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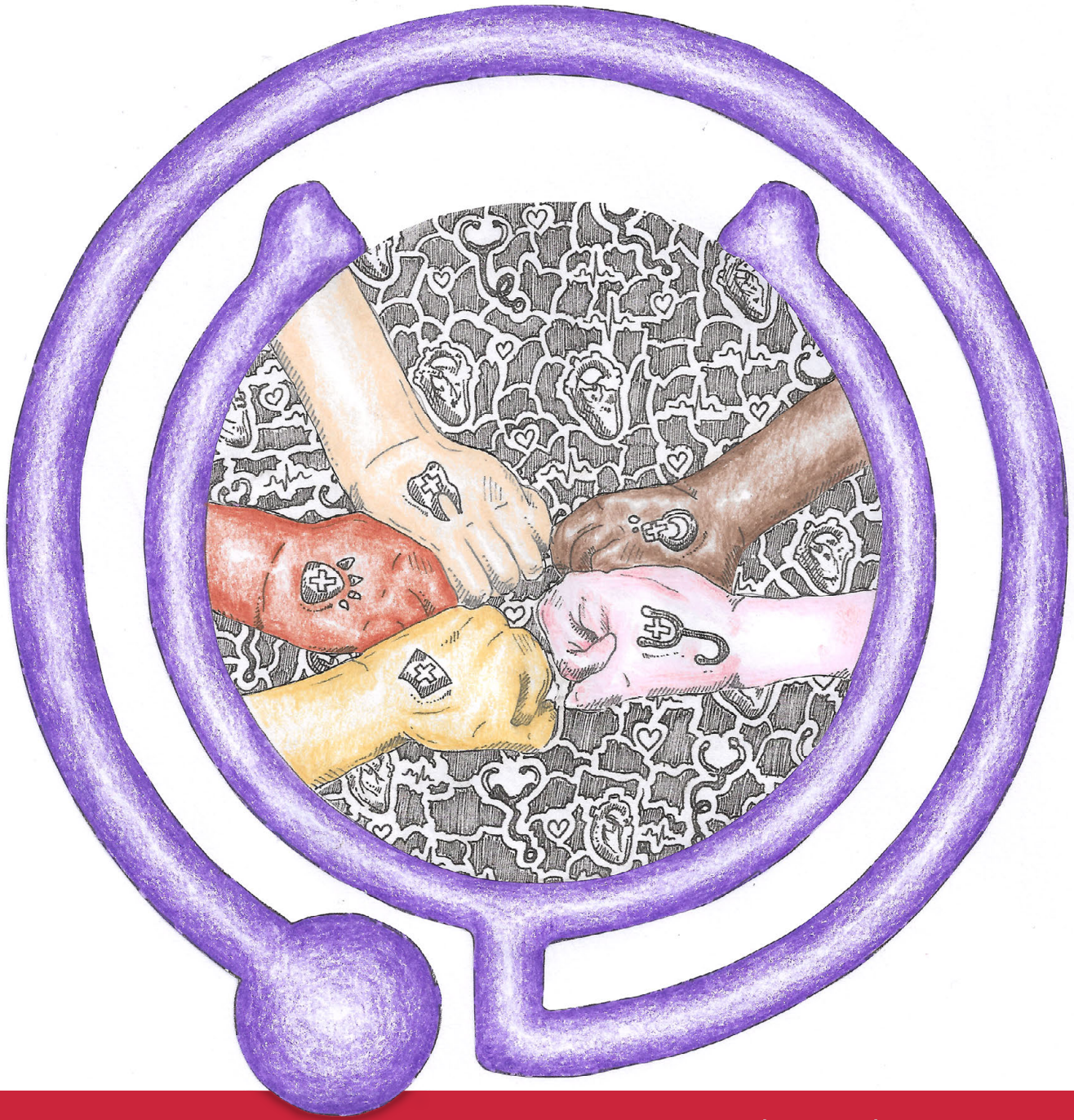

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Student Health Sciences Research Journal

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Welcome to the Autumn 2020 issue of the INSPIRE Student Health Sciences Research Journal: created by students for students

Hello again! 2020 has brought about lots of change for many of us, and the INSPIRE Journal is no exception. Despite having to adjust to the many challenges that this year has thrown at us, our authors have continued to provide us with some fantastic content. This has meant that, for the first time since the journal was created in 2015, we have been able to produce not one, but two issues this year. So, following on from our Summer issue, we are happy to present a further 22 articles for you to enjoy!

Having evolved as part of the INSPIRE scheme, which aims to provide students in medical schools across the UK with an opportunity to take part in research and to encourage them to incorporate research into their chosen career path, the INSPIRE Journal was created to give medical, dentistry and veterinary students a chance to experience an important part of research: the publishing world. From the authors and peer-reviewers to the editorial board and cover design, every element of this issue has a student behind it – making this a true student journal!

With topics across the medicine, dentistry and veterinary science disciplines, we have really enjoyed working on all of the articles in this issue and have learnt from each and every one of them. For example, were you aware of the role that exosomes play in breast cancer invasion and metastasis? Or have you heard of the 'Horse Boy' method, in which horses are used therapeutically to treat children with autism and neurocognitive conditions? Perhaps you are interested in the efficacy of chlorohexidine-containing gels for periodontitis management, or wish to learn more about how behavioural traits can be used to identify sub-clinically ill cattle from healthy cattle? You can find out about these topics and more inside of this issue! In addition, please don't forget to check out our blog pieces at **www.inspirestudentjournal.co.uk/resources**.

As the new academic year is beginning, and we welcome back old students and new ones too, we really hope that this Autumn issue will motivate individuals across all health sciences disciplines to really think about how you might integrate research into your studies and future careers. Ultimately, we really hope that you enjoy reading this issue of the INSPIRE Journal!

Best wishes,

The INSPIRE Student Health Sciences Research Journal Senior Editors

FRONT COVER

The central image of the cover represents the interconnection between the three healthcare disciplines (medical, dental and veterinary sciences), whilst encompassing the diversity of student culture, background and career aspirations. The black and white background was originally designed as part of an SSC project by Hannah Walter.

Cover credit:

Concept: Hannah Walter (Year 2, Medicine, University of Plymouth) and Nirmal Jayakrishnan (Year 3, Medicine, University of Plymouth)
Design: Hannah Walter

Contents

The strengths and weaknesses of whole-genome sequencing

Emily Ferguson
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Introduction

Recent advancements in genetics have increased our DNA sequencing capabilities. The sequencing of the whole genome has become more commonplace, primarily due to the development of next-generation sequencing (NGS).[1] NGS platforms sequence millions of fragments of DNA in parallel, allowing the entire genome to be sequenced at once.[1] Bioinformatics piece these fragments together using the human reference genome.[1] In this way, the nucleotides in the human genome are sequenced multiple times, providing accurate data much quicker than previous methods.[1] This technology can also be used to sequence the protein-coding region of the genome (the exome), which is called whole-exome sequencing (WES).[1] Both of these methods have led to breakthroughs in genetic research, allowing diagnoses and extending our knowledge of disease mechanisms and potential therapeutic targets.[2] This article seeks to discuss the potential benefits and challenges associated with the use of whole-genome sequencing (WGS).

Advantages

The most obvious advantage of WGS is that the entire genome is scrutinised. This means that, in one test, every single variant in the genome is identified, whether small (a single nucleotide variant) or large (a copy number variant or translocation).[2] This information is incredibly valuable and could identify a monogenic disease, for example, thalassaemia, or could identify a predisposition to developing a polygenic disease, such as type 2 diabetes mellitus.[3]

WGS can be used to diagnose genetic mutations that would affect a particular individual, but it could also act as a screening tool that could allow identification of genetic carriers of recessive diseases, such as cystic fibrosis.[3] This could aid family planning by encouraging partners to be fully tested, and would allow future parents to receive genetic counselling or even pre-implantation genetic screening.[4]

The first ever genome cost 2.7 billion US dollars to sequence, but with the advent of NGS, the cost continues to plummet and it seems possible that, in the future, it will cost less than $1,000 per genome.[5] Despite the obvious cost associated with this, many would argue that the identification of disease and disease risk could save money in the future.[6]

Although not commonly used in clinical practice, WGS in cancer research could allow the identification of genetic drivers of tumours and new biological therapies.[7] However, NGS means that WGS can be provided in a clinical environment due to reduced cost and time frame. If the results can be provided within a clinically relevant time frame, it could have an impact on a patient's cancer management.[7] This is called 'precision oncology'; if WGS can be used to genotype cancer cells, we can ascertain which genes have become mis-regulated and provide a more personalised treatment plan.[7] Non-small cell lung cancer is an example where molecular profiling of the tumour has been proven to be key in order to provide the optimal treatment plan for each patient.[8]

Disadvantages

The major difficulty associated with WGS is the sheer mass of information provided, which must be analysed and assessed to determine what is important or what is not.[9] Although our knowledge in genomics is growing, the roles of many genes are still undetermined and huge numbers of variants across the genome have not yet been distinguished as being benign or pathogenic. This means that, although WGS can produce a large volume of data, most of this may be misleading or useless.[9]

The large amount of data produced by WGS will not only need to be analysed, but it will also need to be stored. This in itself raises some challenges, not limited to the large capacity and cost required for this, but also to the privacy of data, which could raise ethical dilemmas with insurance companies and family members.[10]

WGS may uncover unsought secondary findings; it may reveal a diagnosis of a genetic condition that is untreatable and may not present itself for many years, such as Huntington's disease.[3] This could have a negative psychological impact on the individual and also on family members.[3] It could affect family relationships, as other family members may not want to be aware of such information whilst others would rather know. In addition, it raises the question of which, if any, results should be disclosed to a patient.[3]

Is there already a solution?

Many researchers have turned to WES to overcome some of the challenges of WGS. WES is a more cost-effective method because only 1% of the entire genome needs to be sequenced and over 85% of the mutations are located here.[11] It also means there are fewer variants of unknown significance detected and requiring analysis. WES has already been used successfully to locate genes in which variants can increase the risk of breast and colorectal cancer.[12,13]

However, it can be difficult to detect structural variants using WES, and researchers have found that DNA variants outside of exons, which would only be picked by WGS, can be pathogenic. Not only this, but it is difficult to sequence areas of DNA that are rich in GC nucleotides using WES, which can cause inaccurate sequencing leading to both false negatives and false positives.[14] The large number of false negatives produced by WES means all the variants need to be confirmed by Sanger sequencing (a method of DNA sequencing), which is time consuming, wasting valuable research time. [1,14]

Conclusion

Both WGS and WES have their own set of strengths and weaknesses (each outlined in Table 1), not limited to those mentioned in this article. Nonetheless, both are valuable research methods and will undoubtedly be used to translate the variations between individual human genomes into medically useful information.[14,15]

Table 1. WGS vs WES.

Advantages	Disadvantages
WGS	
Detects both coding and non-coding variants	High cost (currently around $1500 per genome)
Detects structural variants	Huge volume of data to process and store
	Genetic variants need validation using Sanger sequencing
	Variants of unknown significance: limited knowledge to fully understand the implication of each variant and huge numbers of variants (~ 3.5 million) can be found in non-coding regions, which could be relevant or not
WES	
Only around 20,000 variants to analyse	Difficult to detect structural variants
Reduced cost	Sequences only coding DNA
Less data produced so less to be filtered, researched and stored	Difficult to capture sections of DNA with a high GC nucleotide percentage, leading to false positives and negatives
	Genetic variants need validation using Sanger sequencing

Table based on data from[14,15,16]

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Interview

Success in academic primary care: interview with Dr Matthew Ridd

Reader in Primary Healthcare, Bristol Medical School

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Despite his relaxed appearance and no-shoes-at-work policy, Dr Matthew Ridd is a busy GP, researcher and lecturer at the University of Bristol, specialising in skin problems and patient–doctor relationships. His down-to-earth approach and enthusiasm for teaching has seen him supervise numerous successful INSPIRE award recipients, all of whom now have publications and conference presentations to their name.

How did you first get into research?

The truth is: by accident! As a student, I hadn't set out to intercalate, but there was an opportunity to do a funded BSc looking at T-cell signalling. Academic medicine wasn't on my radar at all as a medical student but I actually really enjoyed it and made me think, 'yes I really like the clinical life, but I also like that different mode of thinking, that time to think about one thing in depth'. I had some success with getting data, an abstract, published and haven't looked back since then really, moving from one opportunity to another!

What do you love most about your job as a clinical academic?

- Variety
- Flexibility
- Making a difference

Variety is definitely one! For example, over the course of the last few weeks I've been to conferences, treating patients, teaching, examining, supervising students and writing up research. Another is the flexibility; for example, if you have a paper that needs writing in 6 months' time, you can decide if you're going to write it now or in 5 months; so you can go with your own style of working.

But an important one is the feeling of making a difference; it's probably a reason a lot of us became doctors. Someone once said to me, "doctors who work 30/40 years will change thousands of lives over their career, one patient at a time. If you teach, you'll probably be helping hundreds of thousands of lives because you're teaching the future doctors. But if you do research, potentially it's millions of lives". Of course, most of us won't find the cure for cancer, but we'll all be contributing to the knowledge base and, hopefully, change things for the better.

What are the difficulties of a career in research?

It's definitely not an easy career option but you need to think of it in terms of the long game. It probably is tougher earlier on, getting your clinical career and postgraduate exams sorted whilst fitting in the academic work alongside. But if that research really is what you're interested in, then that will help you to be happy as a doctor on your clinical days. You've got 30/40 years of working life to enjoy so it is a long game. That's true of the research too. If you have a great idea today, it might be 5 years before you get funded, results published and clinical practice changed. It's a different time scale to clinical practice, where you get more short-term wins, but the rewards of research can be greater, just with a longer wait.

Why do you enjoy supervising INSPIRE students?

I enjoy it since all medical students are clever and bright, so, from the get-go, they already bring lots of skills and knowledge. Whilst I get to teach students through lectures, often INSPIRE is an opportunity to have a slightly longer-term relationship. What's great about INSPIRE projects in particular is the chance for students to develop and get their head around research whilst having ownership of a project.

> *Someone once said to me, "doctors who work 30/40 years will change thousands of lives over their career, one patient at a time. If you teach, you'll probably be helping hundreds of thousands of lives because you're teaching the future doctors. But if you do research, potentially it's millions of lives".*

Your past INSPIRE students have gone on to publish, present at international conferences and win distinguished prizes. What's the secret to the success of your INSPIRE students' projects?

Their success may be no reflection on my supervision whatsoever! I think all medical students are very capable individuals, so it's ultimately about them and support from schemes like INSPIRE. It's a bit of a marriage of interest; if someone comes to me saying they're interested in eczema, I've got the topic knowledge to help guide that into an achievable project. Otherwise, it can be quite difficult if a student has an interest in a disease but they're not quite sure

where the research need is, and to know where they can fit into that, particularly if you've only got a 3–4 week project.

I see it as a symbiotic relationship because students get something out of it, like a presentation or publication, that will stand them in good stead when applying for clinical jobs. Whilst, for me, it's an opportunity to do bits of work which helps move my thinking on or support a bigger piece of research.

Would you be happy to host students for INSPIRE days/projects in future?

Of course!

Contribution statement JC conceived the article idea, undertook the interview with Dr Matthew Ridd, edited the piece into the required format and revised it following peer review. JC and Dr Matthew Ridd both provided final permission for the article to be included in the INSPIRE Student Research Journal.

A reflective account of a dental elective in Pokhara, Nepal

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Introduction

Dental electives have an impact in the communities in which they take place and also hold value for the students, both academically and personally. The aim of this account is to reflect on our visit to Pokhara, Nepal, and the opportunities that accompanied this, whilst discussing the differences between dental practice and dental health in the UK and Pokhara.

Why do an elective abroad?

Alongside observing the differences in dental diseases and practices, the travelling aspect of an elective abroad encouraged us to gain independence. For example, we were forced out of our comfort zones by immersing ourselves into a new environment with language barriers and cultural differences. Consequently, we feel that we are now more confident in our practice and when we approach colleagues in the dental profession, regardless of communication difficulties.

Additionally, we had the opportunity to meet other healthcare students from all over the world in the elective accommodation. This has led to long-lasting friendships, as we explored the city together and created memories. Furthermore, we had the opportunity to learn about each other's exciting experiences in the hospital, discovering how hospital care is carried out in different departments.

Why did we pick Pokhara?

Pokhara is situated in the Himalayas, which provided stunning scenery and trekking routes, making our experience even more memorable **(Figure 1)**. The people and the city are extremely welcoming.

Figure 1. View from the Work the World accommodation.

We decided to undertake our elective for 2 weeks in Manipal Teaching Hospital in Fulbari, Pokhara, Nepal, through Work the World, a company that organises healthcare-related electives. Manipal Teaching Hospital has 750 beds in order to provide tertiary care to all members of society.[1]

This placement specialised in maxillofacial surgery, which allowed us to witness rare dental diseases that are uncommon in the UK. According to the 2009/2010 Annual Report by the Government of Nepal's Ministry of Health and Population,[2] in Nepal 392,831 citizens suffer from dental decay or toothache. In addition to the 73,309 suffering from periodontal diseases, 62,747 have other tooth disorders and 113,819 have oral ulcers, mucosal lesions and other related diseases.[2] These statistics are significantly higher than in the UK.[3] Through this placement, we believe we made an impact by contributing to the treatment of dental diseases within the community.

What we saw and learned

We were overwhelmed by the contrast in the way that care was provided at the hospital, as compared with the UK. The first thing we noticed was the lack of cross-infection control in a particularly small working environment. There were three active dental chairs in a small room **(Figure 2)**, with the dentists sharing burs and endodontic files between patients. This was particularly shocking for us as these are single-use instruments in the UK.[4] We had to accept that this was the norm in the practice in Nepal due to a lack of funding.

Figure 2. Three-chair dental surgery.

As our entire UK curriculum is centred around prevention,[5,6] we were surprised to witness the drive for intervention of dental disease over any preventative measures. In addition to this, the intervention was only provided once the patient had paid the full fee, regardless of the pain or extent of infection. This was upsetting for us, as we struggled to turn away patients in pain; this would not happen in the NHS.

Moreover, the importance of communication with the patient was overlooked and no shared decision making was carried out. We considered this to be old-fashioned dentistry and were taken aback by the lack of discussion about treatment and the risks involved. This seemed foreign to us as we are expected by the General Dental Council (GDC) to carry out patient-centred care and to gain valid, informed consent.[7]

With regards to the maxillofacial department, we were fortunate to witness 'textbook' diseases that we would not frequently see in the UK. Some examples, which were significant to us, were a buccal space infection, a haemangioma of the tongue and trauma.

The buccal space infection was caused by a self-conducted extraction of two molars using a screwdriver under no anaesthetic. This patient resided in a remote village and they could not afford to attend the hospital to have them removed. We were stunned by their circumstances and it was distressing to see the extent of their pain and learn of the financial burden caused by having to pay for a hospital bed. However, from this, we had the opportunity to help the consultant drain the buccal space infection over several days, which meant we were able to see the patient's improvement throughout our time there.

Furthermore, we had the chance to be present in the operating theatre whilst the excision of a haemangioma was carried out on a child **(Figure 3)**. This enabled us to witness the entire surgical procedure from start to finish, including general anaesthetic administration and follow-up care. This was something we could not have predicted we would have the opportunity to observe, but found extremely valuable.

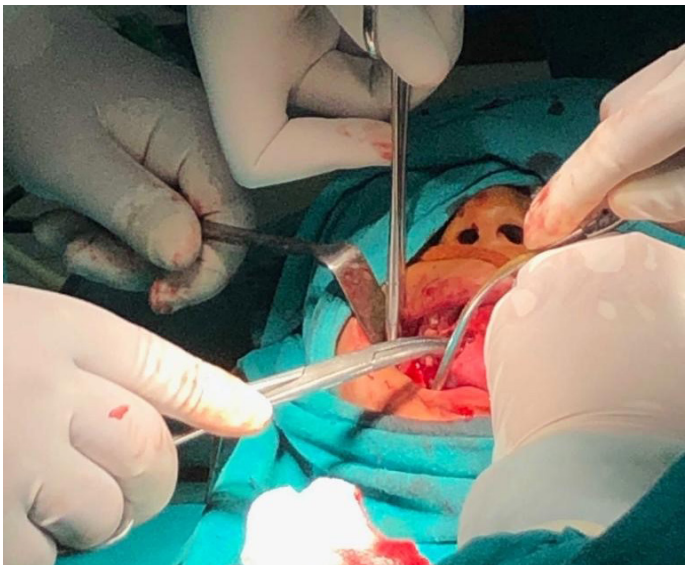

Figure 3. Exclusion of haemangioma.

On our final day of the elective, a patient presented in the Emergency Department with multiple injuries from a road traffic accident. Whilst several consultants were conducting their assessments, we were lucky to closely observe the maxillofacial consultant conducting inter-maxillary fixation openly in the emergency room. This was the most memorable case as we were aware that these injuries are more prevalent in Nepal due to high motorbike use in comparison with the UK.[8,9] As dental students, we rarely encounter procedures like these during our time studying. Hence, observing this was invaluable to our learning as it applied what we only get to learn in theory.

What we took away from the experience

Personally, we both feel that our knowledge, management and problem-solving skills were enhanced greatly by witnessing varying cases; we are now more confident to apply these new skills to our practice, whilst treating patients as students.

