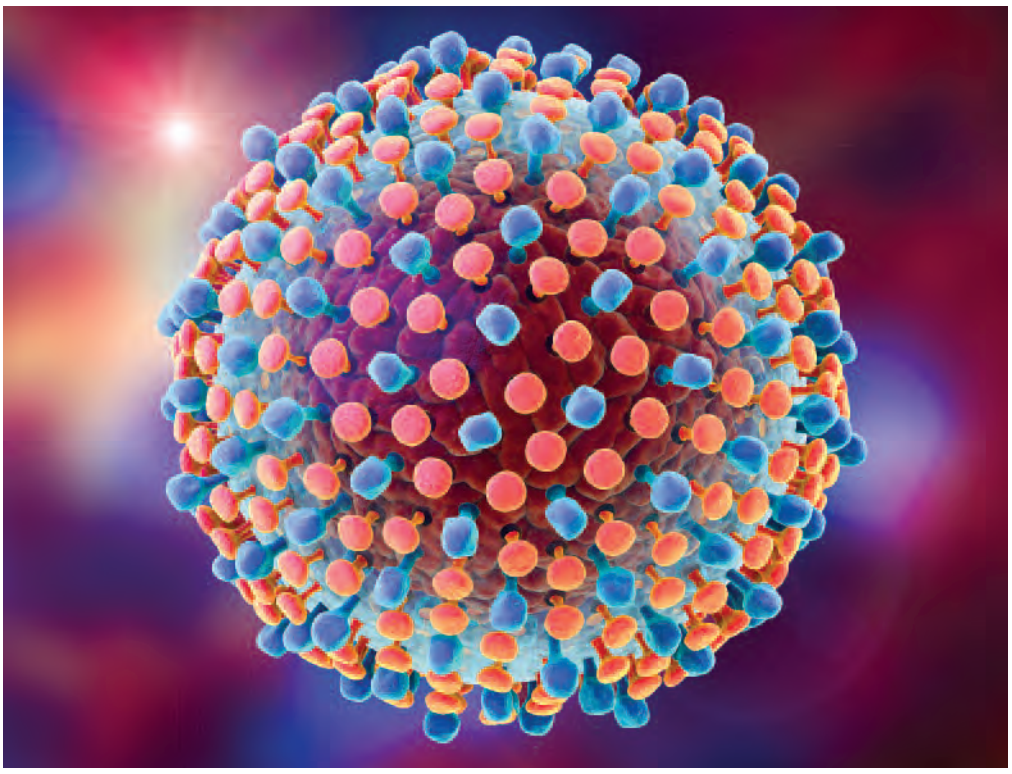
Bullseye: direct-acting antivirals are changing the game in hepatitis C and hepatocellular carcinoma



Abstract

Chronic infection with hepatitis C, a virus affecting over 130 million people around the globe, is responsible for one-quarter of hepatocellular carcinomas (HCCs) as well as half a million annual liver disease-related deaths. The treatment of chronic hepatitis C virus (HCV) infection has been a matter of ongoing concern, as previously investigated treatment options have produced suboptimal rates of sustained virologic response (SVR) in patients with compensated liver function and have been largely unsuccessful in those with decompensated cirrhosis. The arrival of direct-acting antivirals (DAAs) has enabled SVR rates in excess of 90% to be achieved in HCV-infected patients and has catalysed rapid advancement in established treatment regimens. The prohibitive cost of DAAs (in excess of $60,000 USD for 12 weeks of treatment) is the primary barrier to their immediate widespread usage. This article reviews the link between HCV infection and the development of HCC, and compares previous treatment regimens with the recent success of DAAs in terms of successful virus elimination and hepatic transplantation.

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Introduction

As the third most common cause of cancer-related deaths worldwide, and the second most common cause of cancer deaths in low-income countries, primary liver cancer (most frequently hepatocellular carcinoma [HCC]) and its established risk factors, as well as breakthroughs in treatment, have been of ongoing interest in the scientific community.[1] One of the established primary risk factors for HCC is chronic infection with hepatitis C virus (HCV), a virus to which 25% of HCC cases and 500,000 annual liver disease-related deaths may be attributed.[2,3] Globally, between 130 and 150 million individuals have chronic HCV infection,[4] which places them at a risk of developing HCC that is 17 times higher than uninfected individuals.[5] Previous treatment of HCV, focusing on interferon (IFN) therapy in conjugation with ribavirin, has been shown to achieve sustained virologic response (SVR) in approximately 50% of patients.[6]

A recent revolution in treatment owing to the development of direct-acting antivirals (DAAs) has resulted in an improved cure rate, a superior side effect profile, and SVR of greater than 90% in some HCV genotypes.[7,8] The development of DAAs has the potential to alter the projected epidemiology of HCV, and the incidence of HCC and other global burdens resulting from HCV complications. Unfortunately, at present the cost of DAAs is a prohibitive factor for their widespread use, particularly in low- and middle-income countries.[9] The exorbitant cost of 12 weeks of treatment was exemplified by the entry of simeprevir and sofosbuvir (two DAAs used in HCV treatment) onto the US market, at costs of $66,000 and $84,000 USD, respectively.[10] This is a clear indicator that significant initiatives are required in order to make these medications accessible to all HCV-infected patients.

HCV as a cause of HCC

HCV is an enveloped virus, with high genetic diversity and a single-stranded, positive sense RNA genome approximately 9.6kb in length.[11] Chronic HCV infection primarily affects the human liver and is associated with the development of liver fibrosis, cirrhosis, and HCC.[5,12] Despite the evidenced increased risk of HCC development associated with HCV infection, the mechanisms responsible for tumourigenesis are incompletely understood,[12] although a number have been implicated.

Direct cytopathic effects as well as indirect hepatocyte destruction and microRNA (miRNA) instability have been shown to play important roles in progressive liver injury.[13-15] A large polyprotein precursor containing approximately 3,000 amino acids is encoded by HCV's RNA genome and subsequently cleaved into a number of structural and non-structural proteins.[16] One of the structural proteins, termed "core protein", is involved in direct mechanisms of hepatic carcinogenesis by inhibiting both p53 tumour suppressor and the retinoblastoma (Rb) family of growth suppressor and tumour factors. Carcinogenesis is stimulated through the inhibition of essential checkpoints, resulting in inappropriate activation of cell division and growth, and inhibition of regulators of apoptosis.[17,18]

A number of indirect mechanisms of HCC development have also been proposed; namely, an immune system response and damage to the liver that is thought to occur as a consequence of HCV core proteins.[19-21] The proposed immune system effect involves the release of proapoptotic signals when fighting the replication of HCV. CD81 in combination with other receptors is responsible for the infection of hepatocytes.[22] Infected hepatocytes in turn experience diffuse cell death, which causes the proliferation of hepatocytes to maintain the required synthetic functionality capabilities of the liver.[23] Indirect damage to the liver as a result of the presence of HCV core protein may result in the development of HCC over time.

Variations in miRNA expression have been repeatedly associated with the development of HCC;[24] miRNA alteration has a resultant impact on the transcription of a number of proteins and consequently is an important component of cytological processes. While a unique indicator of HCC in the form of miRNA has not yet been identified, there is ongoing investigation into miRNA's roles as HCC tumour markers, markers in surrounding tissue, and prognostic indicators.[25-27]

The clinical implications of HCV's genetic diversity (seven genotypes and nearly ten times as many subtypes) has necessitated genotyping prior to the initiation of treatment, as the most effective treatment varies with viral genotype.

Antiviral HCV therapy

The incidence of HCC is influenced by a variety of factors, including lifestyle, viral, and concurrent liver disease factors. It is also varied by geographic region and ethnicity. The clinical implications of HCV's genetic diversity (seven genotypes and nearly ten times as many subtypes) has necessitated genotyping prior to the initiation of treatment, as the most effective treatment varies with viral genotype.[28,29] A 2002 study indicated that approximately 25% of HCC may be attributed to HCV infection, which is one of the main risk factors for the development of HCC.[2,30] In a 17-year study of the

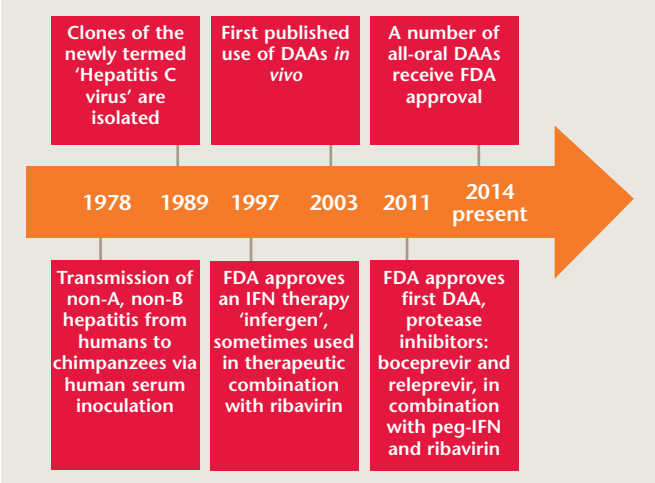

FIGURE 1: Timeline of HCV therapy development.[16,52,53]

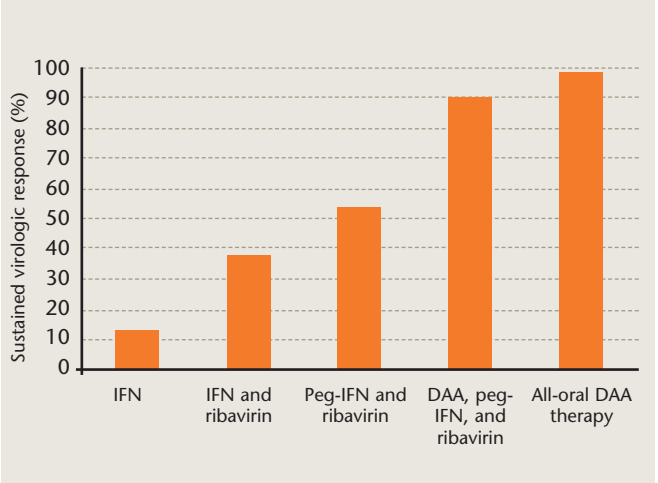

FIGURE 2: Sustained virologic responses achieved with various HCV therapeutic options.[7,35,39,47]

natural history of HCV in 214 infected, Child-Pugh class A participants, in which a negligible number received interferon antiviral therapy, clinical status remained stable in 72% of study participants.[31] This study showcased that some HCV-infected individuals maintained stable clinical status longitudinally in the absence of antiviral therapy, but others continued to deteriorate to, in some cases, liver failure.

Unlike hepatitis B virus's DNA genome, the RNA HCV genome requires an intermediate replication agent in order to continually infect host cells. This continuous infection is mandatory for the development of HCV-induced HCC; thus, eradication of the viral infection has the potential to eliminate HCV-induced HCC.[32] Early clinical trials focused on long-term IFN therapy in HCV patients with compensated cirrhosis (cirrhosis in the absence of major complications). Early studies of IFN therapy **(Figure 1)**, which aimed to inhibit viral replication and improve the immune system's ability to distinguish infected from non-infected cells, indicated that while the viral load, histologic inflammation, and serum transaminase levels were decreased, disease progression was often not altered. In addition to an SVR of only 13%, a relatively high frequency of adverse events was also observed **(Figure 2)**.[33-35] In a 2014 study comparing adverse event profiles of DAA therapy without interferon to a triple therapy that included interferon, the adverse event profile of the triple therapy was significantly worse, with 57% of patients discontinuing therapy due to adverse effects versus none in the non-interferon treatment group.[36]

Subsequent studies investigated the impact of combined IFN and ribavirin, a nucleoside analogue with a stimulatory effect on T cells. Combination therapy with both IFN and ribavirin reduced both the extent and progression of fibrosis.[37] In patients with genotype 1 HCV (the most common genotype worldwide), this combined therapy has only achieved an SVR of approximately 38-50% over a standard treatment length of 48 weeks.[35,38,39] The subsequent use of pegylated IFNs with ribavirin resulted in slight improvements in SVR rates;[40] however, with suboptimal SVRs observed in patients with compensated liver function and a lack of successful treatment options for patients with decompensated cirrhosis,[41-45] there has been an ongoing search for treatment options that will provide complete viral eradication and improved liver function. A heterogenous group of compounds that target various stages in HCV's replication cycle, DAAs have appeared as a promising treatment option and target both structural and non-structural proteins,[46] with the potential to result in viral eradication.

Initially, DAAs were utilised in combination with IFN and ribavirin, achieving SVRs of approximately 90%.[7] The use of this combined therapy was associated with a number of side effects; however, recent research has investigated new DAA therapeutic options including all-oral, IFN-free regimens. Current trials with members of this diverse group have attained remarkable short-term results. This was exemplified in a randomised, double-blind, placebo-controlled trial conducted with 706 patients with chronic genotype 1, 2, 4, 5 or 6 HCV infection (excluding patients with decompensated cirrhosis), which achieved an intervention group SVR of 99%.[47] It should be noted that the generalisability of these preliminary results is limited by the exclusion of those with decompensated cirrhosis and specific HCV genotypes.

In previous IFN-based therapies, elderly populations suffered from a reduction in efficacy and increased adverse event-related medication withdrawals.[48] A study of elderly patients (>65 years of age) using genotype-dependent, IFN-free DAA regimens had patient SVRs of

98% overall, and in those who completed at least 80% of the specified treatment duration the rate of SVR was 100%;[49] in this large cohort study, rates of adverse events were not significantly increased. Additionally, a recent clinical trial has shown that patients with genotype 1 HCV and decompensated cirrhosis, a patient population for whom liver transplantation had previously been the sole treatment option, may be treated effectively with DAAs and may also achieve early liver function improvements.[50] Few trials to date have evaluated the use of DAAs for patients who have had HCCs. Notably, one such study found a high rate (27.6%) of tumour recurrence in patients who have been cleared of HCV following DAA treatment regimens.[51] This study reinforces the necessity for further longitudinal studies into the safety of, and benefits achievable by, DAAs in diverse patient populations.

DAA accessibility – a realistic goal or a distant dream?