On the other hand, the benefits were not purely academic. Travelling to a new country allowed us to mature in multiple ways, such as having the confidence to navigate ourselves in a foreign country. We were also able to completely immerse ourselves into a new culture by learning the language and cooking local cuisine as part of the Work the World scheme.

Conclusion

In conclusion, this experience encouraged us to grow as individuals by pushing us out of our comfort zones and understanding the difference in dental care in a less developed country as compared with the UK. We have noticed the influence on our academic, clinical and personal lives and appreciate that the elective is responsible for these changes.

This account is a reflection of our elective and there is plenty of scope to extend the experience further, such as conducting research on the prevalence of dental disease in the country that you choose to do your elective, or providing care in remote villages.

Therefore, irrespective of where, what and how you conduct your elective, from students-to-students, we highly recommend considering any opportunity to carry out one.

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Review

Does at-home, vital tooth bleaching with carbamide peroxide deliver greater patient satisfaction than treatment with hydrogen peroxide?

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Abstract

Introduction The current increasing demand for tooth-bleaching procedures has led to a variety of products becoming available. This review aims to determine whether treatment with hydrogen peroxide (HP) or carbamide peroxide (CP) bleaching products deliver greater overall patient satisfaction when used for at-home, vital tooth bleaching (on teeth with a living pulp).

Methods Searches were conducted in The Cochrane Central Register of Controlled Trials and The Database of Systematic Reviews; MEDLINE and Embase (via Ovid); Scopus; and Web of Science. Two review authors independently assessed trials for eligibility and the included trials were assessed for risk of bias.

Results Nine RCTs were included. Five of included trials were judged to be at high risk of bias. There was weak evidence to conclude whether at-home, vital tooth bleaching with CP or HP provides greater patient satisfaction. There is some evidence that both CP and HP cause dental sensitivity; however, the degree of this could not be determined.

Conclusions It is advised that dental practitioners ensure patients are fully informed about the risk of side effects of at-home, vital tooth bleaching, including dental sensitivity, in order to manage expectations and provide greater post-operative patient satisfaction.

Introduction

In recent years, there has been an increasing trend in the number of patients seeking cosmetic dental procedures, commonly tooth whitening.[1] This rise could be attributed to the increase in social media usage over the past 10 years, influencing social norms regarding body image and redefining the determinants of what is regarded to be an 'acceptable' dental appearance.[2] The belief that whiter teeth signify a higher social status, improved health and greater beauty could explain the increasing desire for tooth bleaching treatment.[3] This has led to a wide variety of products being available, both over-the-counter and dentist-prescribed, with the most common being carbamide peroxide (CP) and hydrogen peroxide (HP). This has resulted in some uncertainty amongst dental professionals as to which treatments they should be recommending and prescribing to their patients. Here we aim to conduct a systematic review of the literature in this field, to answer the PICO question, 'Does at-home, vital tooth bleaching with CP deliver greater patient satisfaction than treatment with HP?' **(Figure 1)**.

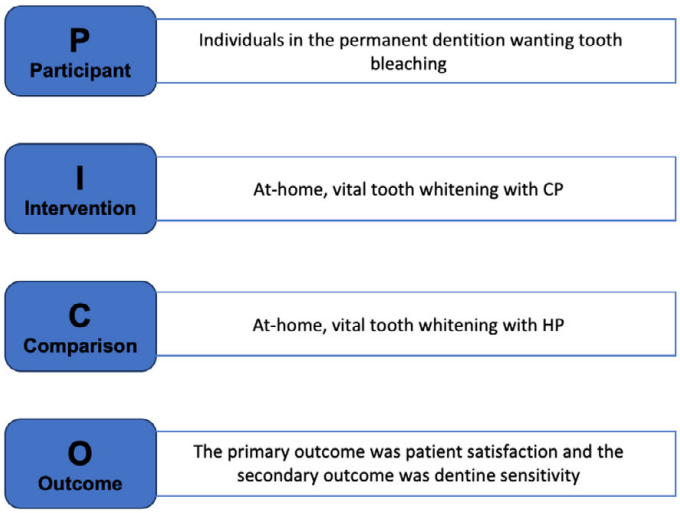

Figure 1. Depiction of the PICO-style question answered throughout the systematic review.

Methods

Searches were conducted in The Cochrane Central Register of Controlled Trials and The Database of Systematic Reviews; MEDLINE on Ovid; Scopus; Embase on Ovid; and Web of Science.

To produce a manageable sample size for this review, search results were limited to include:

- Papers written in English Language
- *In vivo* studies
- Trials published in the last 5 years
- Randomised control trials (RCTs)

Study participants included individuals of any age in the permanent dentition (with adult teeth) seeking at-home, vital tooth bleaching treatment. Studies investigating the effect of vital tooth bleaching on participants with congenitally discoloured teeth, tetracycline staining and fluorosis were excluded.

Nine RCTs comparing the use of HP, CP or both in at-home, vital tooth bleaching were included **(Figure 2)**.[4-12] Two review authors independently assessed trials for eligibility and the included trials were assessed for risk of bias.

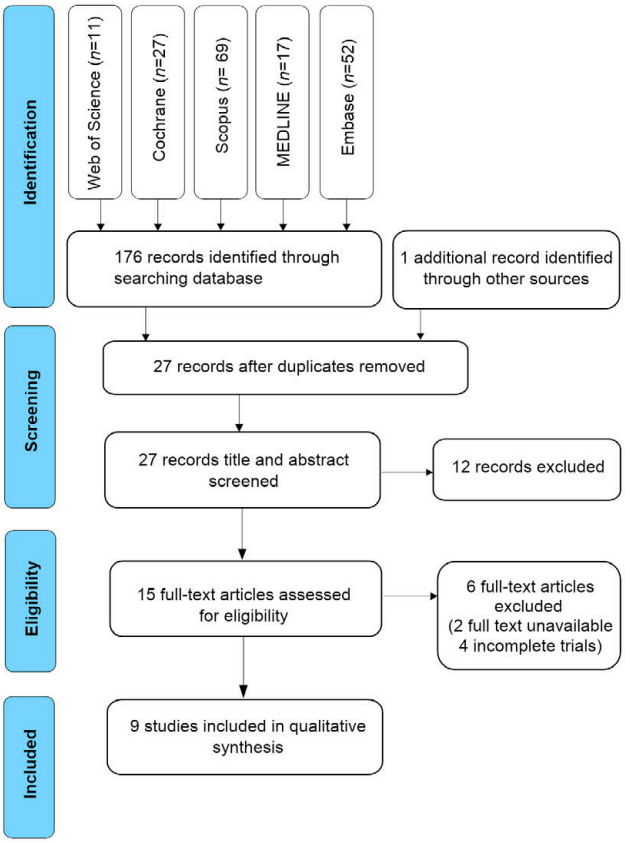

Figure 2. Flow chart of search strategy. A flow chart to show the search strategy used to identify articles with information on patient satisfaction and dental sensitivity following at-home, vital tooth whitening with either HP or CP. The search resulted in nine studies that were further critically appraised.

Results

Nine RCTs were included. Three directly relate to the review question and compare CP with HP, and the primary analysis is based on these trials. A further two assess CP alone and four assess HP alone. Five trials were judged to be at high risk of bias, due to either sponsorship, inadequate blinding or a lack of methodological transparency **(Figure 3).**

Treatment with both CP and HP produced similar results with regard to patient satisfaction. In general, participants were satisfied and accepting of bleaching protocols with either HP or CP, with customised trays (personalised to fit the participant) providing slightly greater satisfaction than stock trays (one-size-fits-all tray) or strips.[6]

Seven studies that directly measured sensitivity found an increase in sensitivity following treatment with both ingredients, with five finding this increase to be significant.[5-7,9-12]

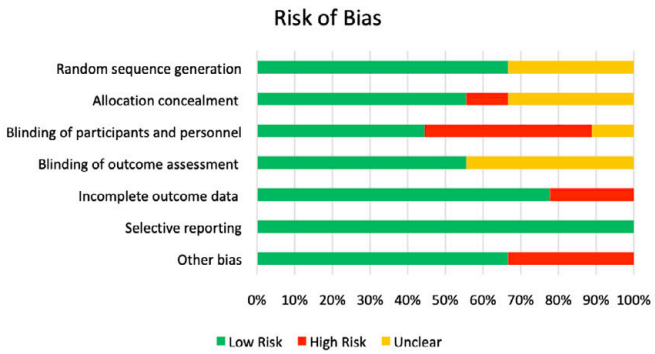

Figure 3. Risk of bias. The graph shows the authors' judgements of each risk of bias category presented as a percentage of all the included studies.[13]

Discussion

With regard to patient satisfaction, there is some evidence to suggest that satisfaction is greater when customised bleaching trays are used compared with stock trays or strips.[6] It appears that treatment with CP more commonly utilises customised trays whereas HP is more often delivered as a strip, and so one could, therefore, infer that the application method generally used for CP is preferred with regard to comfort.

However, despite the level of patient satisfaction, it is important to note that the studies provide a moderate evidence base upon which to suggest that at-home vital tooth bleaching with either HP or CP will lead to a degree of increased post-operative dental sensitivity. However, the intensity and duration of the sensitivity were not explored.

One study reported that, despite treatment with CP improving patients' perceptions of their own appearance, the resulting sensitivity made maintaining oral hygiene measures more difficult.[10] This raises concerns over whether it is ethical and justified to be prescribing treatments that may potentially compromise the oral health of a patient in exchange for improved aesthetics.

Overall, the relative strength of evidence is weak due to a small sample size and each study measuring patient satisfaction differently, hindering the ease with which direct comparisons can be made. Moreover, five trials were considered to be at high risk of bias due to sponsorship by the manufacturers of the bleaching products being tested, as well as inadequate blinding of participants and personnel **(Figure 3)**.

Finally, due to the limited presentation of baseline characteristics of the study participants, we cannot be sure of the degree to which the studies are truly representative of the general population and, therefore, how readily the results can be applied.

Conclusions There is limited high-quality evidence to conclude whether at-home, vital tooth bleaching with CP or HP provides greater patient satisfaction. There is some evidence that both CP and HP cause dental sensitivity; however, the degree to which this is the case cannot be determined owing to inconsistencies in measuring sensitivity and the high risk of bias amongst trials. Therefore, we advise dental practitioners that it is prudent to ensure patients are fully informed about the risk of side effects of at-home, vital tooth bleaching, including dental sensitivity, in order to manage expectations and provide greater post-operative patient satisfaction. Due to the increasing popularity of this cosmetic treatment, further qualitative research is essential to confidently determine the optimal treatment protocol that provides the greatest patient satisfaction with the least side effects.

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Contribution statement Tilly Houston and Hannah Wilkins both analysed the data, wrote the article and approved the final version for inclusion. Both authors are the guarantors of this work.

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Review

Digital dentistry: the revolution

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Introduction

Over the past decade there have been many developments in the world of dental technology. Digital dentistry is the use of technology to either carry out dental procedures or produce materials, minimising the dependence upon mechanical tools. One such example is digital scanning, which has revolutionised chairside dentistry through the use of computer-aided design/computer-aided manufacturing, better known as CAD/CAM. Manufactured by Mörmann and Brandestini, the first clinical device of its kind was the CEREC system.[1] It has enabled clinicians to produce chairside restorations, including crowns, bridges, veneers and implant abutments.[2] The benefits of living in a world of technological advancement means that virtual reality (VR) now has its place within the dental profession. VR enables students to learn anatomy and to treat patients using this 3D technology; the possibilities of VR in training is endless, making it likely that it will be introduced to dental schools in years to come.[3] This article will focus on the technology that is used in dentistry to produce chairside restorations, discussing their longevity as well as exploring the benefits of the CAD/CAM system within the profession.

The CEREC system

The original CEREC 1 system has been modified since the 1990s, making it advanced enough to produce accurate restorations on completion of intraoral scanning, without the use of impression materials or compounds. These scans are subsequently used to design and modify restorations with a virtual wax impression that can be 3D-printed. When designing the restoration, the software is able to scan the dentition and determine the anatomy adjacent to the restored tooth. The clinician is then able to make adjustments within the programme before 3D printing and cementing the restoration. These steps minimise the role of the dental technician, whilst also saving a considerable amount of time for the patient and clinician.

Literature search

Ovid was used to search Embase, using free text and subheadings. The date of publication and year of study of included articles were of paramount importance to ensure that the data were current. Furthermore, it was ensured that the studies included were conducted over a period of up to 30 years to allow discussion of the longevity of the restorations produced through the CEREC system. After the initial search, papers were screened based on length of study and sample size.

Longevity of CEREC restorations

One study conducted by Degidi et al[4] followed the success of CEREC restorations over a 2-year period, looking at implant-supported lithium disilicate fixed prosthesis. The study found that all 23 fixed dental prostheses analysed lasted satisfactorily over the study period and there were no damaged prostheses identified.[4] Another study was conducted in 2018 whereby 65 patients with CEREC 1-manufactured feldspathic ceramic inlays and onlays were followed up 27 years after placement, totalling 141 restorations. The success rate of 87.5% at 27 years was deemed to be acceptable for the dentist and patient population. The failures in the devices at follow-up were mostly due to fractures of the ceramic or the tooth, but some also stemmed from carious (18%) and endodontic (4%) origins.[5]

A retrospective study conducted in 2018 by Nejatidanesh et al[6] analysed the long-term success of ceramic laminate veneers created using CAD/CAM. It identified 197 ceramic veneers placed in 21 patients and found that the success rate of ceramic Empress CAD veneers was 97.8%, while for e.max CAD laminate veneers it was 100% following a 5-year period.[6] When comparing this data to the conventional preparation of porcelain veneers in the laboratory (see **Table 1**), it appears the survival rate of the CAD/CAM veneers is higher than those that are laboratory-made, though a robust comparison cannot be made due to varying tooth vitalities.

Table 1. Comparison of CAD/CAM- and laboratory-prepared veneers

Veneer type	Survival rate after 5 years
Porcelain laminate veneers (laboratory preparation)	94.4% (non-vital teeth showed a significantly higher failure risk)
Ceramic Empress CAD veneers	97.8%
e.max CAD laminate veneers	100%

Based on data from Beier[7]

Benefits and limitations of CAD/CAM systems within dentistry

With growing aesthetic concerns and patient expectations, CAD/CAM is beneficial in providing a pre-treatment image of the proposed outcome. In addition, in an age where many dentists are taught to preserve tooth structure, this technology is beneficial as more of the tooth can be preserved during the preparation stages as the material of the restoration is thinner.

Digital scanning also has the potential to replace conventional impressions as it takes less time, requires fewer physical materials and is less uncomfortable for the patient.[8] Furthermore, when taking full-arch impressions with guided scanning, the precision is greater than the current technique used for alginate impressions.[9]

However, this system does have its flaws. When reviewing the literature, the main disadvantage listed is the provision of restorations in subgingival margins due to the difficulty in scanning these areas. Therefore, in these instances, the conventional impression technique would be the obvious choice. With all restorations, the longevity is highly dependent upon the material selected. CAD/CAM is no different and many of the materials used within this system are ceramic based. Ceramic materials are typically brittle and known to fracture and to need replacing, as well as causing abrasive wear of naturally opposing teeth. Hence, despite robust data on restoration longevity, the CEREC approach is not without its detractors.

An article in DentistryIQ highlighted that many within the dental profession are unlikely to switch to CAD/CAM technology based on the learning involved for use of the equipment, preferring to "stick with what they know". However, as a new cohort of dentists continue to enter the profession having learnt CAD/CAM at university, they are unlikely to be able to use such systems in general practice due to the cost of the technology.[10] Thus, the cost of the equipment limits its current use to the private sector.

Conclusions

Despite its perceived shortcomings, digital dentistry is likely to revolutionise the way we practise, ensuring that patient comfort and expectations are met. Furthermore, it opens the path for more patients to be seen because of reduced waiting times from the laboratory and less of a need for making adjustments, which can be made prior to printing. The evidence surrounding the success of digital scanners and CAD/CAM systems in practice is considerable. These systems have the ability to replace the need for a laboratory and a technician with advances in the technology. Therefore, digital dentistry has proven to be an exciting new era for clinicians and patients alike.

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Review

The role of exosomes in breast cancer invasion and metastasis

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Background

Within the UK, breast cancer is one of the top ten causes of female deaths. The metastasis of breast cancer into the circulatory system and, consequently, to organs, has made it increasingly difficult to treat. There has been growing evidence to suggest that exosomes (extracellular organelles) contribute to breast cancer invasion and metastasis. These nanosized vesicles can carry and release a wide range of metastatic-stimulating components, including microRNAs (miRNAs) and other tumour-promoting factors. This article will explore the way in which exosomes contribute to the journey of breast cancer in situ to secondary metastasis.

Introduction

Breast cancer is a heterogeneous disease that primarily affects female individuals. It can present in various ways, from a raised lump to a peau d'orange appearance. There are several subtypes of breast cancer that are categorised based upon the presence/absence of oestrogen receptors and progesterone receptors and amplification of human epithelial growth factor receptor 2. These receptors are all found on the epithelial cell surface of breast tumours.[1] Triple negative breast cancer, which lacks all of these receptors, particularly contributes to the growing health concern regarding metastatic breast cancer due to its resistance to current therapeutics, such as tamoxifen and herceptin.[2] Gaining insight into the establishment of the tumour microenvironment (defined as the environment permitting migration and invasion of tumour-initiating cells)[3] and the consequent metastatic cascade of breast cancer (outlined in **Figure 1**) could help determine targets for new therapy.

Exosomes derived from breast cancer cells and formed from the fusion of multivesicular bodies with the plasma membrane[4] contain increased levels of cargo involved in the metastatic cascade.[5] Such cargo includes miRNAs,[6-11] catalytic and extracellular matrix (ECM) proteins,[12] and hypoxia inducible factors.[13] The significance of exosomes in breast cancer metastasis is explored in this article, identifying potential therapeutic targets for the future.

Literature search

Initial data collection focused on obtaining an understanding of the steps involved in breast cancer metastasis. The topics presented below were chosen based on the volume and breadth of information found for both the metastatic cascade and the exosome's involvement. The search engines Ovid, PubMed and Google Scholar were used for data collection. Use of up-to-date and relevant information was key for the analysis and write-up; thus, only research spanning from 2000 to 2018 was included.

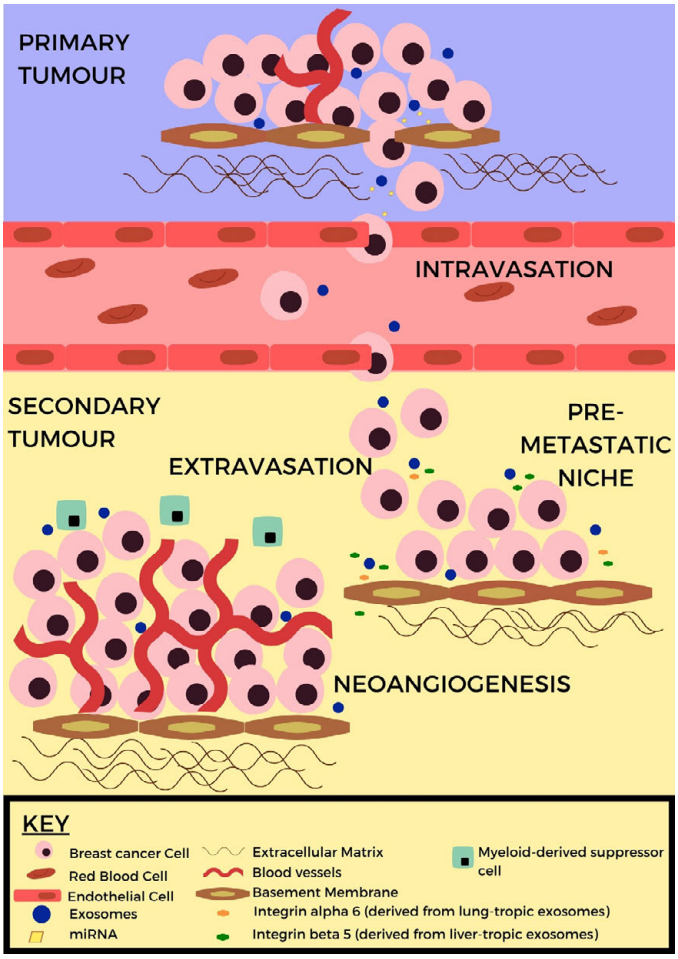

Figure 1. Metastatic cascade of breast cancer. This is a schematic diagram outlining the key steps and contributing factors to breast cancer metastasis.

Processes involved in breast cancer metastasis

Epithelial mesenchymal transition and migration In breast cancer, cell composition is altered by a process known as epithelial mesenchymal transition (EMT). Molecules that form cell–cell adhesion junctions, such as E-cadherin and N-cadherin, are downregulated and upregulated in breast cancer, respectively. This contributes to the migration of tumour initiating cells from the basement membrane to the neighbouring stroma.[14] Proteolytic factors, such as matrix metalloproteinases and urokinase plasminogen activators, also aid in ECM degradation, further contributing to breast cancer cell migration.[15]

With regard to exosomes, their carrying capability contributes to cancer cell migration. Research has shown that a specific miRNA, miR-105, derived from the breast cancer cell line MDA-MB-231, is contained within exosomes. miR-105 reduces the expression of another known adhesion cell molecule, tight junction protein 1, which may be suggestive of exosome involvement in cell migration.[10]

Organotropic metastasis Once cell migration and consequent intravasation occurs, organotropic metastasis proceeds. This involves the establishment of migrating cancer cells to another site known as the pre-metastatic niche[16] (see **Figure 1**). Current research demonstrates that integrins that promote cancer cell adhesion to parenchyma are contained and released by breast cancer-derived exosomes. For example, integrin alpha 5 has been linked to higher risk of lung metastases in breast cancer,[17] demonstrating exosome involvement in determining the metastatic site.

Neoangiogenesis promotion As metastasis occurs, neoangiogenesis (the formation of a vascular system) is required[18] (see **Figure 1**). The hypoxic environment of tumours has been shown to initiate an 'angiogenic switch',[19] resulting in neoangiogenesis. Evidence has also shown an increase in exosomes, as well as factors that promote angiogenesis activity. For example, miRNA-201 has been shown to be upregulated during hypoxia. miRNA-201 is involved in endothelial cell tubulogenesis,[20] a process whereby pre-endothelial cells transform from cuboidal to squamous cells and translocate to the periphery, lining the vessel lumen.[21]

Escape of immune response Avoiding the immune response is important for tumour progression.[22] The neoantigens present on a cancer cell's surface make it an immune target; however, exosomes have been shown to prevent cancer cell destruction by immune cells.[23] The increased number and frequency of myeloid-derived suppressor cells in metastatic breast cancer, responsible for premetastatic niche formation and T cell inhibition, are as a result of exosomes.[24] Additionally, the downregulation of NKG2D, a natural killer cell lectin receptor, from breast cancer-derived exosomes (vs exosomes not derived from breast cancer) has been shown to permit further tumour progression.[25]

Conclusion

In summary, exosomes play a role in breast cancer metastasis. The research discussed in this review, which used highly metastatic cell lines, are hugely insightful. Nonetheless, there are a few gaps that were evident in the data included. For example, stages in the metastatic cascade, such as intravasation, were not mentioned in this review due to insufficient data on the exosome's contribution. Although this may suggest that exosomes do not play a role in intravasation, further research is required to determine this. Additionally, although research has identified relevant carrier proteins involved in breast cancer metastasis, knowledge on the mechanisms regarding the specific trigger factors, exosomal transport and cargo release is scarce. This was evident in the literature surrounding neoangiogenesis, a new and emerging topic in the field of breast cancer metastasis. This highlights the need for further research in this area.

Excitingly, it is important to note that research into the use of exosomes as drug carriers is being investigated. Due to their nanoscale, endogenous and easily fusible structure, exosomes could be useful in future breast cancer management, particularly for patients with triple negative breast cancer in whom current treatment is ineffective.[26]

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Review

Mendelian randomisation: a potential tool to resolve the age-long gut microbiome–depression conundrum

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Introduction

Depression affects about 350 million people and is a leading cause of disability and mortality worldwide.[1] Antidepressants work in about 50–75% of patients and may have undesirable side effects, constituting a major public health challenge.[2,3] This inefficacy of treatment may be due to the current lack of understanding of the pathogenesis of depression. The leading hypotheses for the cause of depression are: neurotransmitter imbalance,[4] and dysfunctions of brain neuroplasticity,[5] the hypothalamus–pituitary–adrenal (HPA) axis[6] or the immune system.[7] However, these hypotheses are not universally accepted.[8]

The gut microbiome is believed to influence the functions of both the gut and the brain by modulating the host's neural, immune, and endocrine pathways. Also, there is a consensus of an alteration in the abundance and distribution of gut microbes in depressed subjects.[9–11] This suggests that the development of therapeutics that perturb the gut microbiome could be the solution to the current challenge of treating depression. Hence, a role of the gut microbiome in the pathogenesis of depression is now a major focus of research and public interest, and this is enabled by advances in sequencing technology. This review aims to discuss the existing evidence for a causal relationship between the gut microbiome in depression and proposes Mendelian randomisation (MR) as a new paradigm to investigate this relationship.

The gut microbiome–depression hypotheses

Hypothesis 1: a change in the gut microbiome causes depression
Rodent studies of faecal microbiome transplantation, germ-free mice, and vagotomy indicate that the gut microbiome influences brain physiology and, thus, mental health, directly through activation of the vagus nerve, and indirectly through the production of microbial metabolites that ultimately enter the brain.[12–21]

Hypothesis 2: depression causes a change in the gut microbiome
Studies that used olfactory bulbectomy and stress models to induce depression-like behaviours in rodents have reported that depression influences the HPA axis and immune responses, resulting in a change in the gut microbiome.[22–25] Mice exposed to chronic social defeat, used as a stress model, demonstrated transiently elevated levels of IL-10^{+} T regulatory cells, which preceded reduced diversity and reduced microbial richness in the mice.[25] Mice that underwent olfactory bulbectomy have been reported to exhibit increased HPA axis activity, significantly greater colonic motility, and altered microbiome composition. It is believed that activation of the HPA axis increases colonic motility, leading to changes in the gut microbiome.[23]

Limitations of the current evidence of the gut microbiome–depression relationship

The hypothesis that a change in the gut microbiome causes depression and not vice versa may be significant in the development of effective therapeutics for depression. However, the evidence for the gut microbiome–depression hypotheses mentioned above has come from animal studies. Unfortunately, translating findings from animal models into effective therapeutics in humans frequently fails due to inter-species differences in biochemistry, behaviour and physiology.[26,27]

Human studies have shown correlations between specific gut bacteria, their metabolites and depression,[15,28–31] but these have all been observational studies that do not infer causality, and can be affected by unmeasured confounding factors.[32,33] A randomised controlled trial (RCT) is the gold standard design to infer causation between two variables,[34] and RCTs involving faecal mass transplantation may provide an answer as to whether there is a causal role of the gut microbiome in depression in humans. However, RCTs can be expensive, time-consuming and impractical.[35] Hence,

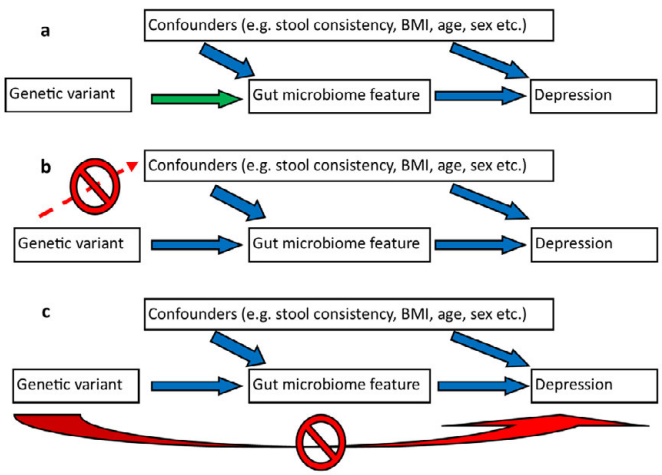
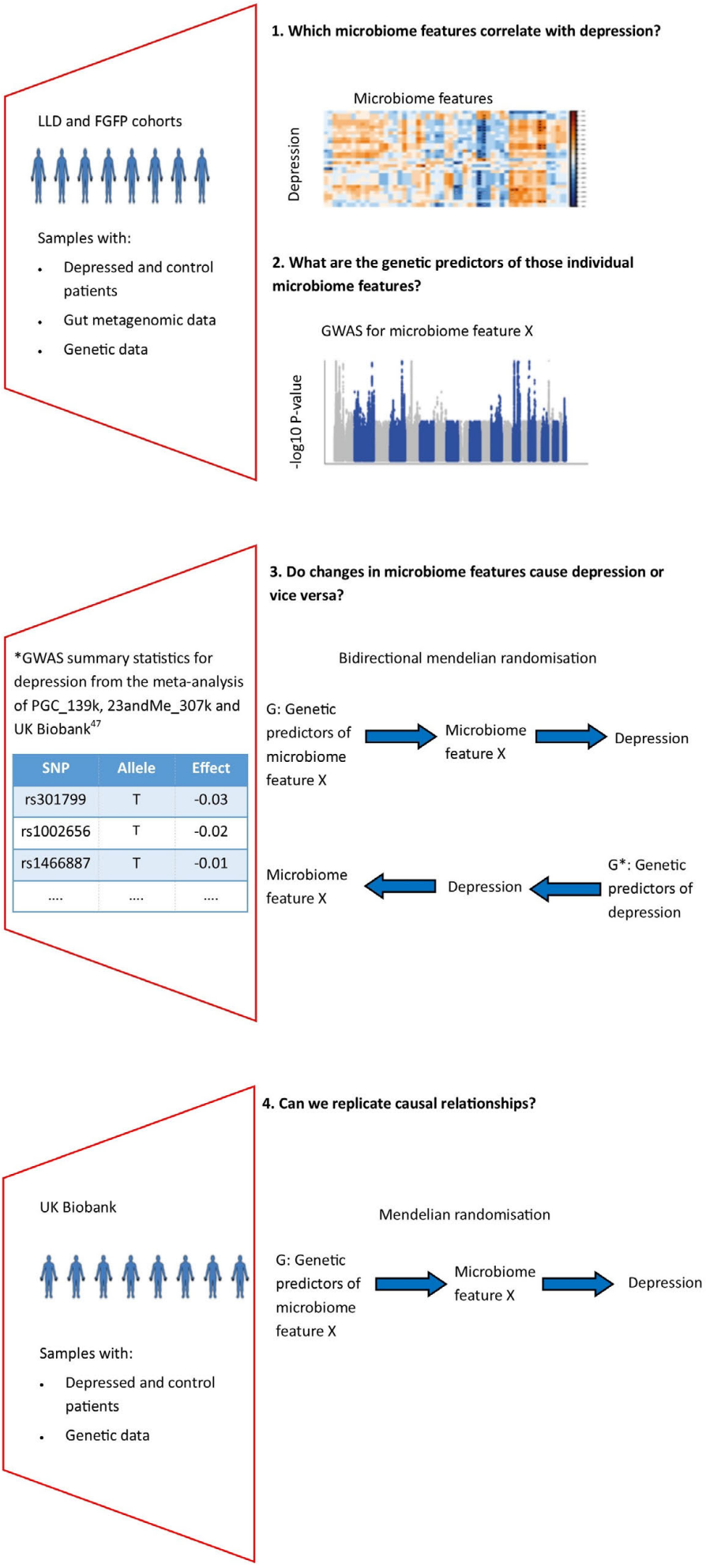


Figure 1. An illustration of the MR method and its assumptions for investigating a causal relationship between the gut microbiome and depression. (a) Assumption 1: the genetic variant must be reproducible and directly associated with the gut microbiome feature. **(b)** Assumption 2: the genetic variant must not be associated with confounders. **(c)** Assumption 3: the genetic variant should only be associated with depression through the gut microbiome feature. Figure adapted with permission from Sekula et al.[35]

Figure 2. Schematic representation of a proposed MR study to test for a causal relationship between the gut microbiome and depression. Microbiome features refer to metabolites, pathways, and unique taxa. Figure adapted by permission from Springer Nature, from Sanna et al.[41]



MR is proposed as a novel tool to detect a causal effect of the gut microbiome in depression in humans.

MR as a tool to investigate causality

MR is a method that uses genetic variants as instrumental variables to investigate the causal relationship between modifiable risk factors and health outcomes in observational data.[36] MR is comparable to RCTs because genetic alleles are randomly assorted and fixed at conception, making the MR method less likely to be affected by confounding or reverse causation than conventional observational studies.[37] Various studies have shown that it is possible to detect variants in the human genome that influence the composition of the gut microbiome.[38–40] Using these genetic variants, the MR approach can be used to identify whether any gut bacterial species has a causal effect on depression.[41] Some authors have reported that environmental factors play a bigger role than host genetics in the host's microbiome composition.[42] However, MR could still be used to investigate the gut microbiome, as demonstrated by recent studies investigating a causal relationship between the gut microbiome and metabolic diseases.[41,43]

A proposed MR study to investigate the gut microbiome–depression hypothesis

As a proposed MR study, genome-wide genetic data, gut metagenomic sequencing, measurements of faecal microbiome-dependent metabolites, and depression status could be collected from cohorts such as the Belgian Flemish Gut Flora Project (FGFP) and the Dutch Lifelines DEEP (LLD) cohorts.[28] Once the microbiome features (metabolites, pathways, and unique taxa) associated with depression are established, data from genome-wide association studies (GWAS) from the LLD and FGFP projects could be used to identify the independent genetic variants that are associated with each depression-related microbiome feature.

The MR approach must satisfy three assumptions **(Figure 1)**: firstly, that the genetic variant selected as the instrumental variable is strongly associated with the gut microbiome feature; secondly, that the genetic variant is not associated with any unmeasured confounders of the gut microbiome feature and depression relationship; and thirdly, that the genetic variant is associated with depression only through gut microbiome features, not through other pathways.[32,37] However, it is difficult to ascertain that none of the MR assumptions are violated. Thus, any findings of a causal relationship in the proposed study cohorts (LLD and FGFP) should be validated in an independent cohort, such as the UK Biobank.[41] Previous articles have provided details on how to conduct MR and assess the plausibility of MR assumptions.[32,35–37]

Although the MR approach as described above could provide inference of a causal relationship between the gut microbiome and depression, it does not distinguish the directionality of a causal association. Bidirectional MR is an approach that could be used to determine the directionality of a causal association by investigating the hypotheses that depression causes a change in the host's gut microbiome and vice versa.[32,36] Three recent GWAS have reported reproducible genetic variants for depression.[44–46] These studies culminated in a genome-wide meta-analysis of depression which reported 102 associated variants that were replicated in an independent sample.[47] The variants had an equivalent direction of allelic effect across the three studies that contributed to the meta-analysis, suggesting a robust association between the genetic variants and depression.[47] Hence, if MR assumptions are met, MR could be used to investigate the hypothesis that depression causes a change in the gut microbiome. **Figure 2** summarises a proposed MR study that could be used to investigate a causal role for the gut microbiome in depression.

Conclusion

Currently, there is no consensus on the pathogenesis of depression. Advances in sequencing technology have enabled large observational studies, which implicate the gut microbiome in the pathogenesis of depression. However, conventional observational studies do not infer causality and are affected by confounding factors. MR analysis of observational data reduces the likelihood of data analysis being affected by confounding factors and reverse causation. If MR analysis reports that the imbalance of specific gut bacteria and their metabolites causes depression, this could lead to the development of effective therapeutics targeting the gut microbiome, helping to overcome the major challenges faced in treating depression.

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Review

How perceptions of obesity are constructed through modern social media in Western culture

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Background

This review looks at the role of social media in the general perception of obesity amongst the public and healthcare professionals. The power of these platforms to contribute to a skewed perception of body image and self-worth amongst obese individuals, often preventing them from seeking professional help, is unmistakable.[1–3] This review outlines the need to regulate the increasing influence of social media on body image and self-worth through legislation, and to change the use of these very platforms to promote social acceptance of obese individuals through supportive blogs and forums.

Introduction

Information propagation in the modern world is predominantly through social media and similar digital media platforms. These have very extensive reach and the ability to influence all age groups because the user can become both a reader and a contributor of information.[4] Social media has been shown to play a role in the general perception of obesity amongst the public, propagating a biased perception of body image, often aggravating low self-esteem amongst obese individuals.[1]

Obesity, should we be concerned?

Obesity is defined as an "abnormal or excessive fat accumulation that may impair health"[5] and can be measured in terms of body mass index (BMI).[5]

$$BMI = weight(kg)/height^2(meters)$$

The World Health Organization (WHO) has called obesity an epidemic of alarming proportions, stating that at least 2.8 million people per year die due to this condition.[5]

The fact that obesity leads to a myriad of physical health problems has been discussed in detail in modern medical literature;[5] however, the contribution of obesity to psychological problems, such as low self-worth and feelings of emptiness, has not been discussed to the same extent. The psychological problems experienced by obese individuals are often due to the stigma attached to obesity in almost all societies internationally.[6] Goffman[7] describes stigma as "an attribute that in our minds, reduces an individual (different from most of us) to a discounted, tainted kind".

Literature search

As part of this review, a literature search was conducted to investigate the influence of social media on the stigmatisation of obesity. The resources were found on the Peer-Reviewed Instructional Materials Online Database (PRIMO) and PubMed. The search terms used were "social media", "Obesity" and "body image". The search returned over 1500 results. A peer-review filter was then applied, leaving 870 articles for inclusion, and, of these, 130 papers were taken forward based on their titles and abstracts (papers were only retained if they explored the impact of social media on obesity). Full-text articles were further assessed for relevance to the Western world, particularly the USA, UK and Australia, resulting in 20 of these articles being included in the literature review.

Moreover, the University of Plymouth and Life Sciences Resource

Centre (LSRC) libraries were searched for books that met the inclusion criteria.[7,8] In addition, searches for the terms "obesity", "fat shaming", "fat people memes" and "fat jokes" were conducted on Instagram, Google and YouTube.

Body image and the media

The perception of ourselves when we peer into the mirror can vaguely be defined as body image. To define body image precisely, however, can be onerous. Thompson and colleagues[8] attempted to define it in 16 different ways. One strand of body image is obesity. In the social context, being thin is often viewed as being healthy.[9] However, "health is a state of complete physical, mental and social well-being; and not merely the absence of disease or infirmity".[10] Morgan et al[11] proposed the "mass communication model" wherein they stated that "mass media plays a central role in creating stereotypes of beauty and body image". The social agents (i.e. media), and society at large, has contributed hugely to the belief that outward appearances are important.[12]

Social media: the modern information source

Modern social media networks, including websites and platforms such as Facebook, Twitter and Instagram, have replaced conventional media, such as magazines, newspapers and television channels, as sources of information.[4,13] A study found a steady decline in viewership of conventional television amongst young adults between 2010 and 2011.[13]

In the author's view, modern social media uses its capacity for instantly creating, accessing and processing an idea or opinion to entice people. The ceaseless ability to access these platforms is alluring to young adults craving attention and adulation. These technologies allow the user to personalise communications, "thereby transforming formerly passive mass-media receivers into full-fledged communicators, enhancing autonomy and personal agency".[14]

Eternalisation of the weight stigma

An obese individual is often derided, decried and rejected on social media platforms. This verbal abuse is responsible for causing anxiety, depression and low self-esteem.[2] Chou et al[2] found that of the 1.37 million posts from social media platforms, 92% related obesity with negative misogynistic or derogatory words. A search for the term "fat people memes" on Google in July 2019 revealed memes that were outright abusive and offensive to overweight people. A similar search on YouTube in July 2019 showed videos ridiculing fat people. Many of these videos had millions of 'likes' and 'views'. On Instagram in July 2019, #fatpeople yielded 37,000 posts and also led to pages such as #fatpeoplefalling and #daily_fat_people_pictures.

Users of social media platforms feel empowered due to their ability to stay anonymous.[15] It has been suggested that aggressiveness and 'toxic inhibition' may result due to lack of eye contact (an important social cue) when using social media.[15] This affront aggravates the feeling of low self-worth in targets of the abuse and, to worsen matters, these individuals may not have the necessary tools to protect themselves from the negative impacts of these stressful experiences.[16–18]

The social media paradox

Modern social media ridicules the obese but also advertises and promotes a cornucopia of weight-loss therapies; from fancy diets and magic potions to exercise plans.[2,3] The domination of these platforms is such that the vulnerable obese population easily fall prey to such advertisements. These dieting regimens generally do not work, and the individual feels cheated and misled.[3]

The vulnerable healthcare professional

Research conducted by Teachman and Brownell[19] in the USA showed that people in the healthcare community had an 'implicit negative association' towards individuals who were overweight. A study on UK trainee dieticians, doctors and nurses showed similar trends of negative connotations towards overweight individuals.[20] Although these studies were limited due to the sample demographic, the results are alarming. The very group of professionals who know that obesity is a multi-factorial disorder and not just due to individual nonchalance, exhibited a negative bias. It is suggested that this might largely be due to the exposure of healthcare professionals to the same sources that created the negative bias in the public. Therein lies the role of healthcare trusts and medical societies to improve awareness amongst health professionals to improve patient trust and safety and provide overweight patients with a positive experience in a healthcare setting.

Conclusion

Social media platforms are constantly evolving and competing with each other to improve the user experience. Their burgeoning influence means that offensive or unhelpful content with regard to obesity and, subsequently, unhappiness in vulnerable users can only escalate if left unregulated. There is a need for legislation to regulate such vexation towards the vulnerable. It will be an uphill task to bring in such legislation when the often-cited right to "freedom of speech" can be used to defeat it. People downplay the matter by saying "it's just a bit of humour, but is it?

The same social media platforms can be used constructively by forming and promoting online communities, such as 'Fatosphere' (a fat acceptance community)[9] and supportive blogs and forums. In an analysis of Fatosphere, Dickins et al[9] suggested that this site offers another pathway for individuals to resist and respond to social media. Though not suitable for all individuals, many, particularly those who have had undesirable experiences with obesity, have reported developing a more positive relationship with their body. They also found support and a sense of community, which enabled them to deal with any stigma in a more positive manner. In addition, the removal of pressured emphasis on weight loss was found to enable participants to focus on well-being and leading healthy lifestyles, rather than focusing on the highly advertised thin-ideal.[9]

Most importantly, further high-quality research is needed, involving a wider spectrum of people, to find solutions to the ways in which social media affects the perception of body image.