With such promising preliminary results attached to a price tag in excess of $60,000, the question of whether these game-changing drugs will eventually be accessible to the masses affected by HCV remains.[10] Similar cost barriers existed when triple antiviral therapy used in the treatment of the human immunodeficiency virus (HIV) first entered the market in the 1990s. Since then, remarkable reductions in the cost of HIV treatment have resulted in over 10 million people now having access to treatment in low- and middle-income countries.[54] This is a promising precedent for those infected with HCV, with one recent cost projection study forecasting that by 2029 the mass production of HCV combination DAA therapies will enable a 12-week treatment course to range between $100 and $250.[55] In addition to national and international treatment initiatives, mechanisms involved in cost reduction may include previously employed antiviral price-reduction strategies, such as differential pricing (with lower-income countries paying less for drug access than higher-income countries), international donations, and generic product manufacturing.[55]

Liver transplantation in patients with HCV

Cirrhosis caused by HCV infection is the leading reason for liver transplantation in the US.[56] In HCV+ patients with concurrent HCC, there are worse survival rates following liver transplantation than in those with HCC alone, and failure of transplantation is often a result of progressive liver fibrosis in patients with recurrent HCV.[57-59] Previous investigation in patients awaiting liver transplant has focused on interferon-based treatment regimens; however, this is contraindicated in patients with advanced-stage liver disease, with limited efficacy and safety concerns associated with its use both prior to and following transplant.[60-65] A DAA and ribavirin combination therapy has been shown to achieve successful suppression of viral replication in those awaiting transplant, with HCV recurrence successfully prevented in 70% of those with HCV infection (any genotype) and cirrhosis, who had HCC and HCV-RNA levels below 25 IU/ml prior to transplant.[66] Recent studies have also investigated treatment regimens including DAAs in the post-transplantation setting for patients with both compensated and decompensated liver function. SVR rates of greater than 90% have been repeatedly attained in patients with HCV genotype 1 and compensated cirrhosis following liver transplant and 12 weeks of treatment.[67,68] However, lesser rates have been observed in those with severe hepatic disease, especially in patients with genotype 1a. In order to further evaluate the safety and efficacy of DAA treatments in patients either pre- or post-liver transplantation, further longitudinal studies and larger scale investigations of the various HCV genotypes are required.

Conclusions

While recent investigation into DAA-based treatment regimens indicates that high SVR rates and quality of life maintenance is achievable for patients with and without decompensated cirrhosis, there remains a subset of cirrhotic patients who have not yet been able to reap the benefits achieved by others using this type of treatment.[69] Further studies are required to assess long-term mortality and morbidity outcomes for those using DAA treatment (both with and without liver transplantation). Presently, there is limited data on the long-term effects of DAAs on those with concurrent HCC, and early studies have shown an unexpectedly elevated rate of HCC recurrence in patients attaining SVR from DAA therapy. While DAAs appear to offer hope for the millions infected with HCV, without dedicated national and international treatment strategies, this advanced therapeutic option may not become readily and affordably available to many who would benefit from its use.

A committed approach combining integration of cost reduction strategies with government support and simplification of diagnostic and monitoring methods may enable low- and middle-income countries to achieve the significant health benefits associated with the use of DAA therapy in future years. Further studies are required in order to better understand its full potential in terms of HCV eradication in patient populations with HCV-associated HCC, as well as the indirect benefit conferred by the resultant reduction in HCV transmission. With no vaccine available for HCV, eradication of the disease and its complications (including HCC) depends on effective treatment. Oral treatment regimes including DAAs hold great promise for achieving SVR and alleviating these global burdens.

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A stitch in time: the past, present and future of foetal surgery

Abstract

With the introduction of prenatal diagnosis, therapeutic intervention in the foetus became a theoretical feasibility. A number of procedures have since been developed, with the most successful treatments targeting twin-twin transfusion syndrome and myelomeningocoele (spina bifida). A number of other conditions were also initially believed to be suitable for foetal surgical intervention but have yet to bear therapeutic fruit. The purpose of this article is to explore the science behind foetal surgery, what has characterised the procedures which have a good evidence base for their use, and why more congenital abnormalities have not been targeted by this modality.

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Introduction

With the introduction of the prenatal diagnosis of anatomical anomalies via ultrasound, and the elucidation of the natural history of these anomalies via serial sonographic observation, a new potential patient population requiring treatment has emerged: the foetus.[1] While in the majority of cases ultrasound identification of anomalies is useful clinically for planning the method of delivery or for procedures in the neonatal period, there is a subset of patients that have been identified as possibly benefitting from earlier intervention. However, the benefits of the treatment must significantly improve the foetus's prospects outside the womb, as intervention may have a negative impact on someone who is apparently healthy: the mother.[2] Furthermore, the complication identified as the 'Achilles' heel' of these procedures is preterm labour, which remains the largest cause of morbidity and mortality (as measured in disability-adjusted life years) worldwide, and therefore is best avoided.[3]

Two conditions have been proven by large, randomised controlled trials to benefit from prenatal as opposed to postnatal treatment: twin-twin transfusion syndrome (TTTS) and myelomeningocoele.[4]

The successes achieved in these two conditions can be best understood through a thorough exploration of their pathophysiology, and of which features in particular make them amenable to prenatal correction. An examination of the evidence base

Table 1: Recent trials addressing foetal interventions.

Trial	Condition	Total number	Conclusion	Year	Comments
MOMS	Myelomeningocoele	183	Benefit	2011	Follow up with MOMS II underway
Eurofetus	Twin-twin transfusion syndrome	142	Benefit	2004	Included Quintero Stage I
NICHD	Twin-twin transfusion syndrome	42	No benefit	2007	Stopped at request of investigators
TOTAL	Congenital diaphragmatic hernia	Ongoing	Ongoing	Ongoing	1mm foetoscope (not 2mm)
PLUTO	Lower urinary tract obstruction	31	Inadequately powered	2013	Unable to recruit enough cases

behind the regular implementation of these conditions will also be addressed, illustrating the difficulty in establishing true therapeutic benefit in these procedures.

A number of other conditions have also been posited as possible candidates for foetal surgery. A brief overview of the nature of these conditions illustrates problems that can arise in investigating these rare conditions and helps to show the future for foetal surgery.

Twin-twin transfusion syndrome: a foetoscopic success story

A problem unique to monochorionic twin pregnancies (in which twins share a placenta), TTTS occurs when one 'donor' twin loses blood to one 'recipient' twin via shared arterial and venous anastomoses in the placenta. While these anastomoses are present in all monochorionic pregnancies, in TTTS there is an imbalance causing net flow from the donor to the recipient. This is often exacerbated haemodynamically by the existence of two separate amnions, meaning that TTTS predominantly effects monochorionic, diamniotic (MCDA) pregnancies, although it can rarely occur in monoamniotic pregnancies as well.[4]

Excessive blood flow from one foetus to the other results in problems for both foetuses: the donor becomes hypovolaemic, oligouric and oligohydramniotic, producing a 'stuck' twin or foetus, which is adherent to the surrounding amnion; meanwhile, its sibling becomes fluid overloaded, polyuric and polyhydramniotic, leading to congestive heart failure.[4]

As a syndrome, TTTS affects 8-10% of MCDA pregnancies, with poor outcomes for untreated foetuses including intrauterine death and serious neurodevelopmental consequences due to impaired blood flow to the foetal brain.[5] Previously trialed treatments including septostomy and amnioreduction were used to reduce the burden of fluid on the recipient twin amniotic sac, reduce the rate of preterm labour and improve placental haemodynamics by removing pressure from the placental vasculature.[6] However, both of these methods failed to address the underlying problem with the uneven placental vascular bed.

With the development of foetoscopy, a method of directly visualising the placenta *in utero* and using a laser to ablate anastomotic vessels was produced. Concerns, however, existed around: a) whether ablating only the anastomotic vessels one could visualise would be sufficient; and, b) whether such a high level of intervention would result in increased incidence of preterm labour.[7,8]

Two randomised controlled trials from both sides of the Atlantic set out to answer this question: the Eurofetus trial by Senat *et al.*, and a trial in the US sponsored by the National Institute of Child Health and Human Development (NICHD) authored by Cromblehome *et al.*[7,8] While the NICHD paper did not show a benefit for foetoscopy versus serial amnioreduction, Eurofetus reported a statistically significant increased chance of survival to both 28 days and six months, and reduced risk of cerebral hypoxic injury.[7,8]

A number of factors could explain this disparity. While the Eurofetus group recruited 142 women (72 to laser, 70 to amnioreduction), the NICHD trial was stopped at 42 participants, which may have left the study underpowered to detect a statistically significant difference.[7,8] Additionally, the Eurofetus group's inclusion of Quintero Stage I (the lowest level of TTTS, which can spontaneously resolve) may have led them to over-report benefits in both serial amnioreduction and laser foetoscopy.[8] On the current evidence, selective foetal laser photocoagulation (SFLP) is considered the treatment of choice for Quintero Stage II, III and IV **(Table 1)** in affected pregnancies at less than 26 weeks' gestation, although more studies are required to confirm this.[4]

In utero *myelomeningocoele repair*

Neural tube defects (NTDs) are common congenital abnormalities in Ireland, with one in 1,000 births affected. Of these, 49% have spina bifida, or an incomplete fusion of the posterior neuropore leading to exposure of the spinal canal.[9] Myelomeningocoele is the most severe type of spina bifida: there is not only complete herniation of the dura through the defect, but also exposure of part of the spinal cord to the external environment. In normal pregnancy the posterior neuropore closes at 28 days, protecting the developing spine from mechanical and

chemical damage. In myelomeningocoele this does not occur. The combination of loss of CSF through the opening and chemical irritation of the spinal cord leads to severe neurodevelopmental, motor and neurological issues, including Arnold Chiari malformations, hydrocephalus, loss of motor control below the level of the lesion and incontinence. As such, myelomeningocoele is sometimes considered the most complex birth defect compatible with survival.[10]

Given the level of disease burden in these individuals, and the postulated pathophysiological link between the time that the spinal cord is in continuity with the amniotic fluid and worse infant outcomes, myelomeningocoele became a natural target for *in utero* intervention. *In utero* myleomeningocoele repair is a complex procedure performed before 26 weeks' gestation, requiring both obstetric and specialist paediatric neurosurgical input. Initially, the site of the defect is identified and the obstetrician attempts to rotate the foetus into a position *in utero* where the defect is accessible. Following this, a hysterotomy is performed at this site exposing the paediatric spine and the amnion is carefully separated. A myelomeningocoele repair is performed as in the immediate postnatal period, the amnion and uterus are re-approximated, and the pregnancy is continued until an elective caesarean section can be performed at 37 weeks' gestation.[11]

To assess the advantages of prenatal versus postnatal myelomeningocoele repair, a large randomised controlled trial was performed in the US called the Management of Myelomeningocoele Study (MOMS). This study was unique, as all foetal surgery centres outside of the three involved in the study in the US agreed to cease performing *in utero* myelomeningocoele repair until study completion.[9] The study showed a significant reduction in both primary outcomes – the need for cerebral shunting at 12 months and neonatal death – in the prenatal intervention group versus the postnatal intervention group. Additionally, development as assessed by standardised assessment scores was also significantly better in the prenatal versus the postnatal intervention groups. Risks of the intervention included a significant increase in pregnancy complications such as chorioamnionitis, placental abruption and dehiscence of uterine scar. Additionally, the external validity of a trial conducted in three very specialised centres is likely to be low. However, MOMS established that for the correct abnormality, in the correct centre, at the correct gestational age, there is a large benefit to be gained from prenatal as opposed to postnatal intervention.[12]

Problems limiting the expansion of invasive foetal intervention

There are a number of other congenital abnormalities for which prenatal intervention has been posited as curative, for example lower urinary tract obstruction (LUTO), congenital diaphragmatic hernia (CDH) and cleft palate.[1,10,11] There are a number of problems in these scenarios, which make the accumulation of a strong evidence base for their implementation difficult. These congenital conditions in neonates are very rare. Of the three mentioned above, cleft palate is the most common (and has the lowest associated morbidity) with 16 cases per 10,000 births, CDH has a rate of 1.2 per 10,000 live births, while LUTO occurs in 3.34 per 10,000 live births.[12-14] While this is excellent news for the foetus, it is bad news for foetal surgeons hoping to accumulate evidence for the efficacy of a prenatal intervention. As a result, one common characteristic between the MOMS, Eurofetus and NICHD trials is that they were multicentre trials and still recruited, in absolute terms, small numbers.[7-9]

As described in both SFLP and in *in utero* myelomeningocoele repair, preterm labour is a major problem. The insertion of trocars or incision into the uterus is a noxious stimulus, and as the uterus depends on inflammatory cascades for the initiation of labour, this can lead to early parturition and a premature birth. This is a major health problem in its own right, with the vast majority of neonatal deaths attributable to babies born <34 weeks.[3] As such, use of prenatal intervention for low-risk malformations such as cleft palate is probably unwarranted as the potential benefits (there is no scarring if operated on in the womb) outweigh the risks (death or significant cerebral hypoxia due to preterm birth). On the opposite side of the prognostic spectrum are congenital anomalies such as CDH, which have a high associated morbidity and mortality in severe cases. In a randomised controlled trial designed to establish the benefit of foetoscopic endotracheal occlusion (FETO) versus optimal care at tertiary centres, Harrison *et al.* failed to demonstrate a benefit to prenatal intervention, with 73% of foetuses that underwent FETO and 77% of foetuses in the standard intervention group surviving to 90 days.[15] Again, preterm labour was implicated in the failure, with babies who had undergone FETO born at an average of 31 weeks, while babies with best standard care were born on average at 37 weeks. The ability to assess the severity of CDH *in utero* is also quite poor, which may lead to confounding results in these types of trials despite promising animal study results.[15] Finally, improvements in neonatal care in those with CDH (especially in specialised centres) may abrogate improvements that can be made with prenatal intervention.

Possible future directions

Foetal surgery over the last three decades has been inextricably linked with the development of an adequate evidence base and improvements in technology. Both these factors will continue to drive the nascent specialty going forward. The most successful trials in the field have been multicentre, and in order to produce sufficient numbers it is likely that future trials examining *in utero* interventions will need to be multicentre,

international trials with a number of world-class centres contributing patient data to trials. This will allow studies to achieve sufficient power and is already underway, with PLUTO (although ultimately this trial was underpowered) and TOTAL trials occurring across a number of sites and countries.[16]

Technology is also improving and, as in other surgical specialties, increasingly minimally-invasive methods are being tested. For example, a number of European centres have begun using a 1mm foetoscope to perform FETO surgeries and have produced early promising results, although not yet subjected to the rigors of an RCT (currently underway; TOTAL, NCT01240057).[17]

Improvements in tocolysis and the prevention of preterm labour may also be of benefit; however, there is very little evidence for successes on the horizon with few agents of proven efficacy.[18]

Conclusions

Foetal surgery is still very much in its infancy three decades after its inception. Improving technology and international collaboration are key for the development of this specialty, and for the improvement in outcomes for foetuses with rare but serious congenital anomalies. Although it has yet to be proven that 'a stitch in time saves nine' in this patient population, there have been many promising early investigations, which indicate that this approach may be of benefit, if carried out at the appropriate age, and if preterm labour can be avoided. While more careful research is warranted, there is hope that outcomes can be improved for many potentially fatal foetal anomalies.