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Review

Facilitating successful post-school transition for young people with learning disabilities

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Abstract

Aims This article aimed to examine the experiences of post-school transition in children and young people with learning disabilities in order to identify barriers faced and how the process can be improved.

Methods A literature search was completed using the search terms '"transition' AND 'learning disability OR intellectual disability'". Papers were only included if they focused on experiences of the transition process in the UK and could be accessed in full with no charge. No exclusions were made on the basis of publication date.

Results Six studies matched the search criteria and were selected for inclusion. These studies broadly explored transition planning and its effectiveness, wellbeing during transition, and family and carers' perspectives on transition.

Conclusion Experiences of post-school transition vary substantially. Transition planning needs to take place as early as possible with the full involvement of people who know the young person best. A desire for increased adult social care involvement in transition was also demonstrated. There needs to be more informational support for people whose first language is not English so that these individuals have equal access to transition care and opportunities.

Introduction

A learning disability may be described as a difficulty with day-to-day activities due to a reduced intellectual ability. Post-school transition for young people with learning disabilities (PWLD) describes the process of leaving school and beginning further education, training or employment.[1] It is recommended that preparation for transition should begin as early as possible, and no later than age 14.[2] Early preparation allows for more planning and continued support when the young person finishes compulsory schooling at age 16. The transition process is not always without complications; one study showed that only ~25% of carers were content with the process.[3] Measuring patient experience allows for the development of targeted interventions that support improvements to the transition process.[4] This article will, therefore, explore experiences with transition planning, placements, wellbeing during transition and barriers to achieving an effective transition. Positives and negatives of current transition approaches will then be identified and recommendations for improvement made.

Methods

Background information was found on the Mencap and Together for Short Lives websites. The search was completed in April 2019 and the search terms used to find papers were '"transition' AND 'learning disability OR intellectual disability'". The literature was obtained from a variety of sources, such as the PubMed database, the Wiley Online Library and the Elsevier ScienceDirect database. Papers were only included if they focused on experiences of the transition process in the UK and could be accessed in full with no charge. No exclusions were made on the basis of publication date.

Results

Six studies matched the search criteria and are summarised in **Table 1**.

Table 1. Studies included in the literature review.

Selected studies	Research method(s)	Sample size (*n*)	Content/theme
Bhaumik et al, 2011[3]	Postal questionnaires and interviews for carers	79	Carers' perspectives of the transition to adult services and unmet needs
Kaehne et al, 2013[5]	Documentary analysis of all person-centred plans Telephone interviews with families	44	Application of person-centred planning to transition
Small et al, 2013[6]	Two semi-structured interviews with each young person: one at recruitment and one a year later	43	How social networks changed for young people during transition from school to college
Young-Southward et al, 2017[7]	Semi-structured interviews with young PWLD and parents of young PWLD	Young people: 17 Parents: 23	Identifying the impacts of transition on health and wellbeing
Raghavan et al, 2012[8]	Two semi-structured interviews with each young person: one at recruitment and one a year later	43	Family carers' perspectives of transition for young PWLD with special reference to ethnicity
Ward et al, 2003[9]	Questionnaires for parents of young people at various transition stages and interviews with 27 young people and 27 carers	272	The effectiveness of transition planning for young people and their families

Transition planning was one of the most recurrent themes discussed in these studies. Despite recommendations advising early planning, transition meetings were sometimes held near the end of the final year of school.[7] This left little time for young people and their families to discuss their transition plan, which meant that they felt rushed

in making a decision and their needs were less likely to be met. Only 52% of transition meetings were attended by social workers, according to available data in one study.[5] In addition, a combined 67% of young people reported having little to no involvement in transition meetings. Some young people stated that one-to-one meetings with a transition professional were more effective and less daunting than a group meeting.[9]

For young people with severe and profound learning disabilities, the only post-school options were daycare centres.[3] Carers often perceived these placements to be unsuitable due to lack of staff to meet the young person's needs, but felt that there was little choice and had to accept these placements.[6] Young people with mild and moderate learning disabilities mainly expressed desires to go to college or pursue further educational opportunities.[6] There was some emphasis on work placements and employment goals in transition meetings, and these placements were generally enjoyed by young people.[5]

One study extensively investigated the impact of post-school transition on wellbeing, and showed that management of mental health conditions concerned parents more than physical health conditions.[7] In this study, 38.4% of young people scored in the abnormal range in a Strengths and Difficulties Questionnaire (SDQ) and a further 11.5% were in the borderline range. These scores indicated the presence and possible presence of mental health problems, respectively.[7] Parents' accounts mirrored these results as they reported concerns about their child's mental health during the transition period, particularly regarding increased anxiety.[7] This shows that there is scope for transition-specific mental health support or a service to bridge the gap between child and adult mental health services.

Ethnicity seemed to be a predictor of transition experience,[3] as problems, such as role confusion and lack of awareness, were worse for carers whose first language was not English.[8] Bangladeshi and Pakistani carers were more inclined to hand down caring responsibilities to siblings and were reluctant to allow young people to move into supported homes or residential care in the future.[8] Pakistani Muslim carers were worried about the young person disregarding religious beliefs and customs in certain care settings.[8]

Discussion

Here we discuss six studies that analysed transition planning, placements, wellbeing during transition and/or barriers to achieving an effective transition. It was found that transition planning was a recurrent theme that was a major point of discussion in these studies. Interestingly, social workers only attended half of the transition meetings in one study.[5] This reinforces the demand for more social care involvement.[5] However, as this finding was only derived from available data, it could be possible that these figures are not accurate. It was also noted that accessibility to transition meetings for young people could be improved, as 67% of young people said they had little to no involvement.

Post-school placement options seemed to be influenced by the degree of learning disability, since young people with severe learning disabilities were only offered daycare centres.[3] Carers thought these placements were unsuitable for these individuals due to limited staff but felt there was little choice but to accept the placements.[6] This highlights the need for increased care provision, such as respite care, for young people with more complex needs. It must be noted that there was a higher number of young people with a severe and profound learning disability in this study in comparison with the local average,[6] which could make the problems reported seem disproportionately more severe.

One study that investigated the impact of post-school transition on wellbeing showed that mental health problems were present in PWLD during the transition period, and that parents were concerned about these issues.[7] These findings demonstrate that there is scope for transition-specific mental health support or a service to bridge the gap between child and adult mental health services.

Ethnicity was also shown to be important for the transition experience[3] as language and religion[8] were found to influence type of care. In particular, there were concerns that religious beliefs would be disregarded in certain care settings.[8] This demonstrates the need for culturally-sensitive provision, so familial values and beliefs are upheld in post-school placements.[3]

Summary points

- Post-school transition for PWLD can be a stressful process but this difficulty can be mitigated with appropriate support
- There were several shortcomings in transition planning, including late planning and lack of involvement of key stakeholders
- More support is needed to ensure mental wellbeing during the transition process
- A multidisciplinary approach is required in order to synthesise and deliver key information and support individuals through the process

Conclusion Drawing upon the evidence considered in this review, it is clear that experiences of post-school transition vary substantially. Transition planning needs to take place as early as possible with the full involvement of people who know the young person best, so they can collude with professionals to plan an effective transition.[10] A largely multidisciplinary approach to transition is viewed as most effective, and a desire for increased adult social care involvement in transition has been demonstrated.[11] This ensures that young PWLD have adequate social support and suitable post-school placement options. There also needs to be more informational support for people whose first language is not English so that these individuals have equal access to transition care and opportunities.

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Review

Draft NICE aneurysm guidelines: an end to the endovascular era?

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An abdominal aortic aneurysm (AAA) is the dilatation of the aorta to over 50% of its original diameter. The risk of life-threatening rupture increases as the aneurysm expands. Currently, a diameter of 5.5 cm is the threshold at which patients are referred for treatment, either by open surgical repair (OSR), where a synthetic tube graft is sutured in place after laparotomy, or by endovascular repair (EVAR), where a metal stent is placed in the aneurysm via small incisions in the groin. Over the last two decades, the uptake of EVAR has been significant; its minimally invasive nature means that it is associated with shorter hospital stays and it is suitable for older individuals with comorbidities who are deemed unfit for OSR. Nowadays, EVAR is a standard treatment for AAAs in the UK and across the world. The decision of whether to opt for OSR or EVAR is largely based on patient fitness, patient and clinician preference and aneurysm morphology.

In May 2018, the National Institute of Health and Care Excellence (NICE) proposed new draft guidelines stating that EVAR should not be offered for elective AAA repair, regardless of whether patients are suitable or unsuitable for OSR. The guidelines explain that there is a lack of evidence for long-term benefits of EVAR compared with OSR in non-ruptured AAAs, which means that national funding from the NHS is not justified.[1] The exceptions to this are emergency EVAR for ruptured AAAs, as the evidence for this is more compelling,[2] and the use of complex EVARs in randomised clinical trials.[1]

The evidence behind the guidelines stems from the EVAR1 trial, which enrolled patients between 1999 and 2004, comparing OSR against EVAR for elective AAA repair.[3] The study found that, although EVAR had superior outcomes compared with OSR at 30 days and 6 years, there was no longer a statistically significant difference between the two treatments in aneurysm-related and all-cause mortality rates at the 10-year follow-up, mainly as a result of secondary sac expansion and subsequent rupture[4]. A cost-effectiveness analysis also found EVAR to be more expensive than OSR.[5]

The draft guidelines generated much debate within the vascular community. A joint statement made by the Vascular Society of Great Britain and Ireland (VSGBI), the British Society of Interventional Radiologists (BSIR) and the Vascular Anaesthesia Society of Great Britain and Ireland (VASGBI) voiced concerns that the guidelines may prevent patients from receiving appropriate life-saving treatment that they would otherwise receive if residing in other areas of the Western world, as EVAR remains a first-line or OSR alternative for AAA repair according to the European Society of Vascular Surgery (ESVS) and the American Society of Vascular Surgery (SVS) guidelines.[6,7,8] The societies also highlighted the difficulty in assessing patient 'fitness' for OSR, since there are no validated tools or risk scores currently available, stating that as surgeons are likely to be risk averse, the incidence of aneurysm rupture would almost certainly increase.

Another main concern is the impact of the draft guidelines on current practice.[6] Since EVAR is often performed more frequently than OSR, a diverse group of medical professionals will need to make appropriate changes, from adjusting the current surgeon training curriculum, to re-allocation of resources in theatres, wards and intensive care or high-dependency units as a result of longer hospital stays and close monitoring after OSR. The provision of EVAR for ruptured AAAs may also be affected, since surgeons could lose the skills needed for the procedure as a result of a lack of elective EVARs, leading to suboptimal outcomes in ruptured cases. These challenges were recognised by NICE, but the committee believes that the recommendations will, nonetheless, minimise long-term mortality and re-intervention, as well as reduce costs.[1]

Finally, the external validity of the historic data from the EVAR1 trial has been called into question. The trial principally involved early-generation endografts, most of which have since been replaced by later iterations.[9] Although the long-term durability of these newer stents has not been evaluated, they would be likely to have lower associated rates of complications and re-interventions. In addition, other advances in vascular imaging, hybrid theatres and surgeon experience have dramatically improved EVAR outcomes over the last decade in the UK.[10]

The EVAR1 trial also suffered from loss to follow-up, with only 10% follow-up retention of all survivors at 9 years.[4] Therefore, aneurysmal degeneration may not be detected and re-intervention not performed, which can strongly predispose to late secondary rupture.[11] To address these uncertainties, an ongoing research group is using prognostic modelling to identify risk factors for secondary sac expansion after EVAR, based on the EVAR trial's dataset and validated by a contemporary dataset from Finland,[12] which could demonstrate the true outcomes of EVAR in a 'perfect follow-up' scenario.

Although the NICE draft guidelines for AAA management were originally scheduled to be published in November 2018, as a result of its controversial implications on current practice, there has been a significant delay in publication due to the appeals process. In March 2020, the guidelines were fully published by NICE, with the revisions now recognising that EVAR may be the optimum choice for patients under clearly defined circumstances, after anatomical and physiological considerations.[13] Whilst these new changes were well-received by the VSGBI,[14] a separate statement released by the AAA Guideline Development Committee (GDC) again voiced their concerns over the fact that the recommendations do not accurately reflect the evidence behind EVAR and OSR.[15] Whilst historic data and a tight NHS budget support the recommendations made in the draft guidelines, patient and clinician choice cannot be overlooked. Perhaps most importantly, the debate has highlighted the shortcomings of the current evidence base, and further research is a high priority.

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Case Study

The outcome and complications of interposition arthroplasty using an Achilles tendon allograft in juvenile idiopathic arthritis

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Introduction

Movement at the elbow is essential for several activities of daily living, with a 100° arc of flexion and supination required to feed oneself, lift objects and maintain personal hygiene.[1] This case reports a 23-year-old male with a 10-year history of juvenile idiopathic arthritis (JIA) severely affecting the right elbow.

JIA has an unknown aetiology and is characterised by the onset of arthritis before the age of 16 years.[2] Surgical treatment aims to preserve movement at the elbow and reduce pain associated with the disease. Historically, methods have included total elbow arthroplasty, resection arthroplasty, arthrolysis and arthrodesis, all of which produce suboptimal results in the young and highly mobile patient. More recently, interposition arthroplasty (IA) has emerged as a possible treatment. This procedure is well described by Cheng and Morrey[3] and involves positioning a graft between the ulnar and radial surfaces of the elbow joint in order to reduce friction between the articulating surfaces and improve movement at the joint.

IA is often considered a salvage procedure, as it neither restores full function nor completely eliminates pain, but has been shown to improve patients' symptoms, increase range of movement at the joint and prolong the need for total elbow arthroplasty (TEA).[4] This procedure does not carry the same weight-bearing restrictions as TEA, thus is considered a more suitable procedure for younger patients. The graft is expected to resorb and the joint space to vanish over time; however, preservation of bone means that if IA fails, TEA can be easily and safely implemented when needed.[5]

Case presentation

The 23-year-old male patient complained of severe pain and restricted movement in the right elbow. On examination, the patient was held in fixed flexion with only 15° of flexion and 30° of supination. The elbow was erythematous and swollen with crepitus on palpation. There was no family history of inflammatory arthritis or other rheumatological conditions and the patient had no other relevant past medical history. The patient had adapted to become left-arm dominant; however, pain of movement severely restricted both work and social life.

Treatment

At the time of the report, the patient was receiving tocilizumab infusions of 4mg/kg, which had been ongoing for the past year, after failing to respond to methotrexate and azathioprine. Previous surgeries included a right elbow arthrolysis, right radial head excision and ulnar nerve transposition, which were all carried out in a single procedure in 2018 and had little effect in relieving the patient's symptoms. Despite initially responding well to tocilizumab, the patient subsequently complained of increasing pain and reduced mobility of the right elbow 6 months after commencing the treatment, requiring pain management with daily ibuprofen and codeine. At this point, the benefits and disadvantages of TEA vs IA were discussed with the patient leading to a patient-led decision to proceed with IA.

Outcome and follow-up

Four weeks post IA, the patient was reviewed in clinic as relatively comfortable post surgery, no intra- or post-operative complications were reported and the patient was managing with simple analgesia alone (paracetamol and ibuprofen). On examination the posterior scar was well healed with no signs of infection and pin sites of the external fixator were secure, clean and dry. Motor and sensory function of the radial, ulnar and median nerves were intact, and the elbow joint was congruent and nicely detached.

Discussion

The outcome and post-operative complications of IA are still poorly understood, probably owing to the limited number of documented cases to date. Studies so far have categorised patient satisfaction and outcome of surgery according to the Mayo Elbow Performance Score (MEPS). This assigns a maximum of 100 points according to pain, motion, stability and daily function.[6]

A study analysing the outcomes of 38 elbow IA procedures showed a mean overall increase in MEPS of 41 to 65, with 50% of patients rating the elbow as significantly better following surgery, 32% as moderately better, 13% as the same and only 5% as worse.[4] This study concluded that patient satisfaction is most likely due to the increase in functional ability and mobility obtained after the procedure, as pain and elbow stability showed modest, if any, improvement.[4]

Other studies have shown that up to 31% of patients had unsatisfactory results following surgery, and 18% of cases actually failed due to the severity of elbow instability, requiring conversion to TEA.[7] The largest study of IA to date produced similar results, with 29% of patients reporting significant elbow instability.[4] This is believed to be reduced by the application of a dynamic external fixator, which allows tissues to heal whilst maintaining support and promoting mobility. However, the clinical outcome of patients managed with and without external fixation is debatable, suggesting the need for a more reliable method to reduce post-operative instability.

Other post-operative complications include nerve injury, with the most frequently documented cases involving the ulnar nerve, and more rarely the radial or median nerves.[8] Anterior transposition of the ulnar nerve during the surgical procedure has been shown to reduce rates of nerve injury; however, most cases of nerve pain prior to surgery will not be resolved following IA.[8]

Wear rate of the graft is also a consideration, with studies showing an average of a 10-year wear rate for fascia lata grafts.[9] Evidence suggests that Achilles tendon grafts are able to resist longer, which is evidenced in lower revision rates when using these grafts (16%) compared with tendon fascia lata grafts (31%).[4]

The "placebo effect" of orthopaedic surgery may also be a contributing factor to consider in cases such as this. Patients' expectation that invasive procedures will correct the underlying pathology often results in improvement of symptoms, such as pain and dysfunction, based on the biomedical health model of pain.[10] A study into "sham procedures", whereby no surgical intervention was carried out, revealed similar patient-reported outcomes to the comparison group of patients who received surgical intervention.[11]

Whilst a single review can be biased, a case report is a useful way to understand the impact of a disease and intervention on a patient. Patient discussions can often be illuminating as to the important factors in determining the acceptability and success of surgery.

Conclusion Overall, IA appears a viable option for young and active patients, in whom TEA yields undesired results, such as limited range of movement and functionality. IA scores high in patient satisfaction for mobility and range of movement after surgery and can be easily converted to a TEA in the future should the graft fail, making it a suitable pre-prosthetic alternative. Post-operative elbow instability appears to be the most significant complication of IA. With so few cases documented to date, analysis of the procedure outcome remains challenging yet promising.

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Case Study

Informed consent: ethical and legal analysis of a fictional case study

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Introduction

Mrs Jenkins, a 48-year-old professional belly dancer, was due to undergo a laparoscopic sterilisation procedure. She voiced concerns about the risks of needing a large abdominal incision, which would ruin her career, or falling pregnant afterwards, which her and her husband would be unable to cope with. Dr Davies assured her that neither would occur, despite both being established risks. Both complications subsequently arose. In this report, Kantian ethics will be used as a framework to discuss the moral integrity of Dr Davies' actions, focusing specifically on whether his lie was permissible. Following this, the legal implications will be discussed, highlighting that the doctor may be liable for negligence as he did not inform Mrs Jenkins of the risks of the procedure, rendering her consent invalid.

Ethical issues

Deontology is a branch of moral philosophy that focuses on acting from a moral duty.[1] Kantian ethics is a subtype of deontology, named after the 18th century philosopher Immanuel Kant. Central to Kant's theory is his "categorical imperative", which states that we should 'act as if the maxim of your action were to become through your will a universal law'.[2] When applied to this case, this means that if Dr Davies lied to Mrs Jenkins and thought that his lie was permissible, he must condone all forms of lying and consider them all to be permissible. Kant considers this to be illogical as Dr Davies could subsequently not trust Mrs Jenkins, rendering the doctor–patient relationship useless. Furthermore, if lying to a patient about procedural risks was to become universally acceptable, no one would be able to trust their doctors and may even avoid life-saving treatments due to this distrust.

> *We should 'act as if the maxim of your action were to become through your will a universal law'.*

Given that it would be widely damaging to accept lying as a 'universal law', being honest is, therefore, what Kant categorises as a 'perfect duty'; we are morally obligated to exercise honesty in all situations.[3] Conversely, imperfect duties can sometimes be violated.[3] Dr Davies' assurance of Mrs Jenkins reflects a duty of beneficence: that of promoting wellbeing or welfare.[4] However, Kant considers beneficence to be an imperfect duty,[5] with honesty trumping it. This is because, as aforementioned, Dr Davies could not will lying, even for beneficent reasons, to be universalised. As such, a Kantian evaluation of Dr Davies' assurance indicates that it was immoral because he lied, therefore violating his perfect duty of being honest.

Dr Davies could, however, refute this by utilising Ross' interpretation of moral duties. Ross was a 19th century philosopher who believed that all duties are 'prima facie'. This means that individual duties are compulsory but they can be overridden by opposing duties.[6] In this case, Dr Davies could contend that his duty to comfort and reassure Mrs Jenkins trumps his duty of honesty. The concept of 'therapeutic privilege'[7] outlines that 'using lies or deception to preserve the patient's hope, and psychological and moral integrity'[7] can be acceptable in some circumstances. Dr Davies could contend that he applied this here, and it could be argued on this basis that he acted morally.

Nonetheless, Kantian ethics is based on deontological principles, which categorically distinguish between the right and the good.[8] In

> *The concept of 'therapeutic privilege' outlines that 'using lies or deception to preserve the patient's hope, and psychological and moral integrity' can be acceptable in some circumstances.*

other words, what we ought to do versus what action comes from a good motive.[6] It is acknowledged that Dr Davies could defend his action as morally good if the lie stemmed from a good motive, such as wanting to reassure Mrs Jenkins; however, in this case, it was not the right action. This is because reassuring Mrs Jenkins may help her in the short term, but this action involves both lying to her, thus breaking her trust, and violating her right to an autonomous decision (a decision made independently of external governance). Dr Davies may feel that he did the right thing as he promoted Mrs Jenkins' short-term welfare; however, Kant holds that the ability to reason, not feel, is what makes us able to act morally.[8] Thus, Dr Davies should recognise that the moral *rightness* of respecting Mrs Jenkins' right to autonomy and being honest trumps the moral *goodness* that may underpin his intentions when he lied to her.

Legal issues

The legal issue at hand pertains to whether, through withholding information regarding the risks of the procedure, Dr Davies acted negligently.[9,10] In common law, a claim of negligence must satisfy a tripartite test in order to be successful; the claimant must prove, on the balance of probabilities, that they were owed a duty of care by the defendant, that this duty was breached, and that the breach by the defendant was what caused harm to the claimant.[11]

The relevant duty owed by Dr Davies is that of disclosure. He must gain valid consent from Mrs Jenkins for the procedure, meaning she must have capacity, consent voluntarily, and have an adequate understanding of the risks and benefits.[12] Usually, before a surgical procedure, the patient would have the risks listed to them. In this case, Mrs Jenkins is presumed to have capacity,[13] but is left unaware of the 'material risks'[14] of the procedure due to Dr Davies' non-disclosure, thus rendering her consent invalid and leaving her unable to make a fully informed, autonomous decision.

'Material risks' are those that Mrs Jenkins would deem significant to her personally.[14] She expresses that she and her husband would not cope with having more children, thus, we can infer that she would likely attach significance to the risk of becoming pregnant after the procedure. Furthermore, she is a belly dancer and specifically asks whether she would need a large incision, thus, it is likely she would also attach significance to the risk of the laparoscopic procedure becoming a laparotomy, leaving her with a large scar. As such, Dr Davies breached his duty to Mrs Jenkins by not disclosing this information to her. The evidence for this breach is further strengthened by the fact that Mrs Jenkins specifically asked for the information. As explained by Lord Bridge in *Sidaway v Board of Governors of the Bethlem Royal Hospital*,[10] Dr Davies must answer Mrs Jenkins' questions regarding the procedure 'both truthfully and as fully as [she] requires'.[10]

Without focusing on the test for causation, it is proposed that if Mrs Jenkins could prove that she would have abstained from the procedure if given this information, she might be successful in her claim of negligence against Dr Davies.

Recommendation

In light of this ethical and legal analysis, it is concluded that Dr Davies should have fully informed Mrs Jenkins about the risks of the procedure. His action to reassure her may have reflected moral goodness, but it was not morally right as it breached his duty of honesty and violated Mrs Jenkins' right to autonomy. Furthermore, Dr Davies could be found guilty of negligence as he failed to disclose important risks to Mrs Jenkins, rendering her consent uninformed and invalid.

Disclaimer The characters in this case study are purely fictional and do not represent real people.

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Rsearch Article

Behaviour as a means of differentiating healthy from sub-clinically ill cattle

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Abstract

Aims While behavioural change associated with clinical disease in cows has been widely studied, the impact of subclinical disease on behaviour is less known. The ability to detect subclinical disease via behavioural changes using targeted monitoring could help to improve cow welfare and decrease economic loss.

Methods This study investigated the possibility of assigning a cow as a healthy control or having subclinical mastitis based purely upon behaviour, by comparing 24 hours of an 'unclassified' cow's behavioural data to reference data and checking the prediction.

Results Predictions were accurate when using the 24-hour data set, but classification using specific time periods or behaviours may also be possible, with view of future automation of the recording, identification and classification of behaviours, which is currently all done manually.

Conclusions Targeted monitoring would be less time-consuming than 24-hour monitoring and better suited for routine cow-health monitoring. To validate these initial findings, further investigation with more focal cows and a larger reference data set is required.

Introduction

Clinically diseased individuals often display sickness behaviour as part of a systemic inflammatory response to infection.[1,2] This can include reductions in physical activity, social behaviour and feeding/drinking.[3] Although inflammatory markers can also be up-regulated in sub-clinical disease,[4,5] the impact of sub-clinical inflammation upon livestock behaviour and welfare remains largely unstudied.

This study formed part of a project aiming to detect behavioural differences between cows with and without subclinical mastitis (SCM). Currently, mastitis detection occurs during milking, as farmers pick up clinical signs and overt sickness behaviour. Since direct behavioural observations of focal cows are extremely time-consuming, we investigated the potential for targeting specific behaviours and/or discrete time periods (1 hour blocks versus 24 hours) by utilising reference baseline data previously collected from a commercial dairy herd to assign health status to a visually healthy cow.

Methods

A reference data set of behaviour had been previously compiled from 24-hour video footage (in 1-hour blocks, long enough to display infrequent behaviours) from pregnant dairy cows without clinical symptoms, using a comprehensive ethogram **(Table 1)**. The cows were assigned to two groups (n=12 control and n = 12 SCM; paired for parity, age, pregnancy state and milk yield). Cows in the SCM group had a somatic cell count (SCC) of >200,000 cells/ml at the time of data collection.

For this sub-study, continuous direct observations were also recorded over 24 hours for an 'unclassified' non-pregnant cow of unknown health status (the investigator was blind to the SCC count). Starting at 00:00 hours on the day of interest, the number of behavioural transitions was calculated for each time period and focal behaviours were recorded. Behavioural data was compiled into two sets: (1) hourly totals; and (2) 24-hour totals for all behaviours (and transitions). No data was recorded at 06:00 hours, 14:00 hours or 22:00 hours, when the cow was in the parlour. When the cow was not visible for 3600 seconds/hour, the behavioural data was adjusted by protracting the duration of the behaviours proportionally over 3600 seconds (=3600/seconds visible×behaviour duration), providing there were over 1800 seconds of footage in which the cow was visible, otherwise the hour was discarded entirely. The '24 hour total' data set was also adjusted to reflect the duration (seconds) or number (n) of each behaviour 'per hour of total time visible'.

Paired t tests were performed, using SPSS, on each behavioural measure within the reference data set. For measures that showed a significant difference between 'groups' (p<0.05), 95% confidence intervals (CIs) were calculated to produce estimates of diagnostic range **(Table 2)**. These diagnostic parameters were then used to assign the 'unclassified' cow to a group (control or SCM).

Results

Of the behaviours analysed, 23/36 were statistically significant in categorising control vs SCM data. Using these 23 behaviours, the '24 hour total' reference data predicted the unclassified cow would fall within the control group: 16/23 behaviours fell within control parameters, 5/23 within SCM, and 2/23 were unclassified **(Table 2)**. In contrast, categorisation of the unclassified cow considering the behavioural data for individual hours was not possible: 20/41 fell within control parameters, 17/41 within SCM, and 4/41 were unclassified **(Table 2)**.

SCC data (SCC = 63,000 cells/ml) confirmed the unclassified cow was a control. Although the continuous observation of 24 hours of behavioural footage enabled us to correctly assign the cow as SCM-free, it was time consuming and labour intensive.

Overall, the division of data into hourly blocks for analysis did not improve correct group assignment. However, there is an indication that 00:00-01:00 hours may be a targetable time regarding social behaviour (or lack, thereof), since 'explore social', 'social all give' and 'social all receive' correctly classified the cow during this period **(Table 2)**. Feeding behaviour and activity levels (measured by behavioural 'transitions') may also prove useful as key behaviours to log at night/early morning: 'feed' correctly classified the cow within the intervals of 23:00 to 00:00 hours and 02:00 to 03:00 hours, whilst 'transitions' led to correct classification between 02:00 to 03:00 hours and 05:00 to 06:00 hours **(Table 2)**.

Table 1. Data from ethogram recording of cow behaviour, including direct behavioural observations, broader descriptive categories and units of measure.

Behaviour	Unit of measure	Definition
Observed behaviour		
Allogroom give	*n*/s	Licking a conspecific
Allogroom receive	*n*/s	Receiving licks from a conspecific
Body push give	*n*/s	Sideways shunt (e.g. when entering crowded area of feed passage barrier) delivered by flank of focal cow
Body push receive	*n*/s	Receipt of body push by conspecific
Brush	s	Use of the mechanical brush
Challenge give	*n*/s	A threatening non-contact gesture towards a conspecific (e.g. a determined approach with a head-down posture)
Challenge receive	*n*/s	Receipt of a challenge from a conspecific
Chin press give	*n*/s	Exerting chin pressure on the lateral posterior of a conspecific
Chin press receive	*n*/s	Receipt of a chin press by a conspecific
Drink	s	Ingestion of water
Feed	s	Actively ingest/chew food (non-rumination)
Eliminate	s	Defecate or urinate
Explore cow	*n*/s	Sniffing a conspecific without physical contact
Explore food	s	Sniffing/nosing food without obvious ingestion
Explore pen	s	Sniffing or licking any part of the barn structure
Explore sand	s	Sniffing a sand bed
Head butt give	*n*/s	Violent striking of a conspecific using a lowered head
Head butt receive	*n*/s	Receipt of a head butt from a conspecific
Head push give	*n*/s	Using the head to gently push/nudge a conspecific
Head push receive	*n*/s	Receipt of a head push from a conspecific
Head swipe give	*n*/s	Sideways swipe of head (usually directed at a conspecific's head)
Head swipe receive	*n*/s	Receipt of sideways head swipe from conspecific
Lick self	s	Licking own body
Lie_head down	s	Head resting on floor/cubicle bar whilst lying (no rumination)
Lie_head on flank	s	Head held against the flank (pointing towards rump) whilst lying
Lie_head up	s	Head held upright whilst lying (with/without rumination)
Lying	s	Shift in vertical orientation from standing to lying
Mutual head butt	*n*/s	Mutual head butting between the focal cow and a conspecific
Mutual head rub	*n*/s	Mutual head rubbing between the focal cow and a conspecific
Mutual sniff	*n*/s	Mutual sniffing between the focal cow and conspecific
Rising	s	Shift in vertical orientation from lying to standing
Rub self	s	Rubbing body upon pen furniture
Run	s	Running
Scratch self	s	Scratch body with leg
Stand	s	Standing
Walk	s	Walking
Calculated behaviour		
Comfort	s	Brush + lick self + rub self + scratch self
Explore non-social	s	Explore food + explore pen + explore sand
Explore social	*n*/s	Explore cow + mutual sniff
Lie all	s	Lie with head down + lie with head up + lie with head on flank
All (non-affiliative) social give	*n*/s	Body push give + challenge give + chin press give + head butt give + head push give + head swipe give + mutual head butt
All (non-affiliative) social give	*n*/s	Body push receive + challenge receive + chin press receive + head butt receive + head push receive + head swipe receive + mutual head butt

s, seconds

Table 2: The classification of cow of 'unknown' health status as being a control (Ctrl) or as having SCM using behavioural data and a reference data set taken from the same herd.

Behaviour	Unit	Reference data				Unclassified cow	
		Control		SCM			
		Diagnostic parameter	95% CI	Diagnostic parameter	95% CI	Value	Classification
24 hour total							
Body push give	*n*	>0.62	0.43, 0.64	<0.43	0.29, 0.62	2.13	Ctrl
Brush	s	>24.2	7.2, 33.5	<6.78	6.8, 24.2	34.8	Ctrl
Challenge give	*n*	>0.16	0.08, 0.30	<0.08	0.03, 0.16	1.3	Ctrl
Challenge receive	*n*	>0.31	0.22, 0.51	<0.22	0.12, 0.31	1	Ctrl
Chin rest receive	*n*	ND	0.01, 0.05	>0.05	0, 0.22	0.1	SCM
Comfort	s	<28.9	28.9, 59.3	>51	29.4, 51	56.5	SCM
Explore cow	*n*	>1.32	0.84, 1.66	<0.84	0.70, 1.32	4.2	Ctrl
Explore food	s	>17	12.4, 23.8	<12.4	11.1, 17	32.9	Ctrl
Explore sand	s	>29.9	22.2, 35.9	<22.2	16.9, 29.9	28.8	Unclassified
Explore non-social	s	>51.2	42, 65.2	<42	38.1, 51.2	74.6	Ctrl
Explore social	*n*	>1.65	1.04, 1.94	<1.04	0.86, 1.65	4.2	Ctrl
Explore social	s	>15.6	7.12, 17.7	<7.12	6.77, 15.6	60.2	Ctrl
Feed	s	<843	793, 935	>935	843, 1070	471.4	Ctrl
Head butt give	*n*	>0.99	0.45, 1.06	<0.45	0.35, 0.99	2.1	Ctrl
Head butt receive	*n*	>0.75	0.49, 0.94	<0.49	0.46, 0.75	0.3	SCM
Head push give	*n*	>0.15	0.07, 0.16	<0.07	0.03, 0.15	1.9	Ctrl
Head push receive	*n*	>0.13	0.08, 0.27	<0.08	0.02, 0.13	0.5	Ctrl
Head swipe give	*n*	<1.68	1.08, 1.86	>1.86	1.68, 2.98	2.7	SCM
Head swipe receive	*n*	<1.43	1.07, 2.73	>2.73	1.43, 2.97	0.5	Ctrl
Lie_head on flank	s	<145	126, 209	>209	145, 232	155.3	Unclassified
Rub self	s	>8.61	4.82, 8.88	<4.82	3.55, 8.61	15.8	Ctrl
All social give	*n*	<3.11	3.10, 4.45	>4.45	3.11, 5.25	11.6	SCM
Transitions	*n*	>53.6	49.7, 57.7	<49.7	43.5, 53.6	64.7	Ctrl
Individual hour							
Brush—23:00 hours	s	<0.49	0, 0.91	>0.91	0.49, 30.7	0	Ctrl
Drink—12:00 hours	s	>34.3	3.9, 67.7	<3.9	14.8, 34.5	0	SCM
Drink—15:00 hours	s	>117	78.1, 157	<78.1	25.5, 117	151.2	Ctrl
Drink—18:00 hours	s	>45.9	17.7, 87.1	<17.7	0, 45.9	0	SCM
Explore non-social—05:00 hours	s	>17.4	0, 198	ND	1.21, 17.4	204	Ctrl
Explore non-social—16:00 hours	s	>85.8	59, 134	<59	32, 85.8	106	Ctrl
Explore non-social—21:00 hours	s	<25.8	12, 42.2	>42.2	25.8, 75.8	7	Ctrl
Explore non-social—23:00 hours	s	>83.4	44.1, 132	<44.1	23.6, 83.4	82	Unclassified
Explore social—00:00 hours	s	<3.4	0.12, 7.38	>7.38	3.4, 18.6	0	Ctrl
Explore social—02:00 hours	s	>6.9	0, 44.5	ND	0, 6.9	57	Ctrl
Explore social—05:00 hours	s	>0	0, 37	ND	0	158	Ctrl

Explore social—16:00 hours	s	<12.2	1.04, 13.5	>13.5	12.2, 89.8	195.8	SCM
Feed—02:00 hours	s	>425	0, 491	ND	0, 425	554	Ctrl
Feed—18:00 hours	s	>446	86.8, 1240	<86.8	0, 446	0	SCM
Feed—23:00 hours	s	<1300	332, 1300	>1390	1390, 2780	373	Ctrl
Lie_all—05:00 hours	s	<3200	2150, 3240	>3240	3299, 3480	3495	SCM
Lie_head on flank—00:00 hours	s	>220	66.8, 533	<66.8	0, 220	11	SCM
Lie_head on flank—11:00 hours	s	<36.1	16.1, 226	>226	36.1, 376	124	Unclassified
Lie_head on flank—13:00 hours	s	<39.7	0, 142	>142	39.7, 438	249	SCM
Lie_head on flank—23:00 hours	s	>0	0, 201	ND	0	169	Ctrl
Social all receive—00:00 hours	s	<7.52	2.4, 19.7	>19.7	7.5, 94.3	0	Ctrl
Social all receive—02:00 hours	*n*	>0.93	0.62, 5.88	<0.62	0, 0.93	0	SCM
Social all receive—02:00 hours	s	>1.85	1.4, 17.1	<1.43	0, 1.9	0	SCM
Social all receive—05:00 hours	*n*	>0.24	0.20, 1.54	<0.20	0, 0.24	0	SCM
Social all receive—08:00 hours	*n*	<5.09	2.6, 8.1	>8.14	5.09, 12.6	0	Ctrl
Social all receive—12:00 hours	*n*	>5.38	1.8, 12	<1.83	1.12, 5.38	5	Unclassified
Social all receive—15:00 hours	s	>37.4	30.1, 62.4	<30.1	17.2, 37.4	277.7	Ctrl
Social all receive—18:00 hours	*n*	>2.28	0.4, 12.1	<0.4	0.22, 2.28	0	SCM
Social all receive—23:00 hours	*n*	<5.64	2.8, 8.3	>8.29	5.64, 15.5	8	Unclassified
Social all give—00:00 hours	s	<1.62	1.6, 15.6	>15.6	1.6, 92.2	0	Ctrl
Social all give—04:00 hours	*n*	>0.391	0, 2.7	ND	0, 0.39	26	Ctrl
Social all give—04:00 hours	s	ND	0	>0	0, 2.5	512	SCM
Social all give—07:00 hours	*n*	<5.82	2.5, 7.7	>7.74	5.82, 14.5	45	SCM
Social all give—11:00 hours	*n*	<1.62	0.8, 4.9	>4.9	1.62, 11.7	19	SCM
Social all give—16:00 hours	*n*	<3.64	3.1, 6.6	>6.58	3.64, 12.4	53	SCM
Social all give—23:00 hours	*n*	<4.5	1.7, 6.4	>6.43	4.5, 11.3	17	SCM
Allogroom give—16:00 hours	s	<6.7	0, 88.8	>88.8	6.7, 128	5.4	Ctrl

Allogroom receive—15:00 hours	s	<1.3	0	>1.3	1.3, 101	17.6	SCM
Allogroom receive—16:00 hours	s	>23	8.7, 50.9	<8.73	0, 23	34.6	Ctrl
Transitions —02:00 hours	*n*	>40.7	8.5, 97.9	<7.67	7.7, 40.7	42	Ctrl
Transitions —05:00 hours	*n*	>18.4	18.4, 40.4	<16.2	6, 16.2	19	Ctrl

ND, no data; s, seconds

Discussion

The possibility of allocating an unclassified cow to a control group based upon 24 hours of continuous observations has been demonstrated. This study provides initial evidence that night/early morning may be interesting times to monitor specific behaviours (social behaviour, feeding and activity) for diagnosing SCM in dairy cattle. Some concerns addressed by this project were ensuring inter-observer reliability (best when using qualitative behaviour assessment)[6] and utilising a comprehensive and unambiguous ethogram.[7] Since the reference data set was compiled using a relatively small sample (*n*=24), including data from more cows will probably increase predictive capacity. Parlour behaviour was not included as the view was to identify freely displayed behaviours suitable for automated video/collar analysis. Hierarchy (possibly influenced by health) was not considered in relation to behaviour variation. Hopefully, in the future, behavioural analysis, combined with non-invasive monitoring of saliva acute-phase proteins (indicative of low-level systemic inflammation[5]), will enable routine herd monitoring for subclinical disease, benefitting farm profitability and cow welfare.

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Research Article

Retention and characterisation of a sustained efficacy chlorohexidine-containing gel within a periodontal pocket model

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Abstract

Aims Periodontitis is a bacterially induced inflammation affecting the integrity of the connective tissues surrounding the tooth, impacting both oral function and aesthetics. Chlorhexidine (CHX) is a common biocide used widely in dentistry and medicine; however, current CHX-containing treatment aids for periodontitis are not well retained in the mouth due to rapid salivary clearance. The aim of this study was to investigate the suitability of a novel material, sustained efficacy CHX (SECHX), in a temperature-responsive gel, as a prospective aid for the management of periodontitis.

Methods Base gels were formulated using the thermosensitive hydrogel Poloxamer 407 (P407) at 30%, 40% and 50% (wt/vol.), and CHX tripolyphosphate (CHX-TPP; also known as SECHX) was added to the gel. SECHX gels were evaluated with respect to physical characteristics and their retention in an in vitro periodontal pocket model.

Results As the concentration of the P407 increased from 30–50%, the viscosity of the gel increased; however, viscosity decreased with the addition of CHX-TPP. The volume of gel retained over time in the periodontal pocket model decreased over time for both the control and CHX-containing gels. In comparison to the control gels, the CHX-containing gels were better retained over the same period of time. A substantial volume (34%) of the 50% p407 CHX-containing gel was retained after 7 days.

Conclusions Retention of the higher viscosity (50% P407) CHX-TPP containing gels may be beneficial in the management of periodontal disease, given their retention time.

Introduction

Periodontitis is an inflammatory disease affecting the integrity of the supporting tissues surrounding a tooth. It ranks as the sixth most prevalent health condition worldwide, with 45% of adults in the UK showing active or historical signs of the condition.[1] It is often life long and recurring, with detrimental effects on both oral function and aesthetics. Left untreated, it may result in tooth loss (see **Figure 1**).

Tissue destruction in periodontitis results from a combination of direct damage by pathogenic periodontal bacteria found in dental plaque, and the immunological and inflammatory host defence mechanisms against these bacteria and their antigenic by-products. Periodontitis has also been associated with systemic conditions, such as dementia, respiratory diseases, and with poor diabetic control, cardiovascular health and pregnancy outcomes.