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Targeting cystic fibrosis pathophysiology is changing the future for children worldwide

Abstract

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7, most commonly diagnosed at birth via heel prick testing. Patients with CF suffer from a variety of complications including lung disease, gastrointestinal disease and pancreatic dysfunction leading to malabsorption and secondary diabetes mellitus. To date, treatment has been largely symptomatic, but the recent development of a new class of drug, the CFTR modulator, may be a game-changer for children with CF. CFTR modulators target the underlying pathophysiological process of CF itself, either the misfolding of protein channels (correctors) or the length of time functional channels remain open (potentiators). This study aims to review the literature to date on ivacaftor, a CFTR potentiator approved for use in CF patients two years and older with G551D mutation; lumacaftor, a CFTR corrector with as-yet unproven benefit; and, lumacaftor/ivacaftor combination (Orkambi), which shows modest but significant improvement in patients with the F508del mutation, specifically focusing on efficacy, safety profiles and current guidelines.

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1938	1949:	1989:	1993:	1997:	2000:	2004:
Dorothy Anderson writes first comprehensive case report on CF	Hypothesis that CF is caused by a single gene defect	CFTR geneis identified	FDA approves dornase alfa	FDA approves inhaled tobramycin	Azithromycin proven to benefit lung function	Hypertonic saline is used clinically for patients with CF

FIGURE 2: Timeline of advancements in CF management to date.

Background

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by multiple mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7, which encodes for cAMP-regulated anion channels on epithelial cell surfaces.[1] Mutations in the gene cause imbalances in chloride ion transport across cell surfaces and dysfunction of sodium chloride and water absorption and secretion across multiple systems.[2] The lungs are most prominently affected, as abnormal ion transport leads to thick, viscous secretions, reduced mucociliary clearance, bronchiectasis, and colonisation with opportunistic pathogens.[3] Pancreatic exocrine function is also affected due to inspissated pancreatic ducts, leading to the malabsorption of fat-soluble vitamins, steatorrhoea, weight loss and failure to thrive.[4]

Over 70,000 people worldwide suffer from CF.[5] Ireland has the highest prevalence of CF in Europe, with at least one in 19 people estimated to be carriers and approximately 50 diagnoses per year.[5] Prior to the introduction of CF screening via neonatal heel-prick testing, the disease usually presented in infancy with meconium ileus, recurrent respiratory tract infections and failure to thrive. However, most cases are now diagnosed in the neonatal period, allowing for earlier treatment and prevention of complications.[6]

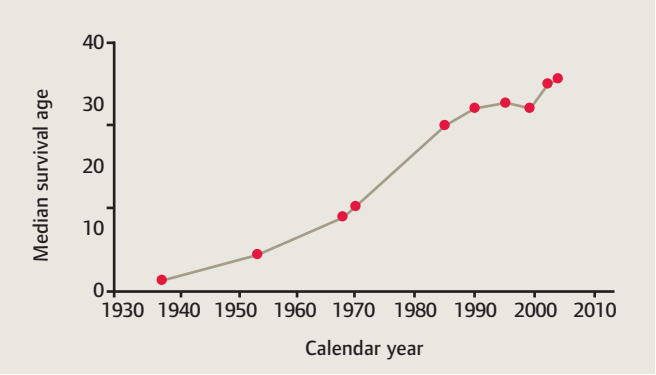

FIGURE 1: Cystic fibrosis life expectancy versus year born (adapted from Davis [2006]).[7]

Currently, life expectancy of CF ranges from the mid-30s to early 40s in Ireland, whereas in the 1930s, most patients with CF could expect to live only a few months to years (**Figure 1**).[7]

Since the CFTR gene was initially discovered in 1989, over 1,900 causal mutations have been identified, with multiple classes recognised.[8] Synthesis or processing mutations cause a reduction in the number of CFTR channels at the cell surface; one such mutation, the F508del, accounts for up to 85% of CF cases. Another class, gating or conductance mutations, decrease the functioning of the CFTR channels themselves. The most common gating mutation is that of G551D, which accounts for 4% of all cases of CF.[9]

Since the first comprehensive case report of CF in 1938, treatment has been entirely aimed at malabsorption and respiratory symptoms, with no disease-modifying therapies available. However, a novel class of drug, the CFTR modulator, has recently been developed and aims to target the underlying pathophysiological process itself.

This article will review the advancements in CF management to date (**Figure 2**), highlighting the latest management guidelines with specific focus on recently approved CFTR modulator therapy.

Historic management of cystic fibrosis

CF is a complex disorder with multiple sites of symptomatology and therefore a broad range of therapeutic targets. The primary components of therapy can be broadly subdivided into respiratory and nutritional management.

The basis of respiratory management is the clearing of viscous secretions from the airways, as these stagnant secretions act as the perfect breeding ground for both common pathogens like *Staphylococcus aureus*, and opportunistic and more severe infections like *Pseudomonas aeruginosa*.[10]

Mucosal expectoration is achieved by a number of means, from basic chest tapping in infants to elaborate physiotherapy vests in

2006:	2008:	2012:	2014:	2015:	2016:
Ivacaftor enters clinical trials	Aztreonam is approved by FDA	Ivacaftor is approved by FDA for patients with G551D mutation CF ages six and older	Ivacaftor is also approved by FDA for patients with one of nine other rare CFTR gene mutations ages six and older (and in the same year extends the age limit to ages two and older)	Lumacaftor/ivacaftor is FDA approved for patients homozygous for F508del ages 12 and older	Lumacaftor/ivacaftor is also FDA approved for patients homozygous for F508del ages two and older.

2016

older children and adolescents. Inhaled DNAse reduces the viscoelasticity of the airway secretions by cleaving extracellular DNA fragments.[11] Inhaled hypertonic saline has also proven beneficial and acts as an osmotic draw within the alveoli, further reducing viscosity.[12] In patients taking hypertonic saline or dornase alfa, inhaled short-acting beta-2 agonists are also recommended, with chronic use based on individualised patient benefit.[13]

Because *Pseudomonas* is a significant cause of morbidity from opportunistic disease, inhaled antipseudomonals such as tobramycin have been approved for prophylactic use.[14]

While chronic bacterial infection with multiple organisms is common as a child with CF ages, acute exacerbations are frequent in many patients and heralded by worsening respiratory symptoms;[15] therefore, children and adolescents with CF often undergo portacath placement due to the frequent courses of IV antibiotics used to treat these exacerbations.[16]

Pancreatic enzyme replacement therapy also plays a key role in CF management.

Because of inspissated pancreatic ducts, exocrine function of the pancreas is severely impaired, leading to malabsorption of fat-soluble vitamins, steatorrhoea and failure to thrive in infants. High-calorie diets are essential to children with CF to maintain adequate growth and meet all developmental milestones.[17]

Patients with CF may also eventually develop endocrine dysfunction in adolescence, with a secondary diabetes mellitus requiring insulin treatment.[18]

In the end stages of disease, respiratory complications are the leading cause of morbidity, with a significant number of patients eventually requiring a lung transplant. However, post-lung transplant complications account for the second highest cause of mortality according to the 2013 CF register.[19]

Newer therapies targeting the underlying pathophysiological mechanisms of CF could potentially circumvent the need for the aforementioned treatments, particularly end-stage lung transplant.

Targeting CFTR channels

CFTR modulators are small-molecule drugs that modify specific defects caused by mutations in the CFTR gene, and can be further subdivided into correctors and potentiators.[20]

CFTR correctors are ideal for synthesis mutations and improve the post-translational maturation and delivery of CFTR channels to epithelial cell surface membranes, resulting in an increased number of functional protein channels and decreasing imbalances in ion transport.[21] CFTR potentiators, on the other hand, improve the flow of ions through already-functional CFTR channels by increasing the time that these channels remain open. This class is best suited for gating or conductance mutations, such as the G551D mutation.[22]

Ivacaftor

Ivacaftor is a CFTR potentiator shown *in vitro* to improve chloride ion transport in cells positive for the G551D mutation. Clinical trials subsequently began on adults with CF, with later studies targeting the paediatric population.

The first major clinical trial by Ramsey *et al.* evaluated ivacaftor therapy in CF patients >12 years of age with at least one G551D mutation, with the primary endpoint being an improvement in forced expiratory volume in one second (FEV_1).[23] The study found statistically significant improvements in FEV_1, favouring the treatment group, after 24 weeks of therapy, as well as improvements in secondary endpoints such as sweat chloride concentrations, weight gain, and quality of life measures. A further study on children between the ages of six and 11 with at least one G551D mutation yielded similar results and led to FDA approval of ivacaftor for this population.[24] While this patient population has milder lung disease at baseline, the percentage predicted FEV_1 was significantly increased from baseline through week 24. Significant improvements in weight gain and sweat chloride concentration were also observed, establishing the efficacy of ivacaftor in the younger patient population.[25]

Table 1: FDA, European and NICE guidelines on CFTR modulator therapy.

	Lumacaftor	Ivacaftor	Lumacaftor/ivacaftor
FDA	Not approved for clinical use	Approved for CF patients >6 years old with at least one copy of the G551D mutation or one of nine other rare gating mutations	Approved for CF patients 12 years and older homozygous for the F508del mutation
European	Not approved for clinical use	Approved for CF patients >6 years old with at least one copy of the G551D mutation	Approved for CF patients 12 years and older homozygous for F508del mutation
NICE	Not approved for clinical use	Approved for CF patients >6 years old with at least one copy of the G551D mutation	Not recommended due to insufficient evidence of cost-effectiveness

A recent study further established the safety and efficacy of ivacaftor in children between the ages of two and five, with at least one gating mutation (G551D or one of nine other rare gating mutations).[26] This study demonstrated significant improvements in respiratory function and weight gain, although transient liver transaminase elevations were noted, which exceeded rises demonstrated in older populations. Recommendations from this study were for the FDA to approve ivacaftor for children over two years old, although this approval has not yet materialised. European guidelines recommend the routine use of ivacaftor for any CF patient with a G551D mutation, as standard of care.[27]
Of note, ivacaftor was proven to have insignificant benefit in non-gating mutations leading to CF, including those homozygous for the F508del CFTR mutation, thus limiting its use to a small subgroup of the entire CF population.[28]

Lumacaftor

Lumacaftor is a CFTR corrector, which was shown *in vitro* to correct defective CFTR processing and misfolding, the major defect in the F508del mutation. Only partial improvement in chloride ion transport was achieved, with maximum levels reaching only 15% of wild-type.[29] Furthermore, in phase 2 clinical studies, the dose-dependent reduction in sweat chloride shown with lumacaftor use did not translate into clinical benefit for patients homozygous for the F508del mutation.[30] As such, it has not been approved for use in any country and is not mentioned in the European Cystic Fibrosis Society's Standards of Care guidelines.[27]

Ivacaftor/lumacaftor

Following the failure of lumacaftor to improve baseline FEV_1 in patients homozygous for the F508del mutation, a trial of a combination of lumacaftor and ivacaftor commenced under the premise that with a combination of both drugs, more correctly-folded protein could reach the cell surface, and of the protein reaching the cell surface, more could remain open to allow for chloride ion transport. This initial phase 2 study assessed treatment with lumacaftor alone for four weeks, followed by the addition of ivacaftor. As seen in previous studies, lumacaftor alone was ineffective in improving respiratory symptoms and FEV_1; however, with the addition of ivacaftor, a statistically significant improvement in FEV_1 (absolute change 3-4%) was seen.[31]
A later phase 3 clinical trial assessed the lumacaftor/ivacaftor combination in patients homozygous for the F508del mutation ≥12 years of age, showing similar efficacy. This trial included a subgroup analysis of the paediatric population between the ages of 12 and 17, and showed favourable responses in the treatment group, with increased FEV_1, decreased pulmonary exacerbations and increases in BMI.[32] These studies led to both FDA and European approval for clinical use of lumacaftor/ivacaftor in patients with CF 12 years of age and older homozygous for the F508del mutation.

Safety profiles

CFTR modulators are relatively new in clinical practice, and studies regarding their long-term safety profiles are limited. Studies to date have shown short-term side effects to include minor adverse reactions such as nasal congestion, upper respiratory tract infections,

dizziness, headaches and rashes.[23] However, none of these side effects has been severe enough to cause study participants to withdraw from clinical trials, indicating good tolerability. As with any new drug, longer-term observational studies on safety profiles are necessary and are ongoing;[33-35] current recommendations are summarised in **Table 1**.

The finding that liver transaminase levels were significantly more elevated in the two to five age group suggests that more frequent monitoring of liver function tests than the current recommendations (baseline and three-monthly checks for one year thereafter) may be necessary.[26] Furthermore, non-congenital cataracts have been reported in children using ivacaftor, and therefore baseline ophthalmology assessments are recommended prior to commencing therapy.[36]

Conclusions

In Ireland, approximately 1,200 people live with CF, with 45% of these patients ≤18 years old. With the highest prevalence of CF in Europe, novel targeted therapies are of paramount importance to the healthcare system in Ireland. According to current European best practice guidelines, ivacaftor should be the standard of care for patients with at least one G551D mutation and clinically-diagnosed CF. However, although FDA approved, the combination lumacaftor/ivacaftor is, according to recently published NICE guidelines, not proven to be cost-effective, with a cost of €131,000 per patient per year and only modest short-term benefits.[37]

The majority of clinical trials of CFTR modulators to date have focused on a mixed adolescent and adult population, with few studies targeting children under 12 years old. However, of the clinical trials that have focused on this younger paediatric population, promising results have been seen, with the efficacy of both ivacaftor and the lumacaftor/ivacaftor combination being established.