Chlorhexidine (CHX) is a common biocide used widely in dentistry and medicine; however, current CHX-containing treatment aids for periodontitis are not well retained orally due to rapid salivary clearance.[3] Traditionally, slow release CHX preparations are used. These perform by releasing an initial high burst of CHX (front-loaded release), which is rapidly cleared, and a dwindling CHX concentration remains thereafter. There are two main problems with this mechanism: an initial high dose of CHX may increase the risk for adverse effects (contact rash, irritation, nausea) and the diminishing supply of CHX that follows may either be ineffective for antimicrobial function or may encourage microbial resistance. Sustained efficacy CHX (SECHX) may provide a good alternative to traditional CHX therapy. SECHX is unique in that it maintains a steady release of CHX, thus minimising the risk of these problems.[3]

The aim of this study was to investigate the suitability of a novel material,[4] SECHX in the form of a temperature-responsive gel (viscosity increases with temperature), as a prospective aid for the management of periodontitis. The developed gels were evaluated with respect to physical characteristics and their retention in an in vitro periodontal pocket model.

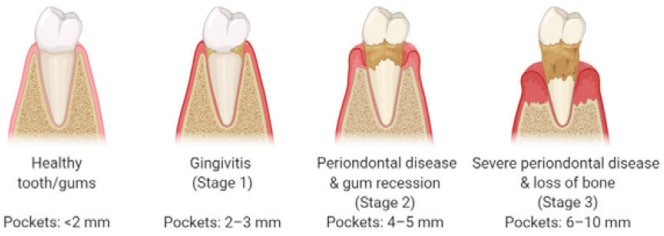

Figure 1. illustration of the progression of periodontal disease. Left to right: healthy gums, gingivitis, moderate periodontitis[2] and advances periodontitis. Created in BioRender.com.

Methods

A model was devised using artificial teeth surrounded by a root surface wax strip and set in silicone, simulating a periodontal pocket upon removal of the wax. Base gels were formulated using the thermosensitive hydrogel Poloxamer 407 (P407; Sigma-Aldrich Company, Dorset, UK) at 30%, 40% and 50% (wt/vol.) concentrations. CHX-containing gels were synthesised by addition of 1% (wt/wt) solid CHX tripolyphosphate (CHX-TPP; also known as SECHX; donated as a sample from Pertinax Pharma, Bristol, UK) to base gels.[4] Control samples contained no CHX-TPP.

Gels were characterised using rheometer oscillation and flow curve experiments, then imaged using differential interference contrast (DIC) microscopy. Retention of the gels in the simulated periodontal

pockets was assessed at days 1, 4 and 7 post-exposure to an artificial saliva bath at 37˚C.

Results

Physical property investigations using rheometry revealed shear modulus elastic component values (G') to be greater than shear modulus viscous component values (G"), confirming the CHX-loaded P407 product as a gel (data not shown). Additionally, rheometry testing indicated that as loading of the gels with CHX-TPP increased, viscosity decreased, whilst an increase in P407 volume resulted in increased viscosity (data not shown).

DIC microscopy demonstrated a grainy appearance of the CHX-containing gel (made with 50% P407) when compared with its control counterpart, indicating an even distribution of the CHX-TPP particles in the gel (see **Figure 2**).

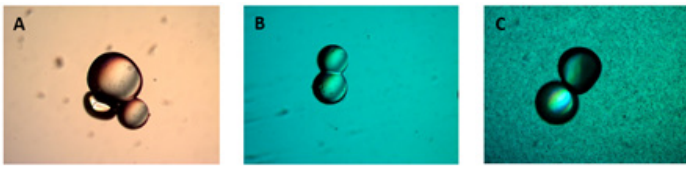

Figure 2. Verification of particle distribution in the gel preparations using DIC microscopy. Bright-field polarised DIC images at ×40 magnification with glass beads. **(a)** Clear control gel (P407 50% without CHX-TPP particles), **(b)** patent blue-dyed control gel (P407 50% without CHX-TPP particles) and **(c)** patent blue-dyed P407 gel (50%) with CHX-TPP particles.

When assessing gel retention in the in vitro periodontal pocket model, retention of both the control and the CHX-containing gels in the simulated periodontal pockets reduced over time. However, the CHX-containing gels were retained better than the controls at each time period. Gels with higher P407 concentration were better retained. A substantial volume (34%) of the CHX-containing gel made with 50% P407 was retained after 7 days (**Figure 3**)

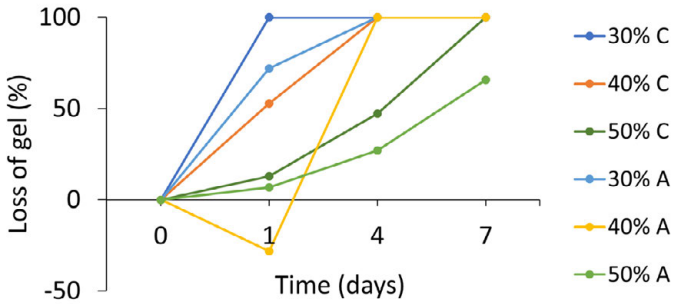

Figure 3. Per cent loss of CHX-TPP gel made with various concentrations of P407 (30%, 40% and 50%) versus respective control P407 gels. Control samples (C) did not include CHX-TPP particles. 'A' refers to samples containing CHX-TPP particles.

Discussion

This study aimed to investigate use of SECHX gel for the management of periodontitis. It was found that as loading of the gels with CHX-TPP increased, viscosity decreased, whilst an increase in P407 volume resulted in increased viscosity. The increase in viscosity with increased poloxamer concentration has also been found in other studies and is thought to be attributed to the closer packing of the lattice pattern within the material.[5]

DIC microscopy demonstrated an even distribution of the CHX-TPP particles in the gel. Clinically, this is important as it suggests a large surface area of the active ingredient (CHX-TPP), resulting in more exposure of the diseased area to this agent and, thus, greater efficiency of treatment.

The findings from the simulated periodontal pocket experiment indicated that an increase in viscosity owing to increased P407 concentration lead to increased retention. However, it was also shown that CHX-TPP containing gels were better retained than the controls at each time period, despite the rheometry findings indicating a reduction in viscosity following CHX-TPP addition to gels. This could potentially be due to a change in the physicochemical properties of the poloxamer gels following incorporation of a drug (in this case SECHX), as demonstrated by Inal and Yaper.[6]

Conclusions Retention of the higher viscosity (50% P407) CHX-TPP containing gels may be beneficial in the management of periodontal disease, given their retention time. Future considerations include testing CHX-TPP containing gels (using relevant control gels) in the presence of commonly found periodontal bacteria, to test their antimicrobial potential and the time period of any antimicrobial action.

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Research Article

Management of severe malaria in children: current practices and development of a paediatric malaria protocol

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Abstract

Introduction Malaria is one of the leading causes of death and morbidity in Uganda. Children are particularly susceptible to severe malaria and account for 70% of total malarial deaths. This audit aimed to analyse the adherence of two Ugandan hospitals to the World Health Organisation (WHO) guidelines for the treatment of severe malaria in children and provide an updated paediatric malaria protocol.

Methods Data was collected from children who were admitted with severe malaria to two hospitals in Masaka, Uganda, over a 6-week period. Each patient's notes were examined to determine whether their clinical management had been in accordance with the eight action points identified in the WHO guidance.

Results Twenty-nine children were included in the study. Artesunate, an anti-malarial drug, was administered correctly in 82.7% of cases. None of the patients had urine output documented and blood sugar was measured in 20.7% of cases. Modal frequency of observations was twice daily (44.8%), with five patients having observations recorded only once during admission. Of the patients who received blood transfusions or paracetamol, 43.8% and 53.8% did not meet the WHO's criteria for either treatment, respectively.

Conclusion The administration of antimalarial medication, the mainstay of treatment, was performed to a very high standard. In contrast, this audit identified large disparities in the provision of supportive treatment and little evidence for effective monitoring of patients during their hospital stay. Therefore, the paediatric malaria protocol used by the hospitals was updated to ensure sufficient monitoring of patients during their time in hospital and clear criteria for supportive treatments.

Introduction

Malaria is one of the leading causes of morbidity and mortality in Uganda.[1] Due to a lack of immunity to the disease, children are a particularly vulnerable group, accounting for 70% of all malarial deaths.[1] Severe malaria is defined as a positive malaria test plus signs of organ failure, including impaired consciousness, renal impairment, pulmonary oedema and shock.[2] The management of severe malaria in children includes three aspects: antimalarial treatment, supportive management and monitoring.[2]

This audit set out to observe the management of severe malaria in children admitted to two hospitals in Masaka, Uganda. It also aimed to analyse the adherence of the two hospitals to the World Health Organisation's (WHO's) recommendations for the treatment of severe malaria in children;[2,3] these are international guidelines collated from reliable evidence.

Methods

Data collection occurred in Kitovu Hospital and Villa Maria Hospital, both in Masaka, Uganda. Records from the 1st June to the 16th July 2019 were examined and all children under the age of 16 years with a diagnosis of severe malaria were selected for inclusion.

The collation of three WHO documents[2,3,4] resulted in a list of eight actions in the management of severe malaria in children. These include: (1) antimalarial treatment, which consists of three doses of artesunate; (2) a 3-day course of Coartem after antimalarial treatment; (3) monitoring urine output; (4) monitoring blood sugar; (5) 4-hourly observations; (6) supportive management with broad-spectrum antibiotics until bacterial infection is excluded; (7) supportive management with paracetamol for pyrexia >38.5°C; and (8) supportive management with blood transfusion if haemoglobin falls below 5 g/dl.[2,3,4]

The adherence rate for each action was assessed by examining medical notes and observation and drug charts.

Results

The sample group comprised of 29 children ranging from 8 months old to 11 years, of whom 16 (55.2%) were male and 13 (44.8%) were female.

Antimalarial treatment All patients received artesunate. However, artesunate was started 24 hours late in one case, and four patients received an incorrect dose of the drug (*n*=3 received too small a dose and *n*=1 had a dose that exceeded the recommendation; see **Figure 1**).

Coartem was prescribed correctly in 100% of cases and all patients were discharged with instructions to complete the course at home.

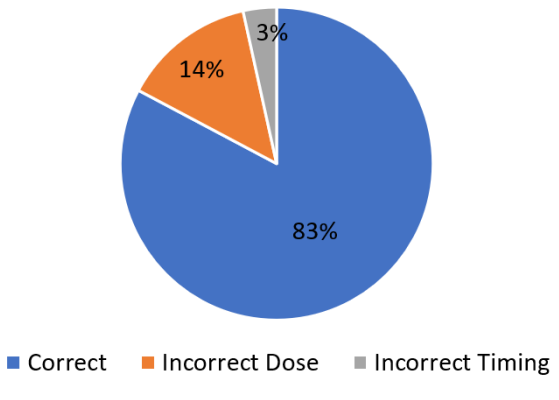

Figure 1. Proportion of correct administration of artesunate and causes of incorrect administration.

Monitoring None of the patients had urine output or fluid balance documented. In contrast, blood sugar was documented for *n*=6 patients (20.7%), of whom *n*=3 were hypoglycaemic and treated accordingly (data not shown). The modal frequency of clinical observations was twice daily (44.8%; **Figure 2**). Observations were done once during admission into hospital in *n*=5 patients.

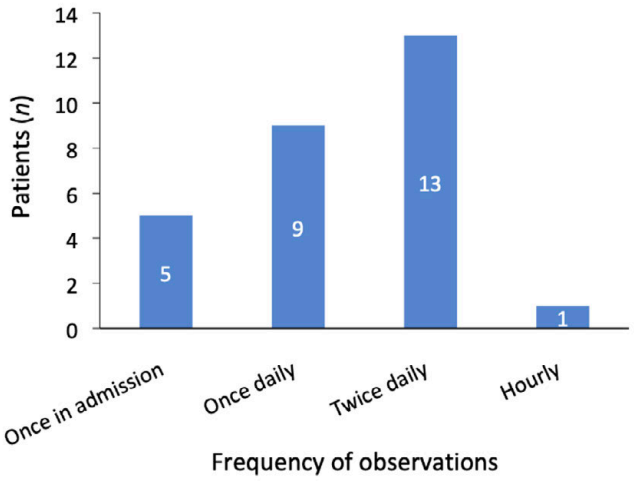

Figure 2. Frequency of clinical observations on the paediatric ward.

Supportive treatment Broad-spectrum antibiotics were started in 19 of 29 patients (65.5%), of which none were stopped upon exclusion of bacterial infection (data not shown).

Of the patients who received paracetamol (89.7%), 53.8% had a temperature <38.5ºC (**Figure 3**). Of the 16 patients who received blood transfusions, *n*=9 had a haemoglobin concentration <5 g/dl (data not shown). Of the patients who received blood transfusions or paracetamol, 43.8% and 53.8% did not meet the WHO's criteria for either treatment, respectively.

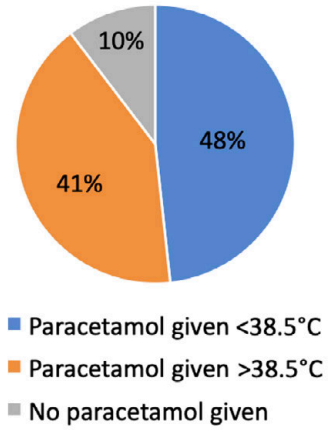

Figure 3. Proportion of patients who received paracetamol, based on whether their temperature was over 38.5ºC or not.

Discussion

The hospitals that this audit was conducted in used the Republic of Kenya Ministry of Health's protocol for management of severe malaria in children.[5] The doctors treating the patients in this study had extensive experience in managing children with severe malaria, yet the results of this audit reflect incomplete adherence to the WHO guidelines. Based on the findings of this audit, the paediatric malaria protocol used was updated (**Figure 4**). The evidence behind each addition to the adapted Ugandan protocol, as well as challenges to adherence are discussed below.

Antimalarial treatment Prompt artesunate administration has the largest effect on survival, reducing the mortality rate of severe malaria from 100% to 20%.[1] The provision of antimalarial treatment was shown to be well-executed by this audit: 96.6% of patients received artesunate immediately on diagnosis and all patients were started on a 3-day course of Coartem.

The wrong dose of artesunate was given to four patients (14%). Whilst records show none of these patients experienced adverse effects whilst in hospital, low dosing could result in treatment failure and malaria recurrence.[2] Furthermore, Xie et al[6] describe that side effects, such as anaemia and reticulocytopaenia, can result from a high dose of antimalarial drugs. The dosing measurements were, therefore, added to the Ugandan protocol and efforts for two health professionals to check the drug dose should be considered.

Monitoring The WHO recommend that clinical observations and blood sugar concentration are recorded 4-hourly in children administered with severe malaria, as well as daily fluid balances.[2,3,4] In this study, however, no children had urine output measured, despite four patients developing renal impairment (data not shown). Furthermore, only 20.7% of children had their blood sugar measured on admission and the recommended 4-hourly observation was not carried out in 96% of patients (**Figure 2**). Monitoring is essential to ensure early diagnosis and management of common complications of malaria, such as shock, hypoglycaemia and acute kidney injury (AKI).[7] One study showed the prevalence of hypoglycaemia in children with severe malaria to be as high as 46.9%[8] and another found 45.5% of children with malaria developed AKI.[7] There are practical implications to increasing monitoring and there were concerns amongst staff in Kitovu Hospital about the cost and time repercussions. However, many children urinated into buckets making urine output an easy and reliable, albeit crude, marker of renal function. Furthermore, the effect that these complications have on mortality rate is so severe[8,9] that it is essential to measure blood sugar concentration and perform clinical observations at least daily.

Supportive treatment Only some of the rationale behind the WHO's recommendations regarding antibiotics, paracetamol and blood transfusions is explained by the literature. Bacterial infection is an important differential diagnosis in a febrile child and co-morbidity of bacterial infection with malaria can be fatal.[9] There is not, however, clear criteria for excluding bacterial infection nor supporting evidence for the use of antibiotics in malaria. This is needed to provide a uniform approach to antibiotic prescription, as only 65.5% of patients received antibiotics in this study, and the reasoning for who did and who did not was not apparent.

From the literature, it is not clear why the temperature threshold for paracetamol prescription in children with severe malaria is so high (38.5ºC). Of the children who were given paracetamol, 53.8% had a temperature <38.5ºC. However, considering temperatures can peak rapidly in children with malaria[4] and paracetamol is cheap and well-tolerated,[10] there are limited negative consequences to this apparent over-prescription.

As with the guidance surrounding paracetamol use, there is also limited evidence for the haemoglobin threshold used to indicate when a blood transfusion is required.[11] WHO guidelines state that the threshold chosen reduces the overuse of blood products and transfusion-related complications.[12] Maitland et al, conducted a randomised controlled trial to determine the appropriate haemoglobin threshold for transfusion, as they proposed that the conservative threshold set by WHO may increase mortality risk.[11,13] However, their study concluded that, although it resulted in longer hospital stays, a transfusion threshold of 4 g/dl did not increase 28-day mortality in comparison to a threshold of 6 g/dl, and it resulted in lower blood use.[13]

In line with the audit findings, prompts for supportive treatment was added to the Ugandan protocol. However, evidence to support the

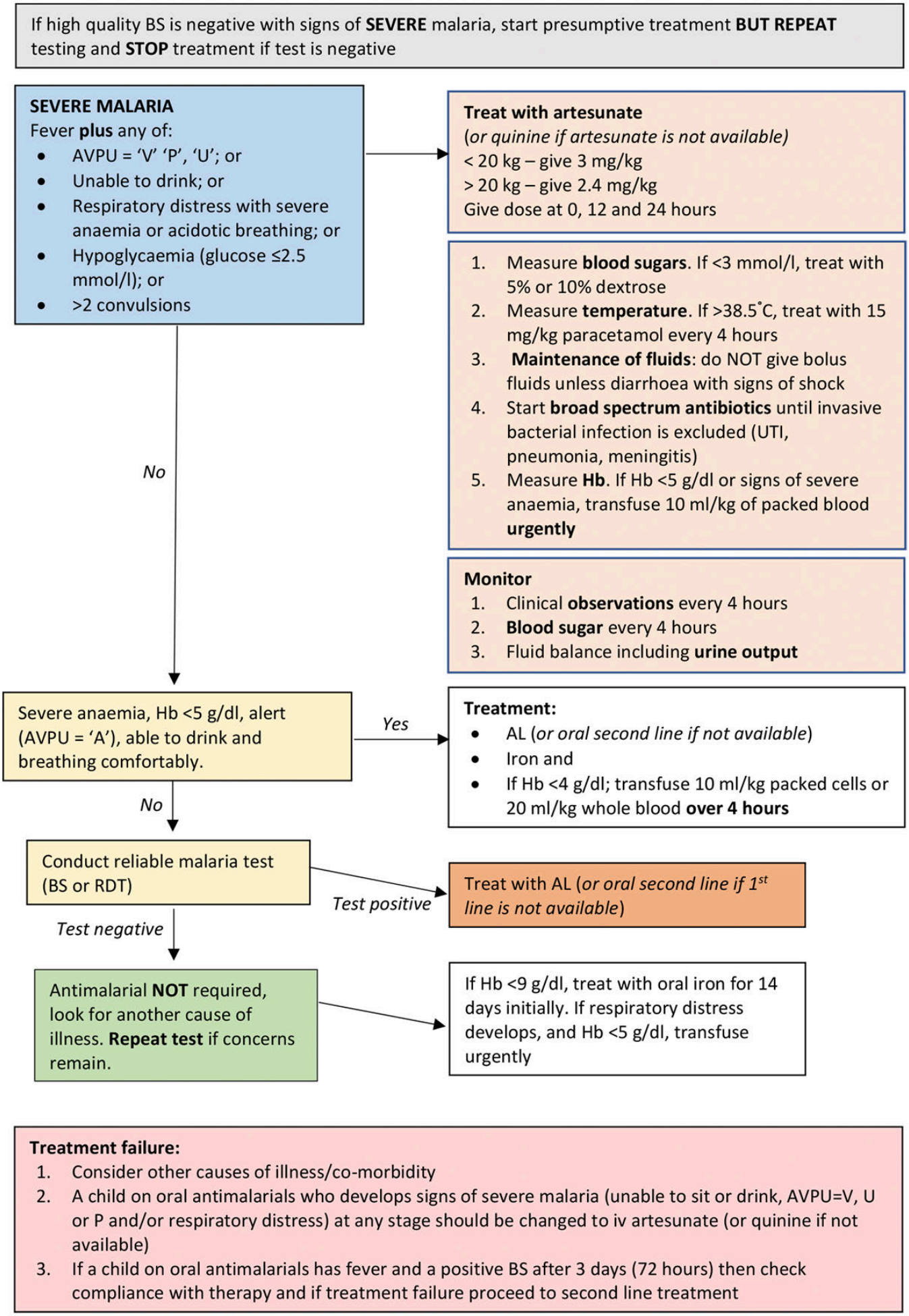

Figure 4. Adaptation to the Ugandan protocol for management of severe malaria in children to include the necessary improvements identified by this audit. AL, artemether-lumefantrine; AVPU, Alert, responds to Voice, responds to Pain and Unresponsive; BS, blood slide; Hb, haemoglobin; RDT, rapid diagnostic test. Figure adapted from the Republic of Kenya Ministry of Health's Basic Paediatric Protocols.[5]

provision of this treatment and guidance on its implementation is still required.