With the routine implementation of CFTR modulators at an early age for patients with CF, there is the potential to enhance quality of life for longer periods of time, and to reduce the need for lung transplantations at early ages. Studies targeting the paediatric population of patients with CF are crucial; with earlier treatment targeting the mechanisms underlying the disease, we can expect to see reduced exacerbations and complications, and longer life expectancies. Already, the life expectancy of CF has increased to the mid-thirties to forties in Ireland, and with the recent developments of CFTR modulators, the life expectancy for our paediatric population of patients has the potential to continue this upward trend.

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Long live the children

MICHELLE OHLE argues that the emergence of multi-morbidity in the paediatric population creates new challenges for primary care.

Introduction

Multi-morbidity is an interesting and challenging concept for primary care, encompassing all of the medical conditions that a patient experiences.[1] A variety of definitions of multi-morbidity exist; however, each is open to interpretation and remains unclear. In clinical practice, it is widely accepted that multi-morbidity refers to a patient having more than one chronic medical condition, but some would argue that this is not sufficiently clear for practical purposes.[2]
In 2013, the European General Practice Research Network aimed to produce a comprehensive definition of multi-morbidity. They developed three components to this definition:

- "any combination of chronic diseases with at least one other disease or biopsychosocial factor or somatic risk factor";
- modifiers of the burden of multi-morbidity; and,
- outcomes of multi-morbidity.

This more comprehensive definition allows for more focused research, targeting of resources, focused prognosis and improved clinical decision making.[1]
Multi-morbidities have a profound impact on both the patient and society. There is a heavy treatment burden for these patients, who are often required to attend appointments within multiple disciplines, navigate their way through complex drug regimens, and self-manage their conditions, all of which can lead to decreased quality of life and functional decline.[3]
When considering the concept of multi-morbidity, the tendency is to think of the older population – typically adults over the age of 65. This would be reasonable, with a recent Scottish study reporting that 65% of people aged over 65, and 82% of those over 85, have two or more chronic health conditions.[4] However, there is an emerging and perhaps counter-intuitive patient population experiencing multi-morbidity: children.

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An emerging population

Advances in both medical technology and healthcare expertise have resulted in many children who historically would have died in infancy now surviving through childhood and into adulthood.[5]

However, not all of these children are living these longer lives in good health. The reduction in mortality comes at the expense of an associated increase in the number experiencing multi-morbidity.[5] Although this patient group only accounts for the minority of the paediatric population, they now contribute to more than 30% of paediatric healthcare costs.[6]

There are several factors contributing to the rise in multi-morbidity in paediatric populations. Firstly, the gestational age at which a baby is now considered viable can be as early as 23 weeks.[7] Preterm birth has significant consequences; those who survive the neonatal period often suffer from numerous health problems throughout their lives, including neurodevelopmental, cognitive, and functional impairment, as well as increased incidence of respiratory disorders (e.g., asthma).[8] Secondly, survival rates among children with congenital heart disease are also increasing; 95% of children with non-critical heart defects and 69% with critical congenital heart disease now survive to 18 years of age, of whom 20-30% experience additional health problems.[9]

Not only are children surviving conditions that were traditionally fatal in infancy, there have also been increases in the life expectancies for conditions that were typically fatal later in childhood. The development of new targeted therapies for cystic fibrosis (CF) means that this disease is now extending from a disease of childhood into a disease of adulthood, with the number of children with CF reaching adulthood expected to increase by 75% in the next 10 years.[10] This increase in life expectancy will subsequently lead to an increase in the number of chronic health conditions experienced by the population as a whole.

Today, eight out of 10 children treated for childhood cancer survive at least five years.[11] Up to two-thirds of these children can experience what are termed "late effects", or medical conditions that can occur months to decades after treatment has been completed; these include cardiovascular disease, renal dysfunction, endocrinopathies and musculoskeletal problems.[12]

Childhood obesity is now a major issue in Ireland. One in ten children aged five to 12, and one in five aged 13 to 17, are overweight or obese.[13] As a consequence, there is now an increasing number of children suffering from type 2 diabetes, hypertension and hypercholesterolaemia, which were traditionally adult-related health conditions.

Current services and new challenges

In the past, Ireland relied heavily on acute hospital services for the delivery of all aspects of paediatric care. Emphasis has now moved from this provision of care to providing more community- and home-based care. This will result in more children with intensive, complex and multiple healthcare needs being cared for in the community by GPs and primary care teams.

When caring for children with multiple morbidities, GPs are faced with a wide variety of challenges, ranging from knowledge deficits to suboptimal communication between tertiary paediatric centres and primary care providers.[14] Additionally, transitioning of the care of adolescents to adult services is a time of challenge and change for both the child and their family. It is also a time during which patient disengagement, poor treatment adherence and poorer health outcomes can occur.[15] GPs are in a crucial position at this time, as they are the single service that does not change as a result of adulthood, and could potentially mitigate the adverse events associated with the transition process. However, little research in this area exists. If a child with multiple morbidities develops any acute illness during childhood, many parents go directly to the A&E department of the hospital where their child has been treated since birth rather than presenting to the GP first. Therefore, GPs are not routinely involved in the care of these children as they are growing up, and problems arise after the transition process when the GP becomes the first point of contact.[15] The GP is expected to manage these highly complex and unusual healthcare needs with little or no previous experience.

In the past, in comparison to the number of adults with multi-morbidities that a GP would routinely see, the number of children with complex healthcare needs would have been small, so GPs would not necessarily have been familiar with each individual condition and especially not those more typical of childhood. There is therefore a need for regular, ongoing training, updates and support in order for them to be able to provide appropriate care.

Another area where challenges arise is in attempting to apply treatment guidelines to complex paediatric patients. As with adults, treatment guidelines are applicable to single-disease entities and are not always suitable for multiple chronic conditions. In adults it has been suggested that future treatment guidelines address more common clusters of chronic conditions; this approach could also be applied to the paediatric population.[3]

Finally, GPs have on average 10 minutes per consultation. A lack of an appropriate amount of time to adequately care for children with complex medical problems is another barrier that GPs face.[3]

Addressing these challenges

Despite the multiple challenges that GPs face in caring for these medically-complex children, there are measures that can be implemented to assist them in providing the highest level of quality care to this vulnerable and specialised paediatric patient group. If a child with multi-morbidities is starting the transition process to adult services, GPs need to become involved in the transition meetings so they can gain a better understanding of the young person's healthcare requirements.[16] Additionally, having a named GP in the GP practice for each child will help to ensure continuity of care and will enable the GP to become familiar with all aspects of the child's care. Annual or biannual reviews are also helpful ways for GPs to link in with the child and the primary caregiver, so as to keep up to date on the child's current condition and care plan.

The Mercy University Hospital in Cork launched the 'My Personal Health Passport' in 2012 for children with complex and multiple healthcare needs. These are patient-held documents, which contain detailed information about the healthcare needs, medical history, and healthcare requirements of each child.[17] If paediatric hospitals across the country could utilise such documents, it would provide

GPs with all the necessary information to treat these children appropriately. To support GPs in their consultation with these children, the use of tools such as 'HEADS AT' can also be helpful.[18] This tool was developed to help paediatric residents in the United States care for medically complex children. The tool covers the seven spheres of the lives of children with medical complexity: home, education, activities, development/mental health, specialist review, ancillary services, and transitions.[18]

Conclusion

Chronic diseases represent one of the largest burdens on our healthcare system.[19] While the majority who experience chronic diseases are over the age of 65, the emerging paediatric population experiencing multiple chronic diseases is increasing and will continue to increase into the future as treatments for chronic childhood diseases continue to improve. GPs need to become cognisant of the need for health screening and health promotion in this paediatric population in order to try to mitigate the adverse effects associated with experiencing multiple morbidities. They need to be included in transition meetings from an early stage. There also needs to be improved communication between the multidisciplinary healthcare teams and GPs, with more regular correspondence providing updates on the healthcare requirements of each child. Finally, but crucially, both adults and children with multiple chronic conditions are routinely excluded from research trials, and this needs to change.[3] More research needs to be undertaken involving this patient population if GPs and other healthcare providers are to provide the most appropriate and evidence-based care.

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Difficult conversations

Discussions with patients about advance care planning and end-of-life care are a difficult but important part of care, says HUGO REYNOLDS.

Introduction

As a result of developments in modern medicine, many high-income countries are facing novel issues that come with an ageing population. These include an increased number of individuals with chronic and complex disease, and increasing strains on healthcare systems looking to provide quality yet affordable care.[1] Healthcare costs in such economies are rising,[2] with studies indicating that these costs surge dramatically in the last 12 months of life.[3,4] During this end-of-life (EOL) period, aggressive treatment of illness often remains the default practice. However, there is a growing body of evidence indicating that this may not be best practice, and that such treatments may not only have little impact on mortality, but may directly contradict the will of patients.[5]

In an ageing population, the number of individuals who are subject to EOL care is increasing,[6] and therefore determining best practice during this time is of great logistical, ethical and financial importance. At present most patients would prefer to die at home (63%); however, relatively few do (35%).[7]

It is estimated that approximately 50% of deaths are considered "expected" due to chronic disease,[4] and with this in mind, it seems feasible that more of these patients could have their deaths managed at home or in a hospice setting. On average, individuals are hospitalised eight times in the last 12 months of their lives,[4] and recent studies have shown that a high number of these patients receive non-beneficial treatments (33-38%) and investigations (33-50%) during this time.[5]

Advance care planning (ACP) is one method proposed to reduce unnecessary intervention and better satisfy the will of patients. It is a structured process of communication by which patients can express their desires to healthcare professionals. In ACP, the patient and their family explicitly discuss their wishes, beliefs and goals as they relate to their treatment at present or in the future. These formalised discussions provide information that can inform future healthcare choices at a time when a patient lacks the capacity to make decisions on their own behalf. ACP often includes the completion of an advance directive (AD), but grants a greater scope of knowledge from which to draw, and provides guidance when healthcare choices push beyond the limits of an AD.

Implementation of an ACP framework has the potential to reduce costs associated with EOL care, and provide care that is more in line with a patient's desires.[8-10] This article looks to define the utility of ACP in EOL care, and discuss the obstacles to its implementation in modern healthcare.

The benefits of advance care planning

Recent research shows that ACP facilitates improved outcomes in EOL care.[4] In studies conducted in Australia, patients with ACP had their wishes followed 86% of the time, compared to only 30% of the time without ACP.[9]

They were also less likely to receive unnecessary interventions,[11,12] and these patients and their families indicated increased satisfaction with their overall care.[11] Individuals with ACP spent 57% less time in hospital than those without, with no decrease in mean survival.[9,12]

Advance care planning is one method proposed to reduce unnecessary intervention and better satisfy the will of patients. It is a structured process of communication by which patients can express their desires to healthcare professionals.

ACP engages with patients and empowers them to make their desires known. Subsequently, studies have shown that patients who undergo ACP are more likely to: complete an AD; take up hospice care; nominate a surrogate; and, die in their preferred place.[9,11] The value of an informed surrogate cannot be overstated. Data suggests that 42% of dying patients require treatment decisions in the final days of their lives; however, 70% lack decision-making capacity.[13] Often, when dying patients are unable to make their own decisions, the burden falls onto family. Prognosis may be poor, but when presented with even the smallest ounce of hope, families will often err on the side of intervention – doing everything they can to save someone they love. The only way to reduce this burden is to make the desires of the patient transparent to his or her surrogate. Studies show that EOL planning not only helps surrogates make decisions that better reflect the will of their partners,[14] but also reduces rates of depression, anxiety and stress in those bereaved.[9,11]

The cost-effectiveness of advance care planning

According to a Dutch study, as much as 25% of a Western healthcare budget is spent providing inpatient care for those in the final 18 months of their lives.[3] ACP may go some of the way towards reducing these expenses by cutting costs generated by non-beneficial treatments and over-admission of patients.[15] A 2016 systematic review provided preliminary data suggesting that ACP may reduce net health expenditures associated with EOL care, despite the costs of its implementation.[10] However, they noted that the heterogeneity of various ACP programmes and incomplete cost assessments made overall savings inconsistent. Of the seven studies included, six showed net cost reduction, ranging from $1,041 to $64,827 USD, with one study showing no overall difference in cost.[10]

A pilot trial conducted in the UK looking at the cost-effectiveness of ACP showed a 53.4% reduction in days spent in hospital when compared to the previous 12 months.[8] The mortality in the interventional and non-interventional cohorts were similar; however, those with ACP spent less time in hospital, and were less likely to die there.[8] The study estimated an overall saving of £143,545 GBP for 80 patients in the intervention cohort, with a cost of implementation of £125,000 for the programme. Other studies have come to a similar conclusion: ACP has the potential to reduce costs by reducing unnecessary hospitalisation and over-treatment of patients.[11]

Obstacles to advance care planning

There are several hurdles that must be overcome in order to establish an effective ACP programme. The first of these relates to the physicians involved. Research indicates that patients expect doctors to initiate conversations regarding their advance care plans.[9] Simultaneously, studies have shown that a doctor's confidence in discussing ACP is directly proportional to the likelihood that he or she will begin said discussion.[16] With this in mind, training of involved personnel is crucial in establishing a framework for ACP. At present ACP is targeted towards the individuals it will most immediately impact. However, identifying these individuals can often be challenging. Naturally physicians tend to be overly optimistic when it comes to patient prognosis,[17] and they are less likely to initiate ACP in diseases considered non-terminal (e.g., COPD).[18] There is no universal time at which ACP must be applied; however, several studies do establish guidelines for triggering ACP discussions.[12] This issue of timing provides perhaps the greatest argument for installing ACP as a part of routine care, since in many cases capacity may be lost suddenly (e.g., stroke), or early in the course of the disease (e.g., dementia). Establishing ACP as a fixed part of care not only removes the uncertainty regarding when to initiate planning, but also reduces the number of individuals who are unable to express their will before losing capacity. It is also worth noting that while ACP can apply to individuals of all ages, it is most relevant to the elderly, who suffer the bulk of advanced disease, and who constitute the majority of global deaths.[19] As such, it seems any routine care would be best focused on these individuals.

According to a Dutch study, as much as 25% of a Western healthcare budget is spent providing inpatient care for those in the final 18 months of their lives.