Limitations and conclusions An audit of the management of severe malaria in 29 children in two hospitals in Uganda revealed that, whilst overall management was sufficient, there was incomplete adherence to the WHO guidelines. The small number of patients included in this study limits the significance of these findings as they cannot be generalised to every child admitted with severe malaria in these two hospitals or the wider population. Furthermore, the study was conducted over a short time period of 2 weeks and longer duration studies are required. The lack of complete documentation was also a major limitation of the study as it made it hard to comment on whether actions had been carried out or not. Despite these limitations, this audit identified similar trends across all patients. The administration of antimalarial drugs, the mainstay of treatment, was performed to a high standard. There was, however, limited monitoring of patients and variable provision of supportive care. The findings of this audit have been converted into recommendations, which have been incorporated into a potential protocol to provide the best care for children with severe malaria.

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Research Article

Intraventricular haemorrhage in preterm infants: investigating the pathways involved in astrogliosis to improve neurodevelopmental outcomes

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Abstract

Aims Preterm, low birthweight infants have an increased risk of developing intraventricular haemorrhage (IVH). Substantial haemorrhage can cause blood accumulation in the cerebral lateral ventricles, blocking cerebrospinal fluid (CSF) reabsorption. It can also stimulate migration of neural stem cells (NSCs) and inflammatory molecules into the CSF. This project aimed to generate data to therapeutically support and enhance the endogenous repair mechanisms of the infant brain post injury.

Methods Research at the Regenerative Medicine Laboratory has previously demonstrated that the accumulation of CSF in the lateral ventricles of the brain following IVH can redirect NSC differentiation towards astrocytes. In this study, human neural foetal progenitor cells (hfNPCs) were challenged with the CSF from the lateral ventricles of a baby post IVH (IVH-CSF; samples were collected from one patient at two different time points during therapy progression). hfNPCs were also challenged with IVH-CSF plus pharmacological inhibitors of potentially involved astrogliosis pathways. We screened for two distinct pathways, Janus kinase (JAK) and c-Jun N-terminal kinase (JNK), using their inhibitors (JAK inhibitor I and bosentan/SP600125, respectively). The role of glutamate in astrogliosis was also examined using the drugs ceftriaxone and riluzole. The differentiation profile of the hfNPCs was studied by immunochemistry (S100β in astrocytes, Tuj1 in neurons).

Results Treating hfNPCs with IVH-CSF resulted in a non-significant increase in nuclear and cytoplasmic S100β expression. Exposure of hfNPCs to IVH-CSF and pharmacological inhibitors can impede astrogliosis, although this was not statistically significant.

Conclusions These findings indicate that astrogliosis may reflect neuropathological responses in the resolution of IVH, which are responsible for the compromised neuronal development observed in these patients.

Introduction

Forty per cent of preterm infants (below 1000 g at birth) will develop intraventricular haemorrhage (IVH).[1] Consequently, blood accumulation in cerebral lateral ventricles can block cerebro-spinal fluid (CSF) reabsorption, leading to hydrocephalus. Hydrocephalus stimulates the migration of neural stem cells (NSCs) and inflammatory molecules into CSF.[2] CSF is routinely drained in babies with IVH to prevent a build-up in the cerebral lateral ventricles. Previous research from the Regenerative Medicine Laboratory showed that when neural progenitor cells are treated with CSF samples derived from infants affected by IVH (IVH-CSF), the presence of inflammatory markers, such as IL-6, IL-10, TNF-α, in the IVH-CSF redirects NSC differentiation towards reactive astrocytes. This is detrimental because severe astrogliosis together with glial scar formation may account for compromised neurodevelopment.[3] Furthermore, preterm infants with moderate-to-severe IVH (Grade 3–4) are at higher risk of developing cerebral palsy and severe learning difficulties.[4] Currently, treatment for premature infants suffering from IVH injury is supportive management, such as compressive head wrappings and CSF drainage, which carries its own risks. There is no available treatment to repair injury or improve neurodevelopmental outcomes.[5]

The aim of this study was to investigate whether IVH-CSF stimulates astrogliosis in human neural foetal progenitor cells (hfNPCs) in vitro and whether the response varies depending on whether cells are exposed to early CSF (collected 24 days post IVH) or late CSF (collected 132 days post IVH). Moreover, we hypothesised that blockade of two signalling pathways involved in astrogliosis, Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) and c-Jun N-terminal kinase (JNK), using their inhibitors (JAK inhibitor I and bosentan/SP600125, respectively) would decrease the differentiation of progenitor cells into astrocytes and, hence, reduce astrocyte reactivity.[6,7] Since IVH causes neuronal excitotoxicity by downregulation of glutamate transporters, which leads to neurodegeneration, we also investigated the involvement of glutamate in astrogliosis using the glutamate uptake-enhancer drugs ceftriaxone and riluzole.[8,9]

Methods

The method of hfNPC collection adhered to the recommendations set out by the Polkinghorne Committee (1989) and the UK Department of Health guidelines (1995). Ethical approval was in place for use of hfNPCs from the South Wales Initiative for Fetal Tissue (SWIFT) Research tissue bank in Cardiff (UK). The CSF samples in this study were excess samples of CSF fluid drained from the baby post-IVH as part of routine sampling, which was approved by parental informed consent.

hfNPCs, derived from foetal cortical tissue of terminated pregnancies from SWIFT donors in Cardiff, were treated with Accutase (Biolegend, San Diego, CA, USA). The cells were then grown to neurospheres

for 2 weeks in a growth supporting medium composed of Dulbecco's Modified Eagle Medium (DMEM) and F12 (3:1 DMEM to F12); GlutaMax (2%; ThermoFisher Scientific, Loughborough, UK), penicillin/streptomycin (1%; Sigma-Aldrich, Dorset, UK), B27 (2%; Life Technologies), the mitogenic growth factors human epidermal growth factor (EGF; 20ng/ml) and fibroblast growth factor (FGF; 20 ng/ml; Peprotech), and heparin (5µg/ml; Sigma-Aldrich). This growth medium was replenished twice a week and the cells were stored in a humidified incubator with a controlled environment of temperature of 37°C with 5% CO_2.

The single hfNPCs were harvested and seeded in a 96-well plate at 15,000 cells per well in 50 µl differentiating medium, which was composed of DMEM and F12 (DMEM to F12 at a ratio of 3:1); GlutaMax (2%), N2 (1%; ThermoFisher Scientific) and penicillin/streptomycin (1%; Sigma-Aldrich). CSF was collected 24 days ('early') and 132 days ('late') after IVH from one preterm infant.

After 7 days in the differentiation medium, hfNPCs were treated as follows: control; early CSF; late CSF; early CSF+drug; late CSF+drug; drug. Samples were challenged with CSF at a concentration of 20% . The concentration of experimental drugs used were based on published literature **(Table 1)**.[6-9] Each condition was run in triplicate.

Table 1. Details of the experimental drugs used to treat the hfNPCs.

Drug	Manufacturer	Concentration
JAK inhibitor I	Sigma-Aldrich	10 µM and 50 µM
Bosentan	Sigma-Aldrich	15 µM
SP600125	Sigma-Aldrich	10 mM
Ceftriaxone	Tocris	100 µM
Riluzole	Sigma	100 µM

After 7 days of differentiation, cells were fixed then fluorescent dye immunostained with primary antibodies **(Table 2)** for Tuj1 (neurons) and S100β (astrocytes) and counterstained with Hoechst stain (nuclei). Wells were imaged using automated high-content fluorescent microscopy using an IN Cell Analyzer (Cytiva, Marlborough, MA, USA) to quantify nuclear and cytoplasmic intensity in cells positive for S100β (green stain) and Tuj1 (red stain). The average nuclear and cytoplasmic fluorescent intensity values from each experimental condition was calculated to determine S100β or Tuj1 expression.

Table 2. Details of the antibodies used for immunochemical analysis of experiment.

Antibody	Species	Manufacturer
Primary antibodies		
S100β	Rabbit	Dako[a]
Tuj1	Mouse	Biolegend
Secondary antibodies		
Alexa Fluor 488	Rabbit	Invitrogen
Alexa Fluor 568	Mouse	Invitrogen
Nuclear staining		
Hoechst		Sigma-Aldrich

[a]Agilent, Cheshire, UK

Statistical analysis Using the GraphPad Prism statistical analysis programme (GraphPad Software, La Jolla, CA, USA), paired-sample *t* tests and one-way ANOVA were run to assess the significance of differences in nuclear or cytoplasmic expression of S100β or Tuj1 under the different conditions. A result of $p<0.05$ was considered statistically significant. The ratio of the difference between the mean of the two-sample sets and the variation between the sample sets are presented (t(2)); an increasing t(2) value from 0 indicates how the findings becomes progressively dissimilar from the null hypothesis, which could prove that IVH-CSF does have an effect on astrogliosis. The F-value evaluates the ratio of between-group variance and within-group variance (in this case each group is a different drug tested). The higher the F-value, the greater the variance between the means of S100β expression between each individual drug, more than the variance between the samples within each drug.

To analyse the effect of drug treatments, post hoc comparisons using Dunnett's test were conducted to assess the significance of differences between conditions.

Results

Nuclear and cytoplasmic expression of S100β was higher following treatment with early or late CSF when compared with control; however, the differences did not reach significance **(Figure 1)**.

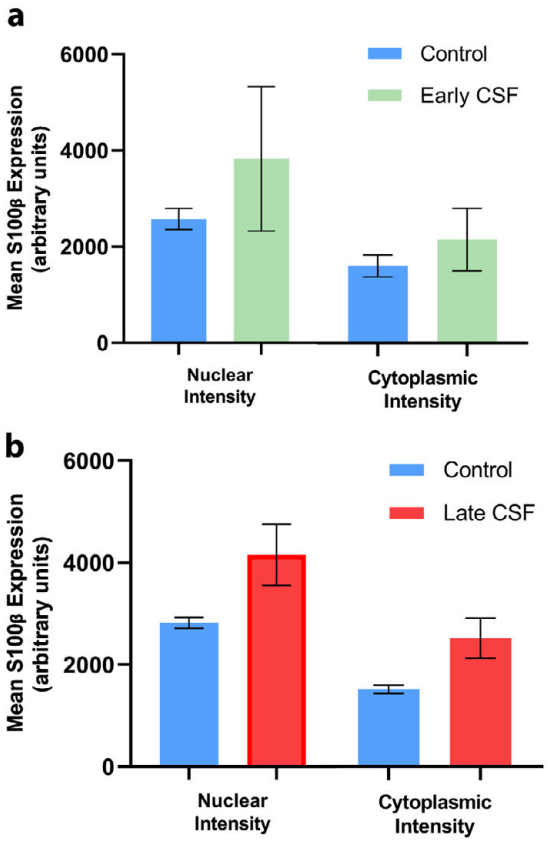

Figure 1. Nuclear and cytoplasmic S100β expression by astrocytes after hfNPCs were left to differentiate for 7 days with or without early or late CSF (20% concentration). Values are presented as mean±SD arbitrary units. **(a)** Evaluation of nuclear (paired-samples *t* test: t(2)=1.689, $p=0.2332$; $n=3$) and cytoplasmic (t(2)=1.230, $p=0.3439$; $n=3$) S100β expression in differentiated cells treated with early CSF. **(b)** Evaluation of nuclear (paired-samples *t* test: t(2)=3.273, $p=0.0820$; $n=3$) and cytoplasmic (t(2)=3.273, $p=0.0820$; $n=3$) S100β expression in differentiated cells treated with late CSF.

Treatment with JAK inhibitor I partially restored the increase in nuclear and cytoplasmic expression of S100β following exposure to early and late CSF; however, this did not reach statistical significance. Treatment with SP600125 resulted in loss of cell viability due to technical issues and so these results were excluded from the statistical analysis. Bosentan treatment non-significantly increased nuclear and cytoplasmic expression of S100β with early CSF and non-significantly decreased nuclear and cytoplasmic expression of S100β with late CSF treatment **(Figure 2)**.

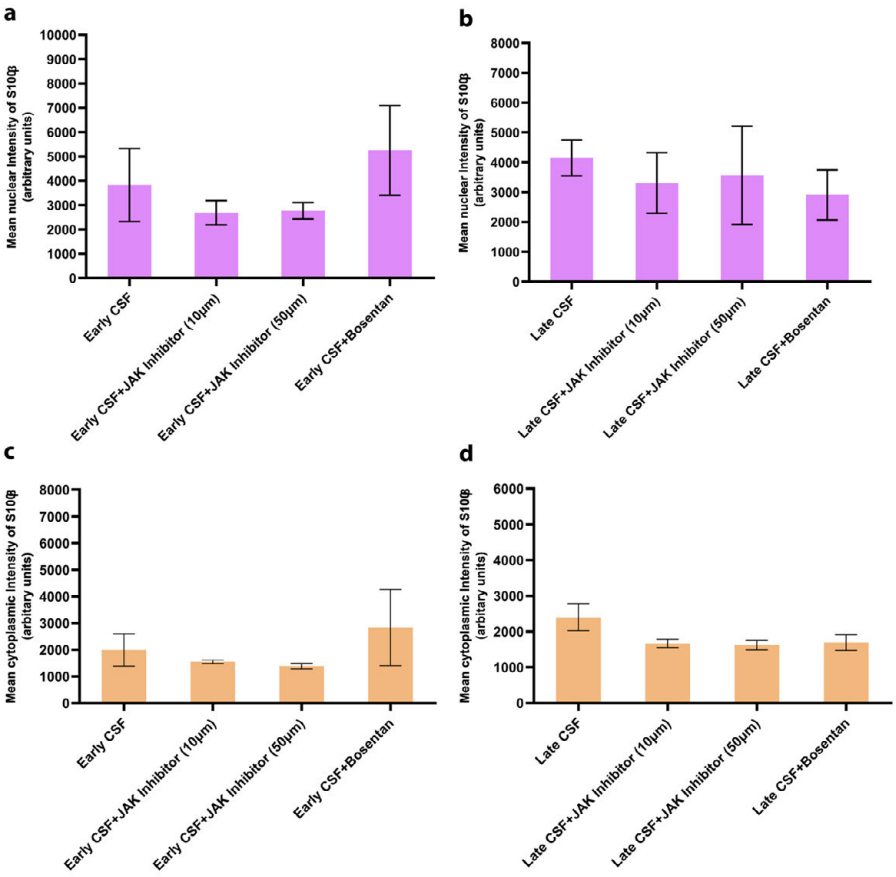

Figure 2. Nuclear and cytoplasmic S100β expression by astrocytes after hfNPCs were left to differentiate for 7 days with early or late CSF (20%), either alone or with the indicated drugs. Values are presented as mean±SD arbitrary units. **(a)** Evaluation of nuclear (one-way ANOVA: F(3,6)=2.401, p=0.2610; n=3) S100β expression in cells treated with early CSF and drugs. **(b)** Evaluation of nuclear (one-way ANOVA: F(3,6)=0.5438, p=0.6031; n=3) S100β expression in cells treated with late CSF and drugs. **(c)** Evaluation of cytoplasmic (one-way ANOVA: F(3,6)=1.672, p=0.3235; n=3) S100β expression in cells treated with early CSF and drugs. **(d)** Evaluation of cytoplasmic (one-way ANOVA: F(3,6)=6.344, p=0.1085; n=3) S100β expression in cells treated with late CSF showed no significant difference. Post hoc comparisons using Dunnett's test revealed no significant differences between conditions.

Tuj1 is a cytoskeletal protein expressed around the nucleus, but the IN Cell Analyzer segments the cell in such a way that there is an overlap in the staining. Hence the IN Cell Analyzer interprets this as a nuclear component. The perinuclear expression of Tuj1 decreased following treatment with early and late CSF with ceftriaxone **(Figure 3)** and riluzole **(Figure 4)**. Cytoplasmic expression of Tuj1 decreased with late CSF and ceftriaxone treatment; however, outcomes were not significant. Cytoplasmic expression of Tuj1 increased with early and late CSF with riluzole; however, the results were not significant.

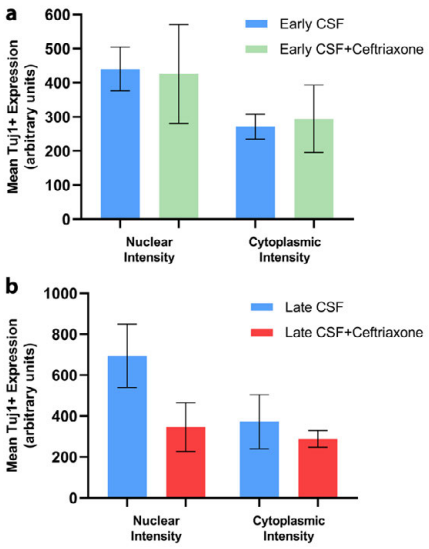

Figure 3. Nuclear and cytoplasmic Tuj1 expression by neurons after hfNPCs were left to differentiate for 7 days in early CSF (20%) alone or in early CSF plus ceftriaxone. Values are presented as mean±SD arbitrary units. **(a)** Evaluation of nuclear (paired-samples t test: t(2)=0.1879, p=0.8683; n=3) and cytoplasmic (t(2)=0.5845, p=0.618; n=3) Tuj1 expression in cells treated with early CSF and ceftriaxone. **(b)** Evaluation of nuclear (paired-samples t test: t(2)=2.578, p=0.1233; n=3) and cytoplasmic (t(2)=0.8461, p=0.4866; n=3) Tuj1 expression in differentiated cells treated with late CSF and ceftriaxone.

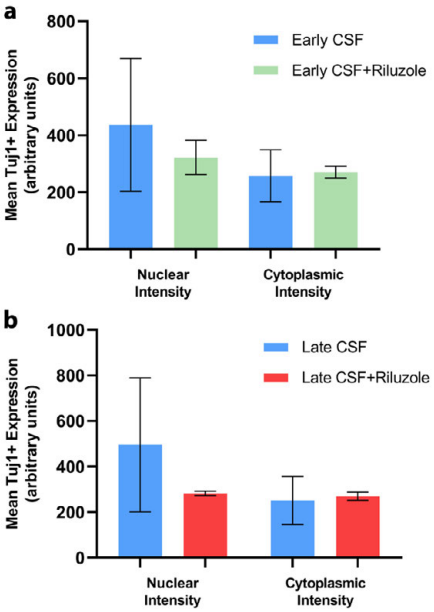

Figure 4. Nuclear and cytoplasmic Tuj1 expression by neurons after hfNPCs were left to differentiate for 7 days in early CSF alone or in early CSF plus riluzole. Values are presented as mean±SD arbitrary units. **(a)** Evaluation of nuclear (paired-samples t test: t(2)=0.7580, p=0.5276; n=3) and cytoplasmic (t(2)=0.1981, p=0.8613; n=3) Tuj1 expression in cells treated with early CSF and riluzole. **(b)** Evaluation of nuclear (paired-samples t test: t(2)=1.223, p=0.3459; n=3) and cytoplasmic (t(2)=0.2963, p=0.7949; n=3) Tuj1 expression in cells treated with late CSF and riluzole.

Discussion

Treating hfNPCs with IVH-CSF showed an increase in S100β expression. Although not significant, this increase could be explained by inflammatory cytokines, such as IL-6, IL-8 and TNF-α, which are present in IVH-CSF, directing differentiation of hfNPCs into reactive astrocytes.

Furthermore, the (non-significant) decrease in nuclear and cytoplasmic S100β expression observed with JAK inhibitor I treatment shows how JAK/STAT3 pathway inhibition might be able to impede astrogliosis following IVH. The inhibition of the JNK pathway with bosentan should have caused a decrease in S100β expression, but instead the outcome of the experiment showed an increase of S100β expression. Although this shows that JNK pathway inhibition can control astrogliosis, the unexpected outcome could be attributed to technical errors that exist from data being derived from the first experimental plate.

The results reported here were derived from one experiment. The statistical analysis shows that although trends could be identified, the results were not statistically significant. Hence, further experiments are required to determine whether the treatments had robust effects on astrogliosis. Future experiments should include more independent replicates to obtain significant findings. This study also highlighted the different effects of early and late IVH-CSF on astrocyte reactivity. Future investigations should study the composition of molecules in the CSF collected at the two different time points from infants with IVH. To increase the validity of the results, more CSF samples could be collected at different time points from different preterm infants with IVH.

Conclusion Preterm infants suffering from IVH can experience future neurodevelopmental complications, such as cerebral palsy. Hence, the underlying aim is to generate data to therapeutically support and enhance endogenous repair mechanisms of infant brain post injury. The observed findings of S100β expression suggest that IVH-CSF leads to astrogliosis, which could be rescued by JNK/STAT3 pathway inhibition. Future investigations should focus on modifying drug concentrations to confirm their ability to control astrogliosis.

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Research Article

The Horse Boy method: an alternative movement method for children with autism and other neurocognitive conditions

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Abstract

Aims 'Move the Mind' is a non-profit organisation that offers an alternative treatment for children with autism and other neurocognitive conditions. They employ the 'Horse Boy' method, in which horses are used therapeutically to treat sensory dysfunctions and improve confidence and communication. The purpose of this research was to observe outcomes of this treatment and openly discuss the outcomes with family members and teachers, exploring the option of it being a viable intervention for autistic individuals.