Physicians themselves have expressed several concerns regarding ACP. Among these, perhaps the two most prevalent include time constraints and lack of uniform practice. Already some countries including Canada, Australia, the US and the UK have begun

remunerating physicians for ACP in some circumstances.[20] Not only does compensating physicians incentivise them to initiate planning, but it allows them the freedom to dedicate entire appointments to ACP, rather than it being an afterthought. Time restraints remain a pressing issue; in many of the current trials, ACP sessions required periods of up to one hour discussing patient choices.[9] Such periods of time are often not feasible, with primary care physicians restricted to limited appointment times. One of the benefits of ACP, however, is that the discussion is an evolving one, wherein a dialogue can be established though shorter discussion spread over several interactions.[4]

This allows physicians to tailor plans around an individual's developing prognosis, and address issues as they develop, while allowing patients to modify their choices as their understanding grows and their priorities shift.

Establishing an optimum ACP protocol remains a pertinent issue. Heterogeneity in implementation throughout current studies makes establishing a superior framework difficult. Current trials utilise a diverse range of strategies and often differ in intervention methods, intervention personnel (e.g., doctor, nurse, social worker, trained facilitator), follow-up and measured outcomes.[15] The primary aim of much of the current research remains to reinforce the efficacy of ACP,[5,15] while additional research will be required to determine which practices provide the greatest benefit.

Conclusion

ACP is the formalisation of a long-respected concept in medicine: treatment should be in accordance with the will of the patient. It provides guidance and support to families and physicians trying to make the difficult decisions that surround EOL care and death. Death is an important part of our lives, and no one should be deprived of their right to die on their own terms. But how can we ensure this if their beliefs are not known in the first place? These are not easy conversations, but they are vital ones. Implementing ACP as a routine part of care ensures that they occur, and helps us to strive toward better care and more dignified deaths for patients.

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Ready for repeal?

SUZANNE MURPHY asks if the Irish health service is in a position to deal with a repeal of the Eighth Amendment.

Introduction

Historically, Ireland has been heavily influenced by the teachings of the Catholic Church. Recent times have seen a sharp decline in Catholic influence in Ireland: a 2012 Red C poll saw the amount of individuals who consider themselves "a religious person" drop to 47%, down from 69% in 2005.[1] A major result of this step away from the traditional teachings of the Church, particularly with regard to termination of pregnancy, has led to a new movement throughout Ireland: a campaign to repeal the Eighth Amendment to the Irish Constitution. At present, the Irish Constitution "acknowledges the right to life of the unborn and, with due regard to the equal right to life of the mother, guarantees in its laws to respect and, as far as practicable, by its laws to defend and vindicate that right".[2] Therefore, abortion is effectively illegal in Ireland, although there are some very tightly-regulated exceptions to this rule. The recent repeal campaign is calling for a change to the Constitution to legalise abortion in Ireland. As many as three-quarters of Irish people say they would support a repeal of the Eighth Amendment;[3] however, independently of personal opinion, one must consider how the legalisation of abortion would impact on the health service. From this perspective, is Ireland really ready to repeal?

The World Health Organisation has developed guidelines for safe abortion, stating that policies should maintain all basic human rights of the women, with particular attention paid to the special needs of women living in poverty, adolescents, rape survivors and women living with HIV.

Training

In many countries where abortion has been legalised, only physicians are permitted to manage and administer abortion procedures independently.[4] However, there is evidence that procedures can be safely performed by other healthcare professionals. A 2015 Cochrane review examined the provision of abortions, both medical and surgical, by various healthcare professionals and found "no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers, such as nurses and midwives, compared to doctors".[5] The World Health Organisation (WHO) has developed guidelines for safe abortion, stating that policies should maintain all basic human rights of the women, with particular attention paid to the special needs of women living in poverty, adolescents, rape survivors and women living with HIV.[6] The WHO further recommends that abortion be delivered at the lowest tier of any healthcare system, suggesting that nurses, midwives and other non-physician providers can be trained to conduct first trimester abortions.[7]

Professional attitudes

Regardless of whether the Irish Government were to allow nurses and midwives to perform procedures or, like their European counterparts, limit it to physicians, consideration must be given to healthcare professionals' willingness to carry out the procedure. At present, research into Irish doctors' attitudes to abortion has been limited. A 2012 anonymous survey of GPs and GP trainees regarding abortion showed that 51% of those surveyed felt abortion should be available to all women in Ireland. However, it should be noted that there was a 44% response rate from the 744 doctors surveyed, so it cannot be considered representative of GP attitudes.[8] A similar study disseminating questionnaires to medical students and recent medical graduates from the University of Limerick had a similar response rate (45%). Among

respondents, 95.2% believed that education regarding abortion should be taught within the curriculum, while 55% felt an abortion should be legally allowed if a woman requests it.[9]

The surveys both looked at the opinions of medics regarding legalising abortion, but neither directly asked if the medics in question would be willing to perform abortions, either routinely or in an emergency situation. In the UK, medics are permitted to refuse to complete the procedure on moral or religious grounds, but they must refer their patient accordingly.[10] The 'conscientious objection' clause also allows medical students to opt out of witnessing an abortion; however, doctors have an obligation to provide care to a woman in an emergency situation, regardless of their personal beliefs.[11] If Ireland was to adopt similar guidelines then it should be considered what the procedure would be in an emergency situation, particularly in rural settings where treatment delays may result in negative consequences for the patient. Even when abortion is legal, there can still be significant stigma accompanying it. One study investigated opinions of obstetricians and gynaecologists in Poland and Brazil, which are both largely Catholic countries. It found that many obstetricians and gynaecologists refused to perform abortions for fear of being judged by colleagues, the media, and the general public.[12]

In the United States, abortion is legal upon request; however, there is a refusal clause whereby healthcare professionals can refuse services, including referral to alternative providers, or even informing a woman of abortion as an option.[13] This provision means there is a divide between the rights of the physician and the rights of the patient. Physicians withholding access to information may be damaging to women who are then unable to access unbiased advice and care. If this clause was established as part of Irish termination guidelines, it could have negative repercussions for everyone involved. Considering the impact a repeal of the Eighth Amendment would have on Irish medics, it is important to consider their opinions. The lack of research into willingness to perform abortions among healthcare professionals in Ireland means that, at present, the HSE cannot definitively establish if they have enough trained staff to offer abortions to Irish women.

Financial impact

The Irish health service is plagued by financial shortcomings. In the first nine months of 2015 alone, the Health Service Executive (HSE) was estimated to be nearly €500 million over budget. Providing the same services in 2016 was projected to cost €650 million over budget.[14] While taking care not to reduce repeal to a fiscal issue, it is important to consider whether repealing the Eighth Amendment would be possible financially. There are costs incurred simply by the development of any new government policy; additionally, training staff regarding all aspects of abortions (pre- and post-procedural assessment, counselling and, when necessary, monitoring and treatment of possible complications) would likely result in a large investment on the part of the health service. Realistically, the cost of carrying an unwanted pregnancy to term vs. terminating the pregnancy is an important consideration. A healthy full-term pregnancy costs the Irish health service approximately €2,780 for a consultant-led unit or €2,598 for a midwife-led unit.[15] US figures estimate the cost to the US health service of the birth (plus the first 12 months of maternity and infant care) to be approximately $12,770 (approximately €11,556).[16] This is for a healthy, complication-free pregnancy; the cost of a pregnancy of a baby born with serious health complications or to a mother with serious physical or mental health issues could be significantly higher. Comparatively, the cost of an abortion procedure is $376 (approximately €340) per procedure,[16] although this figure does not account for possible complications or pre- and post-procedural counselling or consultations. Importantly, women with a history of mental health problems are at an increased risk of further problems after an unintended pregnancy.[10] Although there would be a large financial expenditure in the beginning to establish the provision of abortions, the figures do suggest that long-term costs to the system would be significantly lower if women were provided with the option to terminate unwanted pregnancies.

The Irish health service strives to put patients' welfare first but, like all healthcare systems, it is working under huge pressure and constant demand for greater resources.

Location

At present there are 25 locations across the country that are permitted to carry out abortions in line with current legislation.[17] These locations are all public hospitals, which is logical given the current restrictions on the procedure, but if legislation were changed it would significantly increase demand on these hospitals. Research suggests that specialised clinics are more appropriate for providing support both before and after the procedure.[18] However, building specific clinics to carry out abortions is not an acceptable solution. Aside from the substantial cost of developing an abortion clinic, studies have shown that specialised clinics are far more susceptible to harassment than hospitals that carry out the procedure. A 2014 study in the United States showed that 84% of specialised abortion clinics experienced at least one form of harassment, including picketing and harassing phone calls.[19] A large proportion of US healthcare professionals agree that a specialised clinic is an appropriate location for medical or surgical abortions, as long as they have trained staff able to deal with any possible complications. Some professionals, however, expressed concerns that complications requiring transfer to the emergency department would be distressing for the woman involved.[20] Regardless, with constant reports of extensive hospital waiting lists for inpatient, outpatient or day care, it is not feasible for the current public hospital system to be the only point of contact for women seeking an abortion.

Foetal screening

A debate regarding Eighth Amendment repeal cannot be complete without briefly mentioning the issues surrounding foetal abnormality screening. At present in Ireland, routine foetal screening is only carried out as an "add-on", with expectant parents paying extra for the tests.[21] These tests can be non-invasive and allow for the detection of genetic disorders such as Down syndrome or Edwards' syndrome at as early as nine or ten weeks' gestation.[21] Leading Irish obstetricians have already

called for national guidelines regarding prenatal screening, including when this screening should be carried out in low-risk pregnancies.[22] The risk of false positives is less than 3% in single pregnancies, which reinforces the need for guidelines on when genetic testing should be performed and how it should be interpreted.[23]

Conclusion

The Irish Government needs to ask major questions before a repeal of the Eighth Amendment is a feasible undertaking. The Irish health service strives to put patients' welfare first but, like all healthcare systems, it is working under huge pressure and constant demand for greater resources. A repeal of the Eighth Amendment has far-reaching consequences affecting not only frontline staff, but also those working in the community. The Government needs to consider the points outlined here before abortion could be available in a safe and holistic manner for the women of Ireland.

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KATIE NOLAN explains how vitamin D is a simple answer to an under-recognised problem.

The sunshine supplement

Introduction

While calcium intake is highlighted in the media and regularly prescribed for patients at risk of osteoporosis due to age or hormonal changes, the fact that calcium requires vitamin D for absorption in our bodies is less well publicised. Doctors prescribing calcium supplementation for patients with vitamin D deficiency will not achieve optimum results unless the patient has sufficient vitamin D to absorb the calcium. Clinical hypovitaminosis D is associated with rickets in children and osteomalacia in older adults.[1] The prevalence of vitamin D deficiency is high worldwide, leading many doctors to call for more active clinical management of hypovitaminosis D.[2] Recommendations from the Institute of Medicine describe a target serum vitamin D (25OHD) level of 50nmol/l and suggest reference dietary intakes (RDIs) of 600IU for those one to 70 years old, increased to 800IU above 70 years.[3] While universal vitamin D supplementation may be overzealous, the current research suggests that young children, pregnant women and the elderly would benefit greatly from this cost-effective and easily-managed dietary supplement.[4] If this is the case, then why is the prescribing of vitamin D not routine in nursing homes and care homes where patients are at high risk?

What is vitamin D, and why is it important?

Vitamin D is a fat-soluble vitamin derived from cholesterol that is crucial to calcium absorption and regulation, and helps regulate gene expression. There are two forms: plant-derived vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), which is found in oily fish and animal tissue. We produce 80-90% of our cholecalciferol through the action of ultraviolet light on our skin, and the other 10-20% comes from dietary intake.[5] After modification in the liver, vitamin D increases intestinal expression of calbindin, a calcium-binding protein that enables dietary calcium absorption through the endothelial lumen of the intestines **(Figure 1)**.[6] Vitamin D deficiency causes decreased calcium absorption, which in turn increases parathyroid hormone levels, subsequently increasing osteoclast activity in bone. Active osteoclasts decrease bone mineral density (BMD) through bone resorption, which leads to osteoporosis and osteopenia.[7]

Why does deficiency occur?

Vitamin D deficiency occurs due to inadequate intake coupled with malabsorption or low sun exposure.[8] High-risk groups for vitamin D deficiency include exclusively-breastfed infants (if the mother is deficient), dark-skinned persons, women with low levels of oestrogen, smokers, patients with gastrointestinal disorders, and people with low sun exposure (for example, night shift workers and less mobile elderly people).[9] The link between lifetime vitamin D levels and bone health highlights the importance of monitoring and maintaining vitamin D through diet, sun exposure and – when both of those are inadequate – daily supplementation.[10] However, the question arises of whether, and when, supplementation of vitamin D is high priority on a list that includes vitamin C for healthy skin and immune systems, and omega 3 fish oils for our cognitive health.

High-risk population

One group that could potentially benefit from vitamin D monitoring and regular supplementation is older patients, especially those residing in nursing or hospital facilities. The presence of multiple comorbidities, osteoporosis and polypharmacy among the elderly population

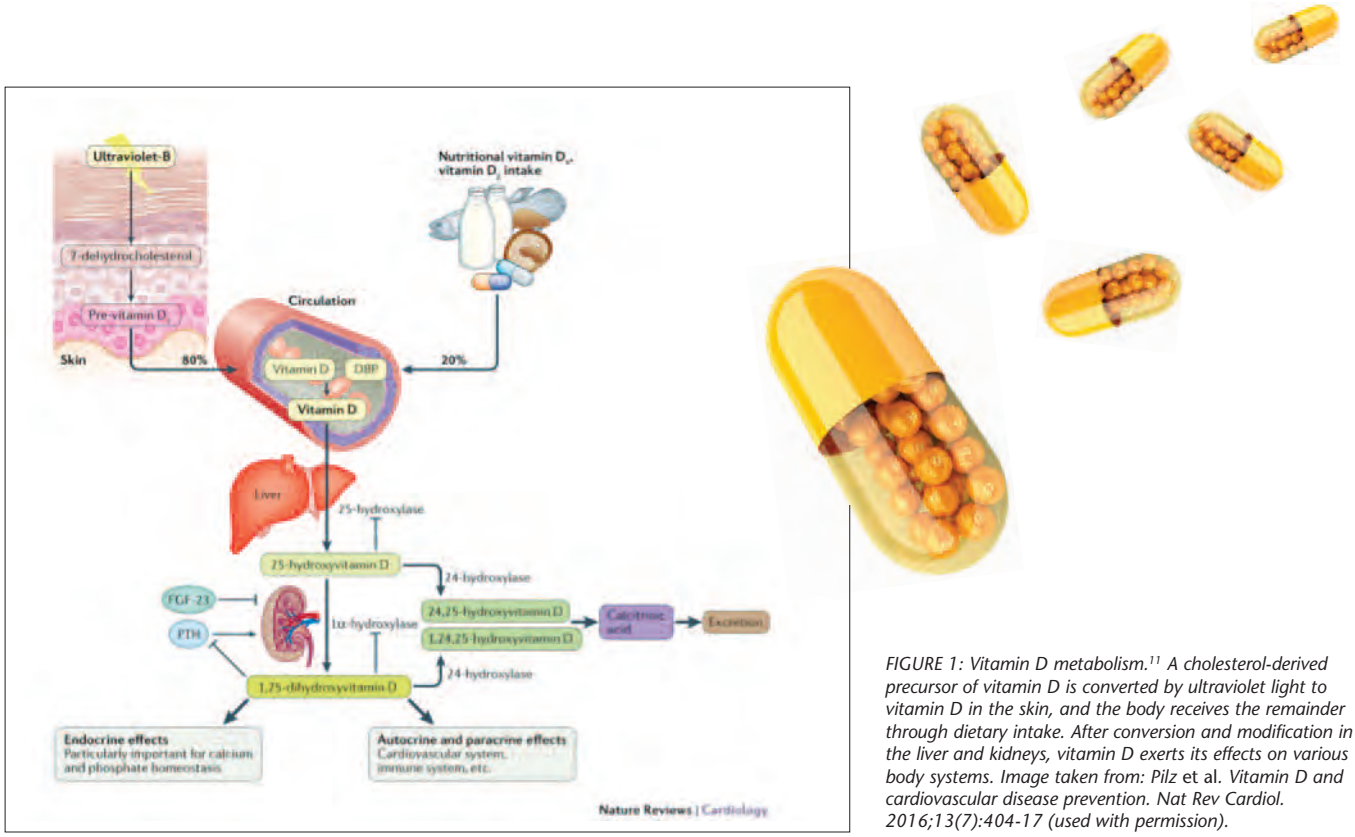

FIGURE 1: Vitamin D metabolism.[11] A cholesterol-derived precursor of vitamin D is converted by ultraviolet light to vitamin D in the skin, and the body receives the remainder through dietary intake. After conversion and modification in the liver and kidneys, vitamin D exerts its effects on various body systems. Image taken from: Pilz et al. *Vitamin D and cardiovascular disease prevention. Nat Rev Cardiol. 2016;13(7):404-17 (used with permission).*

increases the risk of falls and bone fracture.[12] One study found that 97.4 % of patients with a serum vitamin D level of <30ng/ml had a history of falls and minimal trauma fractures.[13] Hip fractures especially can leave patients immobile, cause disability and anxiety, and increase patient mortality. There is an obvious case for vitamin D supplementation here, which could increase the quality of life of nursing home residents by preventing fractures and circumventing some of these problems.

Evidence suggests that community-dwelling older adults and nursing home residents should take combined vitamin D and calcium supplementation to prevent vitamin D deficiency and reduce fracture risk.[10] Encouraging meta-analysis of randomised control trials from the National Osteoporosis Foundation revealed that calcium plus vitamin D supplementation reduced hip fracture risk by 30% and reduced total fracture risk by 15% in participants.[14] Furthermore, joint supplementation of vitamin D and calcium has been shown to increase BMD and reduce non-vertebral fractures in older people.[15] Supplementation with 800IU vitamin D and 1,200mg calcium was found to improve muscle strength and function, which decreased fall risk in addition to maintaining bone density, and was 49% more effective than calcium supplementation alone.[16] Nursing home patients with vitamin D deficiency who received a recommended dose of 800IU daily required on average 12 weeks to improve, while patients receiving a higher calculated loading dose (50,000 units twice weekly) improved in five weeks.[17]

All the data is there to suggest that vitamin D supplementation goes hand in hand with (regular dietary or supplemental) calcium intake in maintaining bone health, so why is it not commonplace for doctors to prescribe 'the sunshine vitamin'?

Barriers to supplementation

Even with this published data, a study from Belgium of 119 GPs found that 54.6% systematically prescribed vitamin D to their patients in nursing homes, while the other 45.4% only prescribed vitamin D upon diagnosis of osteoporosis.[18] Research has linked vitamin D deficiency in elderly nursing home populations with increased mortality risk; however, without proper guidelines, vitamin D supplementation for older adults remains at the discretion of the doctor, and often only occurs on late diagnosis of bone pathology.[19] There is a very real barrier to changing prescribing patterns, and vitamin D supplementation is a new concept, so there is likely to be a quality gap between taking up the idea and implementing it in practice. In the nursing home setting, it is likely that vitamin D is under-prescribed due to doctors' consciousness of polypharmacy in residents and a desire not to compound the problem. That being said, hypovitaminosis D taken at face value is a very real threat to the health, mobility and mortality of these patients, and should be considered just as vital as many of the other medications they are prescribed.

A further study from Belgium identified vitamin D supplementation as a good marker for quality of care in nursing homes and showed that doctors' and nursing staff's supplementation increased from 24.3% to 56.7% with minimal incurred cost or effort after education and co-ordination of caregivers.[20]

At home in Ireland, it is time we emphasised the monitoring of a very real risk to our health and started taking defined steps towards improvement and treatment. A 2015 study found vitamin D supplementation to be the biggest predictor of vitamin D status in older Irish adults, while fortified foods and sunlight could be used to

bolster the effect.[21] The Health Products Regulatory Authority (HPRA) has approved Desunin (Meda Pharmaceuticals, UK) tablets, containing 800IU vitamin D3, and Kalcipos (Meda Pharmaceuticals) tablets, containing 500mg calcium and 800IU vitamin D3, to supplement dietary calcium intake in deficient patients.[22,23] Although it can take a long time for new ideas or practices to become commonplace, there is strong evidence that vitamin D is especially important in older people to maintain bone health and prevent chronic fracture-related morbidity, and thus warrants further monitoring by caregivers.

Got milk?

Knowledge of the importance of calcium for our bones is commonplace in today's world. There are myriad primary school jingles to encourage us to drink our milk and grow strong, but those songs never told us that without some oily fish or a few hours in the sun, all that calcium could essentially be wasted. In more recent times, some 'super' milks have been fortified with added vitamins including vitamin D. Vitamin D deficiency is also associated with other comorbidities such as cardiovascular disease, hypertension, kidney disease and diabetes mellitus.[24]

One Irish research consortium is conducting major research to identify the status of vitamin D deficiency in Europe, and the effect of vitamin D-fortified foods, which could help direct public policy and inform government strategy.[25]

One study found patients that consumed bread fortified with a high dose of vitamin D to have significant levels of vitamin D still present at one-year follow-up.[26] In Ireland, the Health Information and Quality Authority (HIQA), as well as the Irish Nutrition and Dietetic Institute (INDI), have guidelines in place for nutrition in residential homes and call for regular assessment of nutritional needs.[27,28] While both focus on nutritious food for elderly patients, they do not address vitamin D fortification, or the importance of sunlight for utilising the calcium-rich diet they endorse. Again, this merits stressing the futility of endorsing a calcium-rich diet when these patients may be extremely vitamin D deficient; calcium supplementation looks effective on paper but in practice it is a waste of investment.

What's the downside?

Vitamin D is reported to have low toxicity, with the tolerable upper intake level of 10,000 IU per day.[29] However, there is some report of vitamin D intoxication associated with hypercalcaemia, which is attributed to the rise in supplement usage. Cessation of supplement use ameliorates the toxicity.[30]

The Institute of Medicine and American Geriatrics Society endorse supplementation of calcium and vitamin D to prevent the prevalent morbidity and mortality associated with osteoporosis and bone fracture,[31] although research on vitamin risks associated with combination therapy are limited, and risks are not well defined.

The research indicates that daily supplementation of vitamin D is safe and highly beneficial in those most at risk of severe deficiency. Unnecessary supplementation in healthy individuals is not warranted; however, it is clear that a consensus should be reached worldwide regarding standard guidelines and dissemination to at-risk patients.

Conclusion

Vitamin D deficiency is prevalent among elderly people, both in the community and in residential nursing homes, and is associated with increased mortality and comorbidity following falls. Research has shown that regular daily supplementation of vitamin D in combination with calcium can bring patients to a steady-state vitamin D level and prevent bone fractures and osteoporosis, with very limited side effects for most patients. Even in light of this research, vitamin D deficiency is an under-recognised condition and combined supplementation is not a gold standard of care practised in all nursing homes.

This is likely due to a lack of consistent dose guidelines among clinical research that would encourage doctors to prescribe it, and would additionally inform policy and government health strategy. With the rapidly ageing population worldwide, vitamin D supplementation is an ideal solution to a burgeoning health epidemic; such simple, cost-effective measures as supplementation could greatly decrease health risks for older patients and the economic burden on governments and health sectors.

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Teaching, not preaching

MICHAEL BRAVO discusses an approach to medical education for the future doctor.

Teaching is a fundamental part of medicine; it is so thoroughly embedded that even the very first etching of the Hippocratic oath includes a larger section on teaching than on medicine.[1] Even more significant is that the word doctor has its origin in the Latin *docere*, which means "to teach".[1] However, almost our entire focus in medical school is on the science of medicine; we are never taught about how to teach, despite the fact that even as medical tutors or junior doctors, we are expected to train our future colleagues. In one survey of consultant doctors in Northern Ireland, while most doctors were interested in teaching, only 34% had had any kind of educational training.[2] To achieve this goal, we have to understand how we learn, how to teach in the classroom compared to the ward, and how to practice as students.

How do we learn?

In order to know how best to teach, we must first understand how our learning occurs. The basic process of learning, according to the Atkinson and Shiffrin model theory of memory, requires three components: a stimulus; encoding the information; and, our retrieval of that information.[3] When learning a new fact, we take in all types of sensory information, filter that input, weight it differently, and store only certain components in short-term memory; with rehearsal, we store that information in our long-term memory.[3]

The key here is that we retain not just the fact, but all of our associations with it – from the context in which we learn it, to the memories it sparks. When we integrate this new fact with our experiences and culture, we attach meaning to it – this is called semantic representation.[4] In this way, students construct knowledge – it is not simply a transferral of information.[5] That is why different people remember some facts more than others from the same lecture – our own experiences inform what we learn and how we learn it. Is teaching hopeless then? How do we compensate for all these different experiences and cultures to ensure that every student learns what they should? The key here is how we teach, not necessarily what we teach. Teaching requires technique, which is tailored to the type of information we are trying to convey. Thus, to be a good teacher, we need to adapt to where we are teaching – one approach for the classroom and another for the wards.

How do we teach in the classroom?

Classroom learning is where we start in medicine, so understanding how to teach in this setting is vital to students' development. There are four elements recognised as key to teaching in a classroom: self-directed learning; self-efficacy (e.g., students setting their own outcomes); constructivism (e.g., creating the knowledge oneself with active learning); and, reflective practice.[5] Unfortunately, the current model of lecture-based teaching employed by most universities ignores most of these requirements. They are based on a college-specified curriculum, which involves students passively, does not allow constructivism, and requires little reflection. In fact, lectures have been shown as more likely to result in exam failure when compared to active learning sessions.[6] At McGill University, first-year medical students evaluated the effectiveness of lectures and concluded that while they were valuable for providing focus and reinforcing their previous learning, they were inefficient and not better than reading a published set of notes for new knowledge acquisition.[7] However, eliminating lectures completely is unrealistic, as it is one of the most efficient ways to deliver content to large numbers.

To find a marriage between teaching and learning, we can easily modify lecture technique to benefit student learning. For example, the serial position effect utilises the location of important information in a sequence to encourage retention. Essentially, if an important idea is located at the very beginning or the very end of a lecture, it is more likely to be learned; information in the middle is often forgotten.[8] Thus, rather than starting every lecture with learning objectives or definitions, it would be better for students to be given a summary of the major points to remember as the first or second slide.[8] This has the added benefit of priming students for important concepts later in the lecture. Similarly, the von Restorff effect dictates that when we are stimulated with a lot of similar information, it is the one that differs the most that we remember best.[9] To capitalise on this, we can introduce so-called "cognitive wake-ups", which are pieces of unusual information, images, or anecdotes that help the audience remember the key information through association. This sort of prompt forces students into an alert state, which evokes emotions – emotional states are more powerful encoders of memory than neutral ones.[9,10] The more emotional stimuli, the more your students will learn. You might be familiar with many of these strategies from TED talks – they introduce their most important information early on, stimulate with anecdotes and images, and conclude by recapping key points.[11]

Finally, it is not just the structure of the lecture that can be modified, but also how we approach the lecture. Lectures are passive experiences with little active learning, but we continue to use them despite the fact that polls reveal students want active learning environments,[12] which are preferred by a nine to one margin when compared to didactic lectures.[13] One strategy is to incorporate paradigms like the Socratic approach to increase our audience's active learning. The Socratic method relies on asking a series of questions, which help the learners to solve the problem, leading to greater understanding.[14] This is in stark contrast to the "pimping" medical students are so used to, involving rapid-fire questions about rote-memorised facts.[14] Pimping is best used to evaluate students, while the Socratic approach should be used for teaching – it allows us to probe students' knowledge and help form new connections. In short, while lectures may not be the most effective teaching approach, we can change our slide decks to integrate these learning strategies and incorporate a Socratic approach to encourage student retention and interaction.

How should we teach on the ward?

On the other hand, clinical skills require a different method aligned with its distinctive setting. This method should rely on practical procedures, application of previous knowledge to interpret data, and active patient management. It is on the ward, more than anywhere, that having a good teacher is essential to a medical student. One review identified five common characteristics for the ideal clinical teacher: medical expertise, technical proficiency, excellent communication, outstanding enthusiasm, and the ability to create positive relationships.[15] A teacher possessing these skills evokes an emotional response, leading to greater retention, eliciting those same alert states that best encode learning.[15] While some of these characteristics are non-cognitive and thus difficult to learn (e.g., enthusiasm), many can be developed through specific training. As a result of knowing what is valued by students, we can develop our skill set and tailor it to teaching. It is important to note that in clinical teaching, technique is equally important to who teaches. The best approach follows one similar to the Calgary–Cambridge model for consultation, because it focuses on the process of learning, rather than the material we are learning. The ideal approach begins with outlining objectives at the start of each interaction – discuss with students a clear goal for the end of the session, such as having a new skill, concept, or technique.[16] This requires us to establish the students' baseline knowledge; failing to determine a starting point is the most common reason for failing to engage students.[16] Once again, we must encourage active involvement by participating in the skill and building new connections through purposeful questions – merely observing or being didactically taught is ineffective. To close the session, we must give practical feedback with a clear and attainable goal for the student to work towards. Finally, to improve as teachers, we need to be willing to solicit feedback from our students and then have an ability to engage in self-reflection and identify the weaknesses in our approach. In short, while clinical teaching can sometimes be daunting, we can use a straightforward approach that actively involves the students to help guide their learning and give them a direction for improving their skills.

What to take home?

In short, teaching is an integral part of our future roles as physicians, which can involve a number of skills, techniques and approaches to enrich our students' learning ability. However, it can be a daunting one, especially if we leave practicing teaching too late into our medical career. Considering its importance, we have a responsibility to take this role seriously now and to actively improve our skills. Approach studying not only to memorise, but to understand the material in order to teach it. Get involved in any kind of peer tutoring and practice your skills with these different techniques. It is only when we throw ourselves head first into teaching and develop our skills early that we will be able to fulfil the role that Hippocrates set for us so many years ago.

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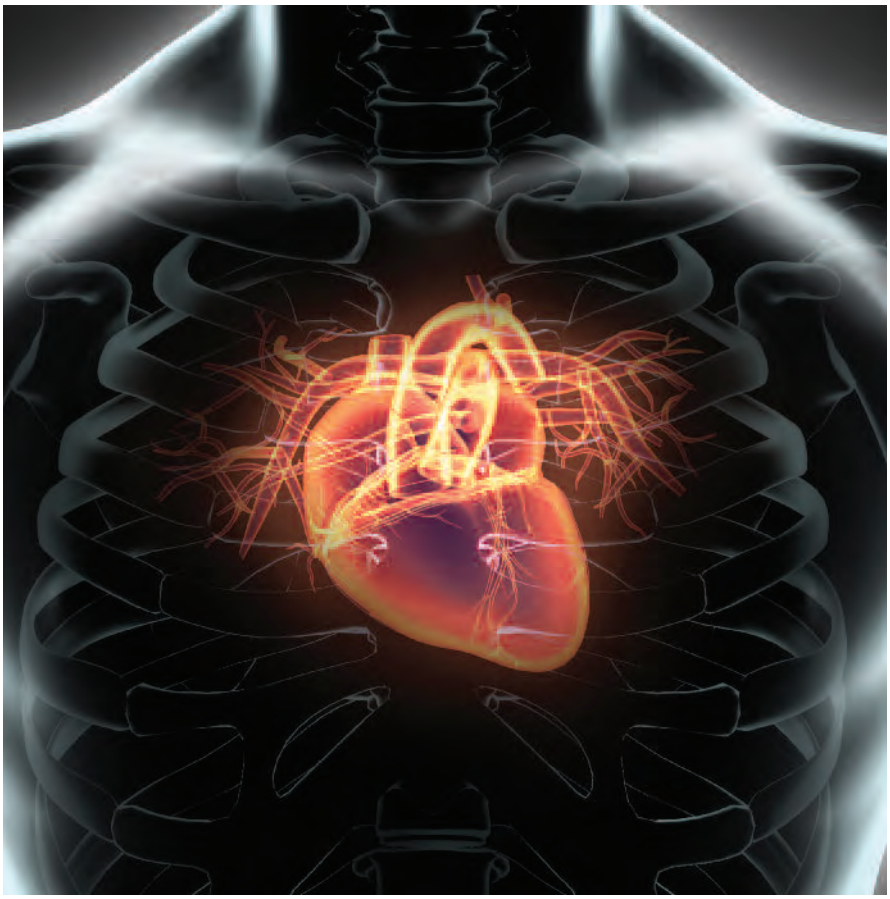
AT THE HEART OF an emerging career

The cardiopulmonary perfusionist is an emerging medical career option with enormous potential, say SAMY BESHAY and MARIA MIKAIL.



Introduction

It is estimated that over three million open heart coronary artery surgeries are carried out each year worldwide.[1] With a growing ageing population, where more people require open heart surgery, novel medical professions have developed, one of which is the cardiopulmonary perfusionist.[1] Unlike in many other medical specialties, the long and vigorous training of medical school is not required; a specialised course has been developed specifically for this career path. Perfusionists can be involved in various surgical cardiothoracic procedures including coronary artery bypasses, valve replacements, and even heart or lung transplants. This highly exhilarating and novel career choice is in high demand, and that demand is only expected to increase from this point forward.[2]

Training entailed

After completing an undergraduate science-based degree, candidates can apply for the specialised training programme and will undergo a two-year comprehensive course in perfusion techniques. In Ireland, this course is currently offered at the UPMC Beacon Hospital in Drogheda, but with demand at an all-time high, it is expected that more colleges will open up perfusionist training spots.[3]

Once the two years of training are completed, students can integrate their didactic learning into clinical practice.[2] As university programmes continue to advance, students learn basic perfusion skills, crisis management of emergency situations, teamwork, and surgical awareness by the use of simulators.[4]

Many hospitals require a perfusionist to complete a minimum of 75 perfusions in order to write the licensing exam required to practise at a hospital.[5] Moreover, as with any medical profession, continuing education on new available treatments and techniques is essential in maintaining certification and advancing in the career. Updated machines and equipment can vary from hospital to hospital, and knowledge of many surgical technologies is essential as a perfusionist in order to improve patient outcomes during high-risk operations.[2] The hours a perfusionist works vary greatly, dependent on surgical theatre times, as well as on the increasing demand and volatile nature of cardiac surgery.[6] As most of the work is a team effort, a surgeon will typically pick which perfusionist(s) they would like based on their previous experience with them.

Perfusionists can be involved in various surgical cardiothoracic procedures including coronary artery bypasses, valve replacements, and even heart or lung transplants. This highly exhilarating and novel career choice is in high demand, and that demand is only expected to increase from this point forward.

Role and patient management of perfusionists

The primary employers of perfusionists are hospitals and large surgical centres. Perfusionists are highly-skilled members of the cardiothoracic team and work alongside the surgeons, anaesthetists and nurses in the operating room. They are responsible for the unique physiological and metabolic requirements of a cardiac surgical patient. This is primarily carried out through the cardiopulmonary bypass machine, which diverts the patient's blood through various "pumps, tubing, gas oxygenators and heat exchange units"[7] to allow the surgeon to operate on a stagnant and unbeating heart.

The perfusionist administers vital blood products and medications, while stabilising the patient's temperature during surgery.[8] They are additionally responsible for monitoring blood anticoagulation, electrolytes, acid–base balance and the blood–gas ratio, in tandem with the anaesthetist.[7]

It is therefore vital that a perfusionist be able to handle stressful situations and pay close attention to details, as a minute miscalculation can result in a catastrophic patient outcome. However, for those who are adept, it can be an extremely rewarding and lucrative career choice; the Mayo Clinic estimated average compensation for a perfusionist in 2012 at just under $110,000 USD (or €100,000) per annum.[9] Furthermore, those with increased experience or working overtime shifts can expect a significantly increased salary.

Conclusion

In the ever-expanding world of medicine, new technologies, techniques and pharmacological interventions are developed on a daily basis. It is no surprise that as a society we have become more specialised and technical in what we do. Perfusionists allow the surgeon to operate without worrying about patient vitals, which in the past has been a major issue during cardiac operations. Moreover, they also allow for improved patient outcomes in a team-based environment; this ultimately has been, and always will be, the mainstay of clinical medicine.[2]

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ZAHRA MERALI had an opportunity to experience the hospitalist-family medicine landscape in North Bay, Ontario.

Ode to the north

I chose to go back to my small home town of North Bay, Ontario, and complete an elective through the Northern Ontario School of Medicine (NOSM) at the end of my elective summer so that I could truly appreciate the Northern healthcare system from the perspective of an 'experienced' medical student. I would never have guessed how fulfilling my four weeks would be.

Before starting this rural Canadian elective, I had already experienced family medicine in rural and urban settings in Ireland, and urban settings in Canada. The experiences throughout both systems were very similar. The emphasis in these settings was on clinic-based care, health promotion and preventive medicine, and outpatient management of acute and chronic illnesses. For this reason, I was quite confused when the first day of my elective in Northern Ontario started with a tour of the North Bay Regional Health Centre (NBRHC)[1] instead of the family medicine clinic. At that time, I was unaware of the unique alternative responsibilities that family physicians in Northern Ontario have outside of their clinic duties.

Hospital privileges

Although NBRHC has 401 beds, there are only four general internists employed by the hospital. How is this possible? Almost all family physicians (GPs) in North Bay have hospital privileges. When a patient from a GP's roster is admitted to the hospital, that GP becomes their internist from Monday to Friday, 7.00am to 5.00pm. Essentially, the GP is in charge of their two to 10 patients in the hospital, as well as their normal outpatient family practice. Since Northern Ontario is an underserviced area, this system allows the hospital to function efficiently despite a limited number of general internists and specialists.

My days started at 7.00am at the hospital. I carried out rounds on our patients, presented them to the resident or GP attending on our team, and dictated admission and discharge notes. We then scooted off to the clinic (a quick five-minute drive) to begin our official day at 9.00am. I took annual physicals, performed diabetic checks, well baby checks and mental health reviews, and treated acute and chronic illness. Whenever there was an issue with a patient on the wards in the hospital, their nurse paged us directly. My attending gave an oral order and we followed up with the nurse after clinic. When a new patient was admitted to our service, I was sent to the hospital to take their admission history during clinic hours, and my attending went to see the patient at the end of our day. Our clinic finished by 5.00pm. Sometimes, the afternoon was used solely for newborn circumcisions. Prior to this elective I was unaware that circumcisions could be performed by family physicians outside of a hospital setting, so this was a novel experience for me.

Since Northern Ontario is an underserviced area, this system allows the hospital to function efficiently despite a limited number of general internists and specialists.

Aerial shot of North Bay Regional Health Centre.

North Bay Regional Health Centre entrance.

Tailoring practice

My GP supervisor had one day off per week. He would usually spend this day (or night) completing a 12-hour shift as the sole physician in the emergency department of a small community hospital in Sturgeons Falls (a 40-minute drive outside of North Bay). As an experienced GP in a rural Northern community, he had the luxury of tailoring his practice to suit his exact passions and preferences.

The most striking aspect of completing a family medicine elective in North Bay was the unique opportunity of being both a hospitalist and a general physician. We had one patient who really left a mark with me. She was a 92-year-old female who presented to our clinic, frail and pale, with undiagnosed rectal bleeding, and we proceeded to admit her to the hospital right away. In fact, my attending deemed this to be an acute situation, and in order to streamline the process he called the emergency department and the ward to confirm that there would be a bed for her. When I visited her during rounds on the following morning, she could hardly open her eyes. I managed her care every day by following up on issues that occurred overnight, performing daily histories and examinations, writing progress notes, ordering investigations to find the source of bleeding, and counselling this patient and her family. Over the course of two weeks she became stronger and brighter. It was rewarding for me to see this patient back at her healthy baseline on her day of discharge, and an even more fulfilling day when she returned to our clinic the following week, cheerful and bright, for her outpatient follow-up at the family practice. Since this patient's GP (and his medical student) acted as her family doctor and hospitalist, she received an individualised management plan and had the benefit of a longitudinal form of care.

The most striking aspect of completing a family medicine elective in North Bay was the unique opportunity of being both a hospitalist and general physician.

I realised that the complete continuity of care that the hospitalist/family physician scheme provides is holistically satisfying for both the physician and patient. Completing a family medicine elective in Northern Ontario was a uniquely rewarding experience. The exclusive opportunities, kindness of all staff and peaceful community surroundings lead me to encourage all students to seek this elective.

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MICHAEL BRAVO saw that calm heads prevail in the stormy atmosphere of a trauma ward while on an elective in Canada.

AVOIDING PANIC, EMBRACING PROTOCOL:

an elective experience in trauma

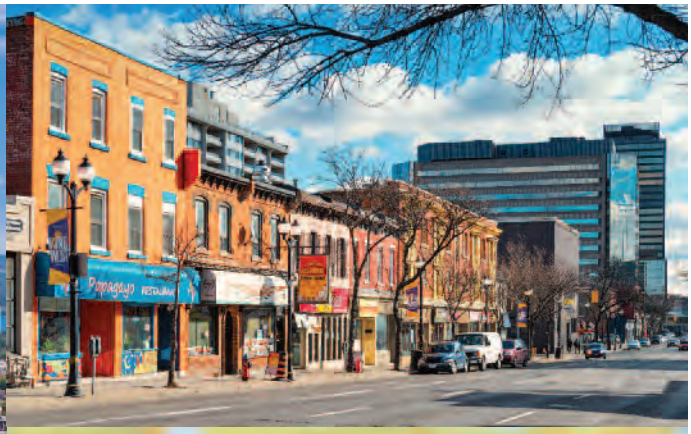
Your basic life support (BLS) course instructors never describe what actually happens to the patient when you perform CPR. The sounds of the compressions, the uncontrolled, almost guttural breathing, or the blank, unfocused stare – these are all things that you cannot imagine and can only experience. It is not until you have started your rhythmic pumping and come to be in the moment of the resuscitation that the scenario becomes real, becomes tangible. I will never forget standing over an 87-year-old woman who had just been in a horrific car crash, pumping her chest furiously while two nurses and three other doctors were doing their best to keep her alive. My experience on a month-long trauma rotation at Hamilton General Hospital in Hamilton, Ontario, Canada last August was eye opening, not only because of the pathologies that I saw, but also because of how visceral the medical experiences were.

Trauma relies on a single person

Inevitably, we students witness difficult moments in medicine while on our school rotations – whether it is breaking bad news, dealing with an angry or combative patient, or seeing patients in their most vulnerable and sensitive states. However, a trauma elective forces you to see all of these moments simultaneously, while under tremendous pressure to save a life. It forces you to push aside your own incredulity, to identify the incongruity between your skill and the demands of the patient, and to embrace the immediacy of the medicine involved. Trauma relies on a single person to guide a diverse team and force control on a chaotic scenario, like Tolkien's proverbial ring, controlling the maelstrom of activity that ensues when a difficult case rolls into the resuscitation (resus) bay. During these acute care rotations, including ICU and emergency medicine, you come to appreciate that leader who embraces protocol, has a superb handle on their medical knowledge, and has an uncanny ability to inspire confidence.

I will never forget standing over an 87-year-old woman who had just been in a horrific car crash, pumping her chest furiously while two nurses and three other doctors were doing their best to keep her alive.

I was lucky enough to observe some fantastic trauma team leaders. They prioritised different issues and used their understanding of physiology to stabilise patients so we could get them to the CT scanner and identify the major clinical issues. Having a clear, calm, focused demeanour in the trauma room is essential, and with repeated exposure to the same sort of



scenarios, pattern recognition takes over. This is what saves you from the chaos that can occur in a trauma ward – having a clear approach based on a set of guidelines (like the advanced cardiac life support (ACLS) protocols) allows you to react instinctively, anticipate the next steps, and prevent a lot of human error. As a student, your approaches to different traumas become more stereotyped, providing a sense of relief and confidence in controlling the situation. It allows you to focus on the next node in the sequence and consider all the other consequences of what has happened. In short, as unpredictable and unique as each trauma can be, having a general approach, combined with all the skill and techniques of your team, can literally save lives.

As ordinary as it is extraordinary

As much as I paint this elective as one of shock and awe, all of the regular components of a medical rotation were present. We did rounds every morning, assessed the patients' progress and adjusted their care until we were able to transfer or discharge them. We co-ordinated with other teams to get the best services for the patient. We discussed the care with the patient, their family and the healthcare staff. We had teaching opportunities and overnight call. But what I will take away from this elective is the importance of having a simple and poised approach, a strong handle on basic medicine and, above all, an ability to communicate in any situation.

During these acute care rotations, including ICU and emergency medicine, you come to appreciate that leader who embraces protocol, has a superb handle on their medical knowledge, and has an uncanny ability to inspire confidence.

The way you develop these skills is unique to North American electives compared to one in Ireland or the rest of Europe, because of how the student is integrated into the team. You are an active care provider – you perform the primary, secondary and tertiary exams; you write the note or speak with the patient; you are the one doing the chest compressions or inserting the chest tube.

The active nature of these North American electives is essential for your learning – active learning forces a synthesis of knowledge and skill that improves your understanding and becomes an integral and valuable part of your education.

I urge you all to consider trauma, emergency, ICU, or any of the acute care rotations for your next elective – you will gain a new appreciation for your profession and perhaps, like me, even find your new favourite specialty.

Collaboration is key

Pharmacy students JENNIFER HOWELL and GRAHAM ENGLISH experienced inter-professional collaboration between pharmacists and physicians in the US, and ask if this can make a difference to patient outcomes.

Spending three months in East Tennessee State University in the Bill Gatton College of Pharmacy as part of an Erasmus+ programme allowed us to experience first hand the impact collaborative care has on improving patient outcomes. Inter-professional collaboration, at its core, involves acknowledgement of different healthcare professionals' skill sets and expertise, and has been shown to contribute to a more efficient and advanced healthcare system, which we saw first hand in ambulatory care clinics and hospitals in Tennessee.[1]

Our experience made apparent the impact a pharmacist can have on optimising and improving patient outcomes when directly involved in patient care as part of a wider healthcare team. The specialised knowledge of the clinical pharmacist was drawn upon by physicians when working in tandem to aid prescribing and medication queries, which not only freed up valuable clinician time, but also allowed the patient to receive more in-depth counselling and medication advice. We were exposed to numerous clinical rotations such as acute care, industrial pharmacy, emergency medicine, paediatric medicine and ambulatory care. In particular, ambulatory care settings facilitate patient-centred care through anticoagulation clinics, diabetes clinics, pharmacotherapy clinics and transitional care clinics. The pharmacist provides vital support to physicians during each of these clinics by delivering key clinical advice.[2]

Impressive

The presence of pharmacists in ambulatory care clinics has been correlated with improvements in mortality, drug costs, cost of care, and length of stays. The rate of medication errors has also been shown to decrease as the ratio of pharmacists to patients increases.[2] We were impressed by how these clinics also give the patient a chance to discuss medication-related issues, which may not always be possible in a busy community environment. We experienced first hand how working in partnership with physicians allowed the pharmacist to directly tailor drug therapy and offer suggestions to maximise care for each individual patient. From our experience, pharmacists in Ireland generally liaise with physicians in relation to changes or queries regarding drug therapies, which can often lead to negative interactions. We personally witnessed how these communication barriers between healthcare professionals can be broken down when working in collaboration, thus improving inter-professional relationships. This inter-professional approach of delivering healthcare has a spectrum of benefits and has been shown to:

- improve patient outcomes;
- identify reasons for treatment failure and non-compliance;
- free up valuable physician time; and,
- reduce costs relating to pharmacotherapy.[3]

Our experience in ambulatory care gave us an insight into how we can advance the delivery of healthcare in Ireland and make the process more efficient for both patients and healthcare professionals. Even as student pharmacists, we were trusted to carry out medication reconciliations with patients, counsel patients on any existing or new drug therapies, and offer suggestions, in collaboration with physicians, as to how to maximise patient care. These rotations, although initially challenging and intimidating, afforded us the opportunity to develop our confidence and knowledge as student pharmacists and future healthcare professionals. It was during transitional care clinics that we really felt the pharmacist's expertise and presence were of most value. The period where a patient is

Clockwise from top left: Graham and Jennifer at Franklin Woods Community Hospital; our day in the simulation lab, where we were given a crash course on how to intubate patients, do CPR and take blood; taking a patient's blood pressure reading during a transition of care clinic.

discharged from hospital and is transitioning back into the community is where medication errors are likely to occur. Working alongside clinical pharmacists in this setting, we saw how steps in this transitional process that cause errors are identified, and how the pharmacist can act to offer suggestions regarding alternative drugs, discontinuation or commencement of therapy, along with any necessary dose adjustments to reduce such errors. The pharmacist's expertise lies in the field of medication and they are at an advantage to identify potential scenarios where medication errors may arise. This allows the pharmacist to intervene accordingly to prevent such errors while working alongside the physician.

Many hands

As William Mayo stated: "As we men of medicine grow in learning we more justly appreciate our dependence on each other".[4] Patient care should not be placed into the hands of any one healthcare professional, but should be distributed among the different healthcare professions.

We experienced first hand how working in partnership with physicians allowed the pharmacist to directly tailor drug therapy and offer suggestions to maximise care for each individual patient.

These clinics are successful because they lead through excellence, collaboration and innovation, something we feel the Irish healthcare system could greatly benefit from. This model of care has proven to have a wide range of benefits as illustrated here, and in Ireland it is past time that we make efforts to transition towards and adopt this evolved healthcare approach. As well as allowing us to grow professionally, our time in East Tennessee has allowed us to develop many personal relationships with new friends in multiple disciplines who truly made this experience golden.

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RCSI Perdana students THEEVIYA MANIVANNAN and KHOO YING YIN spent their elective in Dublin.

East meets west

From left: Mr Madhavan, Head of Department of Vascular Surgery; Khoo Ying Yin, RCSI – Perdana student; and, Theeviya Manivannan, RCSI – Perdana student.

In the summer of 2016, we travelled from the RCSI Perdana University in Malaysia to Dublin, to complete an elective with the vascular surgery department of St James's Hospital, which is affiliated with Trinity College Dublin. Coming from the tropics, the Irish weather definitely took getting used to. Imagine our astonishment at the sudden change in temperature from 30 degrees Celsius to 10!

To begin our placement, we met with the head of the department of vascular surgery and were briefed about the team's dynamic. Everyone in the team worked closely together – the surgeons, physicians, nurses and lab technicians would regularly meet and collectively discuss patients' needs. We learned that every role carried equal weight for the benefit and well-being of the patient. To date, this is one of the most valuable lessons we have brought back home with us. The idea of multidisciplinary team (MDT) work is usually easier said than done – back home, although MDTs exist in patient care, doctors often bear the burden alone of making the ultimate decision in relation to the patient's care. This is not always what is best and we believe it is high time we moved away from such totalitarian traditions.

Everyone in the team worked closely together – the surgeons, physicians, nurses and lab technicians would regularly meet and collectively discuss patients' needs.

Busy schedule

Despite being a busy unit, every member of the team was willing to invest their valuable time in doing some teaching along the way. We spent at least eight to nine hours daily in the hospital. Our schedule consisted of following the daily ward rounds, attending surgeries, and joining the clinics. We had surgeons explaining techniques and giving clinical insights to complement our theoretical knowledge. We also had wonderful nurses teaching us practical aspects of patient care, namely wound care and dressing.

Days in the theatre sometimes lasted 12 hours or more. We had the opportunity to observe numerous surgeries, i.e., endovascular abdominal aortic repair (EVAR), carotid and femoral

Khoo Ying Yin, RCSI – Perdana student, at St James's Hospital in Dublin.

endarterectomy, femoral bypass, and construction of arterio-venous fistulas, to name a few. The endarterectomy procedures were by far the most amazing examples of vascular "artwork" we have come across. The intricacy of the surgeons' dissection of the vessels, removing the plaques, and suturing vessels were beyond both our imaginations. We also learned that the vascular unit in St James's was one of the few in the region that has the expertise in debranching and revascularising the aortic vessels during an abdominal or thoracic aneurysm repair.[1] Being able to experience all of these made us look at vascular surgery in a different light. It is safe to say that this observership has set us thinking about embarking on a career in this specialty! The veins unit on Tuesday mornings had a specialised setting whereby varicose vein surgeries were done on an outpatient basis. It was the first and only unit in Ireland dedicated to such practice, which was not only cost-effective but also convenient for the patient. Back in our home country, our vascular units do not run such specialised services, which we believe would definitely be of benefit to implement.

Patient care

One of the most striking incidents we witnessed in one of our sessions in the outpatient department was when a consultant broke bad news to an elderly patient. He laid out the risks and benefits of proceeding with surgery and gave his opinion on how surgery was not always the best option. At that point, we witnessed the patient break down as she came to terms with her situation. We appreciated the surgeon's ability to walk the patient through it, and the experience highlighted for us the importance of effective communication. His calm and straightforward demeanour did not downplay his portrayal of empathy, which is often an overlooked but essential component in breaking bad news. The patients we saw presented with a range of conditions that are more common in Western society than we would come in contact with in Malaysia, including abdominal aortic aneurysms, coeliac disease and cystic fibrosis. It was an excellent opportunity for us to understand and see for ourselves how such diseases are managed. In fact, these diseases come up frequently in our syllabus and all we could ever do previously was to imagine them. In Malaysia, pulmonary tuberculosis and other tropical diseases are readily encountered on a day-to-day basis; having this opportunity felt like we were given the best of both worlds in terms of learning.

We also learned that the vascular unit in St James's was one of the few in the region that has the expertise in debranching and revascularising the aortic vessels during an abdominal or thoracic aneurysm repair.

All in all, the whole experience was invaluable and too short for our liking, especially given the travel and cultural experiences we had during the weekends. August 5, 2016 marked the end of our attachment at St James's. Given another occasion, we would definitely embark on this adventure again.

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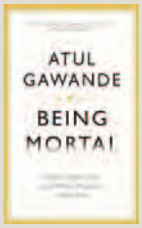
A modern *Ars moriendi*: medicine and mortality

Two moving books inspired DANIEL O'REILLY to consider death both as a doctor and as a human being.



Being Mortal: Illness, Medicine and What Matters in the End
Atul Gawande
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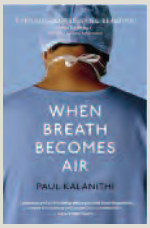

When Breath Becomes Air
Paul Kalanithi
Paperback: 256 pages
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Published: 2017
ISBN-13: 978-1784701994

'*Ars moriendi*' or 'the art of dying' was a 15th century text that gave advice on how to achieve a 'good death'. It is a product of its time, published following the Black Death and in an era when a reasonable life expectancy was in the 30s. A long period of time has obviously passed since its publication, with the Renaissance, the Enlightenment and industrialisation fundamentally changing how the average person relates to death. Unlike the general population, for whom death has become an increasingly abstract concept, death, dying and care of individuals in their final years has increasingly become part of a doctor's workload. Medical students are faced with mortality from their first tentative cuts on a cadaver in the anatomy department, to encountering terminally ill patients in hospitals, to treating the actively dying. So in the 21st century, what constitutes a 'good death'? Two recently published books hope to address this question, engaging the reader on what it means to care for the dying and how we must inevitably face our own mortality.

Being Mortal

Being Mortal – the latest book by Atul Gawande – examines our care of the elderly and dying. Initially exploring this from a purely professional standpoint, the book begins with a visit to a geriatrician's office and meanders through various anecdotes outlining the alternatives to traditional nursing homes and how they were developed. These are informative and touch on such concepts as the infantilisation of the elderly and problems with the current conventional models of residential care. As the book develops naturally from this point to hospice care and care of the dying, Gawande describes his own experience of death, first with his grandfather and his care in his twilight years and eventual death, and finally through his father's diagnosis of terminal cancer. Through the lens of his father's treatment and eventual death, he examines how he relates to patients on such issues as life-limiting illness and emphasises the importance of communication in the care of patients. He concludes with his vision for the future of both care of the elderly and the dying.

When Breath Becomes Air

When Breath Becomes Air by Paul Kalanithi is a personal account of a neurosurgeon's battle with terminal illness. While *Being Mortal* offers an outsider's perspective on how we can do better while caring for people at the end of their lives, this book offers the author's own personal struggle with his identity as he is diagnosed with stage IV lung cancer.

He recounts his life until his diagnosis at 36, including his love for literature, which initially led him to pursue a master's degree in English before returning to medical school, and how throughout much of his education he tried to balance the 'truths' of both biology and literature to discover what it means to be human – and what it means to die. It is a profoundly moving book, which is made more powerful in that it was finished by Lucy Kalanithi, the author's wife, as he passed away before completing the manuscript.

So what do we learn from both of these books? As doctors in training, we will be exposed to death in various forms, be that the personal loss of loved ones or through the passing away of patients under our care.

As someone fortunate enough to live with someone who works in a hospice setting, both books remind me of something I get told regularly after particularly tough days: "There is a lot of living in dying". This is underscored in both of these books, from Paul Kalanithi's description of his relationship with Lucy and the decisions which faced them: to have children; how to provide for her future and his present; and, in a larger sense, what his values were.

Similarly, Gawande's final months with his father are explored in detail as he underlines the change in their relationship following his diagnosis. Ultimately, both books remind us that death is inevitable, and perhaps the secret to a good death is how we incorporate that knowledge into our lives.

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