Methods Movement theory literature was reviewed and group and one-on-one Move the Mind sessions were observed. During a period of 1 month, short-term effects during the session, as well as lasting benefits once sessions had been completed, were noted.

Results The results were overwhelmingly positive with improvements in confidence levels and social functioning being noted. The sessions were child-led, accessible and hugely enjoyable for everyone involved.

Conclusions Some autistic children experience substantial and enduring benefits from the Horse Boy method in terms of their ability to socialise, their confidence, integration with education and family relationships. Clinicians could suggest this method to support traditional therapies.

Introduction

Autism spectrum disorder (ASD) is a lifelong developmental condition[1] affecting the way individuals interact socially. Individuals with ASD may have difficulties communicating, understanding emotions and dealing with unfamiliar situations. They can also experience sensory overstimulation and exhibit repetitive thoughts or behaviours.[2] ASD is present in 1 in 160 children[3] and is considered to be present at birth; however, the cause is not fully understood. It is thought to be multifactorial with a genetic contribution.[1] There is no known association with adverse childhood experiences.[4] Current evidence-based interventions include occupational therapy and social skills training,[5] aiming to increase engagement and communication through play-based strategies.[6]

A potential biological explanation for ASD is disruption of the hypothalamic–pituitary–adrenal (HPA) axis, the system in the body that releases cortisol, a steroid hormone, in response to stress. Chronic stress conditions and prolonged exposure to cortisol can have a harmful effect on a child's brain development. It affects the efficiency of the amygdala and hippocampus, structures in the brain responsible for regulating anxiety and learning emotion.[7] People with ASD are thought to have increased levels of cortisol, resulting from overstimulation by sensory inputs, and a dysregulated HPA response.[8] They end up in a continuous cycle of distress and an inability to learn.[8]

'Move the Mind' uses horses as an alternative therapy for children with ASD. This therapy, known as the 'Horse Boy' method, was developed by a father, Rupert Isaacson, who saw the beneficial effect horse riding had on his autistic son. He put this down to the rocking movements of the horse helping with his son's symptoms. The rationale proposed is that the therapy breaks the cortisol stress cycle by reducing negative sensory triggers and inducing endogenous oxytocin, a hormone thought to combat the stress response by reducing the activity of the HPA axis.[9] This is believed to induce wellbeing, increase social interaction and decrease anxiety.[9]

The purpose of this research was to assess the outcomes of the Horse Boy method for individuals with ASD and openly discuss the outcomes with the children and their families and teachers.

Methods

Movement theory literature was reviewed and both group and one-on-one sessions were observed to see the theory in action. During an observation period of 1 month, short-term effects were observed and discussions were had to identify changes noticed during the sessions, as well as lasting benefits once sessions had been completed. Participants gave consent for their data to be used.

Results

It was demonstrated that a child who is disruptive and aggressive in the classroom may be calm and inquisitive at the farm on which the Move the Mind sessions were held. One child had gone through primary school as a selective mute and, eventually, had to abandon formal education. No other treatment had worked and, although it had been a long journey, at the farm, this individual was now riding, making friends, and helping the younger children. This particular child was now attempting secondary school, something their mother never thought would be possible.

Accompanying teachers bringing children from local schools to the farm spoke of how, by trying new things and socialising in an environment tailored to individual needs and free of adverse sensory triggers, the children were able to develop the ability to express themselves. Parents were finally able to see their child open up socially and make relationships with other children and animals. For one family, witnessing their child's laughter was their first ever social interaction they had seen them make. There was discussion of parents' frustration when their child's sessions had come to an end. However, even after children could no longer attend sessions due

to class rotation, they approached daily activities with new-found confidence.

One parent said, "*[My Daughter] has never had a hobby for herself due to lack of confidence and social skills but now she does! When she's at the farm her face completely changes, and she's relaxed and happy.*"

Another said, *"Having children with complex needs can be very isolating when finding places to take them where they are able to be fully themselves and accepted. My son loves the animals and watching his confidence grow whilst riding has been amazing for him and, as a parent to witness, very special"*

Move the Mind sessions using the Horse Boy method. The collage shows horses being used therapeutically to help children with ASD. These photos are taken from www.movethemind.net/, with permission.

Discussion

The purpose of this experience was to get an insight into the overall impression of the Horse Boy method. Observation and informal discussion revealed that Move the Mind offers multiple benefits and has worked for some children with ASD as a therapy when other methods have failed to improve core symptoms. For the children observed, it improved their confidence and ability to form relationships, enabling some parents to interact with their children for the first time. It is an accessible, natural environment, free of troubling stimulation that has allowed children to open up and explore.

Explaining why the Horse Boy method can have such profound and lasting benefits for children with a complex, resistant and little-understood condition is difficult. We know that children with ASD have been found to have a disruption in their HPA axis.[7] There is evidence that oxytocin can combat this disruption[9] by increasing the number of alpha-2 adrenoreceptors in the amygdala. Alpha-2 adrenoreceptors inhibit the action of noradrenergic neurons that, in turn, influence the HPA axis. The more noradrenaline that is released by noradrenergic neurones, the more corticotrophin-releasing hormone is released with a corresponding rise in cortisol. If an oxytocin-mediated increase in alpha-2 adrenoreceptors can reduce the amount of noradrenaline, it can limit the activity of the HPA axis[9] and, therefore, decrease the stress response. With regards to the evidence behind the use of horses for ASD therapy, oxytocin release is thought to result from rocking movements, such as a mother rocking her baby[8] or sexual activity.[9] Given this, although there is no definitive proof, it seems plausible that oxytocin release might be stimulated by a similar rocking movement such as that created by riding a horse. Given that oxytocin release is also thought to result from stimulation of the skin and increased social interaction,[9] it follows that interacting with horses might stimulate oxytocin release. A structured study is needed to test the oxytocin hypothesis in the context of the Horse Boy method. This would require taking blood, urine or, possibly, saliva samples[10] from children before and after sessions. However, a trial this invasive in children who struggle socially would be ethically questionable.

A strength of this study was that observations were made first-hand and by talking to many individuals; there was a good sense of the impact in most areas of the children's lives, both immediate and long-term. In addition, the data collection was conducted over a 1-month period, offering greater exposure to the effects, rather than a day's snapshot. A weakness of the study is that, when asking for opinions, people are likely to only tell of the success stories and, although it was apparent that every child was engaging and enjoying being there, if the method had not worked for them, they would not have returned or been able to report their experience.

In conclusion, observations would suggest that some autistic children experience substantial and enduring benefits from the Horse Boy method in terms of their ability to socialise, build confidence, integrate with education and have family relationships. If future studies support these benefits, this intervention could become more widely accepted and influence future practice, encouraging clinicians to suggest it to support traditional therapies. Limited availability might benefit from a raised awareness of the work of Move the Mind, which could increase funding from charities or local communities and help create a larger workforce through volunteers and training programmes. Funding would also help families that were unable to pay for the sessions themselves.

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Research Article

A time and motion study in a neonatal intensive care unit

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Abstract

Aims This study aimed to quantify and compare doctors' shift activity in 2019 on a neonatal intensive care unit with 2011 data. Differences in 'wasted' time, workflow interruptions and the most time-consuming tasks since the introduction of quality improvement changes to the unit in 2011 were analysed.

Methods The activity of five doctors was monitored in a time and motion study. Each doctor was followed over a 12 hour shift. Observations and interruptions were recorded using an activity pro forma. Distance travelled by doctors, fluid intake and number of toilet trips were also noted.

Results 'Wasted' time, interruptions and distance travelled per shift reduced by 38% (p=0.01), 80% (p=0.0007) and 55% (p=0.0005), respectively, between 2011 and 2019. The largest proportion of shift time was dedicated to direct patient contact in both 2011 (33%) and 2019 (36%). Fluid intake by doctors was inadequate in 2019, averaging 810 ml per shift.

Conclusions This study has not been able to conclude the areas of workflow that have benefitted from the reduction in 'wasted' time. Further monitoring in this field may help clarify wasted time and improve efficiency further.

Introduction

In 2017, there were 3395 admissions to neonatal units in Wales. Of these, 15% were in the University Hospital of Wales (UHW), the most of any Welsh hospital.[1]

In the hospital setting, wasteful activities can have an impact on the time for direct patient contact. A 2011 time and motion study analysed 4320 minutes of doctor activity on the neonatal intensive care unit (NICU) at UHW. This was inspired by the 'Productive Ward' and 'Transforming Care' initiatives of the NHS, which empower ward teams to redesign and streamline work processes.[2,3] Since 2011, several 'quality improvement' processes have been implemented, focussing on efficiency and reducing unnecessary testing. These include:

- changes to the design of the unit
- introduction of the 'handover and huddle' framework
- availability of guidelines on the intranet
- presence of a senior pharmacist on the ward round
- improvements in staff training

Time and motion studies have been shown to be a reliable tool for the assessment of doctors' workflow patterns.[4] We aimed to determine the impact of these changes on doctors' activity by comparing current (2019) activity with 2011 data, with particular emphasis on 'wasted' time and interruptions.

Methods

The methods used in this study (described below) closely follow that of the original 2011 study.[5] Differences of note are as follows:

- The observer was different between the studies (however, the supervisor of both this and the 2011 study was the same so the guidelines followed remained constant);
- There was one less ITU shift observed in this study as compared with the 2011 study;
- The length of interruptions, fluid status and toilet visits were recorded in this study but not in the 2011 study.

UHW NICU is a tertiary centre with 28 cots (eight intensive care, ten high dependency and ten special care). Per neonatal shift, there are two Senior House Officers (SHOs) and one registrar on ICU, with two to three doctors in high dependency. The activity of five NICU doctors (n=3 SHOs and n=2 registrars) was monitored on a minute-by-minute basis in a time and motion observational study.

Verbal consent was obtained to follow each doctor over a 12 hour ICU weekday shift (09:00–21:00 hours), totalling 3600 minutes of activity. The doctor recruitment was random and the days that were monitored were selected at random. All participants were in good health on the day of participation. A standardised activity pro forma (**Appendix 1**) was used to record observations. The distance that doctors travelled while on shift was recorded, and fluid intake and number of toilet trips were noted to gauge hydration status. Participant activity was timed using a digital stopwatch and steps measured with a pedometer mobile phone application (iOS 'Health' application).

'Wasted' time was defined as any unnecessary motion not related to the task being performed. Examples of wasted time included walking to another computer because the nearest one was being used or looking for notes/equipment that were not in the expected location. An 'interruption' was any event that required the participant to stop their current activity. This study did not require ethical approval as patient information was not used and the identity of doctors has been kept confidential.

Results

The absolute time and percentage of the 12 hour shift that each participant spent on a specific category is presented in **Table 1**. The only activity that was statistically different between 2011 and 2019 was 'wasted' time per shift, which was reduced by 38% (p=0.01) between 2011 and 2019. In total, approximately 49 minutes was lost to 'wasted' time in 2019, as compared with 78 minutes in 2011 **(Table 1)**.

In both 2011 and 2019, the top three activities that had the most time dedicated to them were direct patient contact (which included ward round; the largest proportion of shift time was dedicated to this: 33% in 2011 and 36% in 2019), followed by medical documentation and discussion (**Table 1, Figure 1**). Sepsis screens were the most time-consuming clinical procedure, averaging 26 minutes per shift (data not shown). In 2011, the most performed clinical procedure was capillary blood gases (CBGs), taking up an average of 28 minutes per shift, whilst, in 2019, time spent doing CBGs averaged 3 minutes per shift (data not shown).

Table 1. Absolute time and percentage of 12 hour shift participants spent on specific activities in 2011 and 2019

Activity category	$\bar{x}$ time taken (minutes) over 12 hour shift		*p* value
	2011	2019	
'Wasted' time, i.e. unnecessary motion	78.33 ± 17.55	48.60 ± 11.56	0.01
Teaching/training	57.67 ± 52.72	30.00 ± 39.35	0.36
Medical documentation	162.00 ± 60.06	191.10 ± 38.11	0.37
Discussion	107.33 ± 31.55	96.40 ± 56.75	0.69
Personal hygiene	3.17 ± 3.06	6.50 ± 4.82	0.20
Other (including breaks)	72.33 ± 10.09	81.30 ± 24.42	0.43
Direct patient contact (including ward round)	239.17 ± 64.01	256.50 ± 53.84	0.64
Interruptions	ND[a]	9.60 ± 3.80	
Ward round	107.80 ± 29.10	137.80 ± 40.04	0.18

Data is represented as the mean±SD

[a]The 2011 study only recorded the frequency and not the length of each interruption, therefore no data are present

ND, no data

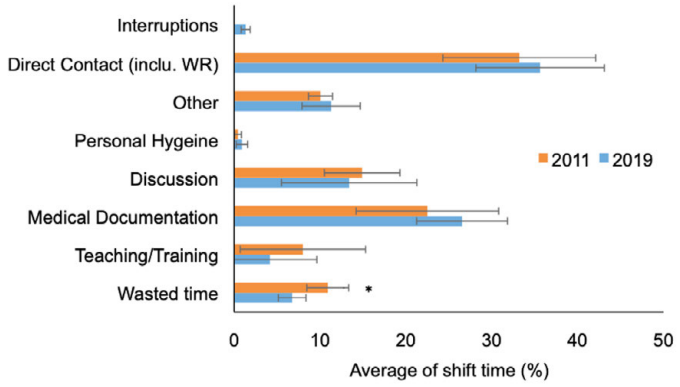

Figure 1. Comparison of the combined average shift activity of NICU doctors in 2011 and 2019. Inclu., including; WR, ward rounds. *$p<0.05$.

Interruptions and distance travelled per shift reduced by 80% ($p=0.0007$) and 55% ($p=0.0005$), respectively, between 2011 and 2019 (**Table 2**). Fluid intake in 2019 was, on average, 810 ml per shift, and participants made one toilet visit.

Table 2. Comparison of participant steps, distance, fluid intake and interruptions between 2011 and 2019.

Variable	$\bar{x}$ over 12 hour shift		*p* value
	2011	2019	
Steps *(n)*	6805 ± 1348	3264 ± 903	0.0007
Distance (km)	5.39 ±1.08	2.41 ± 0.69	0.0005
Amount to drink (ml)	ND	810 ± 286	
Toilet visits *(n)*	ND	1.40 ± 0.89	
Externally prompted interruptions *(n)*	40.67 ± 14.12	8.20 ± 2.28	0.0007
Self-prompted interruptions *(n)*	22.5 ± 10.9	3.2 ± 2.6	0.004

Data is represented as the mean±SD

ND, no data

Interruption frequency was significantly less in 2019, with an average of 8 occurrences over a 12 hour shift, as compared with 41 in 2011 (**Table 2**; $p=0.0007$). A similar pattern was seen in the number of times the doctor interrupted someone else: 23 in 2011 compared to 3 in 2019. In both years, doctors received more interruptions than they initiated. The most common source of interruptions was patient-related queries in both 2011 and 2019 (data not shown).

When comparing activity between registrars and SHOs, two activity categories showed statistical significance: discussion and medical documentation (**Figure 2** and **Appendix 2, Supplementary Table 1**). Registrars spent an additional 91 minutes (21% of shift time) on discussion as compared with SHOs (8% of shift time), whilst SHOs spent 66 more minutes on medical documentation than registrars. Although the percentage of shift time lost to interruptions was similar for both registrar and SHO, the average interruption rate was 9.5 and 7.3 times per shift, respectively (**Appendix 2, Supplementary Table 2**). Furthermore, SHOs interrupted someone else on average five times per shift as compared with registrars (0.5 times; **Appendix 2, Supplementary Table 2**).

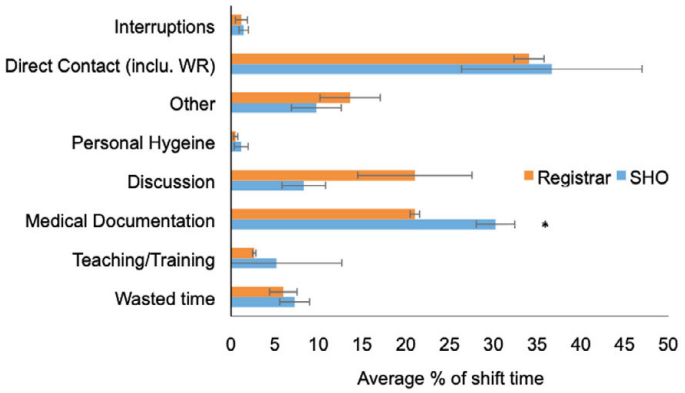

Figure 2. Comparison of the 2019 activity between registrars and SHOs in the NICU. Inclu., including; WR, ward rounds. *$p<0.05$. See **Appendix 2, Supplementary Table 1** for raw data.

Discussion

One potential contributing factor to the reduction in wasted time observed in this study when compared to 2011 was the practical design of the unit investigated. All equipment for clinical procedures was in one location, resulting in less time looking for it (see **Appendix**

3, Supplementary Figure 1a). Moreover, each patient had their own trolley at their bedside containing their notes, making them easy to find (**Appendix 3, Supplementary Figure 1b,c**). Previously, in 2011, all patient notes were stored together, requiring the doctor to leave the bedside to collect them. Furthermore, the introduction of the 'handover and huddle' framework identifies patient safety concerns and increases team members' situational awareness of the management plans for that day.[6] This has led to a culture change on the NICU.

Direct patient contact accounted for 36% of the shift in 2019. In 2011, the most performed clinical procedure was CBGs, taking up an average of 28 minutes per shift. As a result of this, programmes were implemented to reduce the number of CBGs and, consequently, time spent doing CBGs averaged 3 minutes per shift in 2019. This is because they were generally performed alongside phlebotomy or cannula insertion, and not as a separate procedure. The nurse would take the sample to the blood gas analyser for the doctor, thus saving time. Often the nurse did the entire CBG, allowing the doctor to complete other tasks. CBG numbers for 2018 were unavailable at the time of writing, therefore, it is unclear if the time reduction represents a true continued decrease in CBG procedures or if nurses are doing them instead.

Interruption occurrence was significantly less in 2019 than in 2011. Since 2011, training of the NICU staff on not interrupting people was introduced and, consequently, interruptions have halved (unpublished findings). Other changes include the increase in numbers of staff[7] and improvements in training across the deanery.[8] In addition, management guidelines are accessible on the intranet, potentially reducing the need to ask for advice.[9] A senior pharmacist is present on the ward round so any medication-related queries can be addressed during this time.[10] In both years, doctors received more interruptions than they initiated, which agrees with the previous literature.[11]

Registrars spent an average of 21% of shift time in discussion, as compared with 8% by SHOs. This is expected given the greater role registrars play in decision-making, leadership and supporting junior doctors.[12]

On average doctors drank just over 800 ml of fluid and made just one toilet visit during a 12 hour shift in 2019. The European Food Safety Authority (EFSA) recommends a daily water intake of 2.0 litres for females and 2.5 litres for males.[13] Guidance from the UK Health and Safety Executive requires that water is available in sufficient quantities in the workplace.[14] Dehydration by 2% of bodyweight "impairs performance in tasks that require attention, psychomotor, and immediate memory skills".[15] Based on these recommendations, doctors are not drinking enough, increasing the likelihood of errors and potential for patient harm. It is recommended that units install a water dispenser on the ward to improve accessibility and encourage doctors to remain hydrated while on shift.

There are several limitations of this study. For example, the interpretation of activities/interruptions by the observer was subjective, making reproducibility of the data difficult. In addition, the time-consuming nature of the study makes collecting data on large sample sizes highly demanding in terms of resources and impractical. Therefore, the results may not be reflective of all NICU doctors. Moreover, human error in time recording is likely to affect the accuracy of the data. It is also difficult to overcome the Hawthorne effect, in which clinicians may change/improve their behaviour in response to being observed.[16] In addition, the EFSA guidance on water intake is the recommended amount over a whole day; however fluid intake from doctors was only measured over a 12 hour period. Therefore, doctors could have potentially drunk enough each day if the fluid they consumed outside of shift hours was included.

For future studies, a pilot study to train multiple observers and compare their agreement in interpreting activity may be useful. This will ensure uniformity and improve the reliability of the results.[11] It may also be worth considering influencing factors, such as the demographic of the doctor, including age, sex, experience working on the unit and if training was in or outside the UK. To better assess dehydration, researchers could consider performing bioelectrical impedance analysis, which is accepted to be a reliable method of measuring total body water. The values obtained from bioelectrical impedance correlate closely with the values derived using the recognised 'gold standard' for measuring total body water, isotope dilution.[17] It may also be useful to record the number of CBGs carried out by both doctors and nurses to determine if there has been a reduction in the number of procedures performed.

Conclusions 'Wasted' time, interruptions and distance travelled all decreased from 2011 to 2019. Other areas of workflow showed little difference. The observed changes may be the consequence of multiple unit changes and the conscious effort of clinicians to be more efficient in their work. Fluid intake by doctors was inadequate and this may impact their performance. This study has not been able to conclude the specific areas of workflow that have benefitted from the reduction in 'wasted' time. Further monitoring in this field may help clarify wasted time and improve efficiency further.

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Contribution Statement All authors of this work meet the following authorship criteria: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; drafting the work or revising it critically for important intellectual content; and final approval of the version to be included in Inspire. Cora Doherty is the guarantor of this work.

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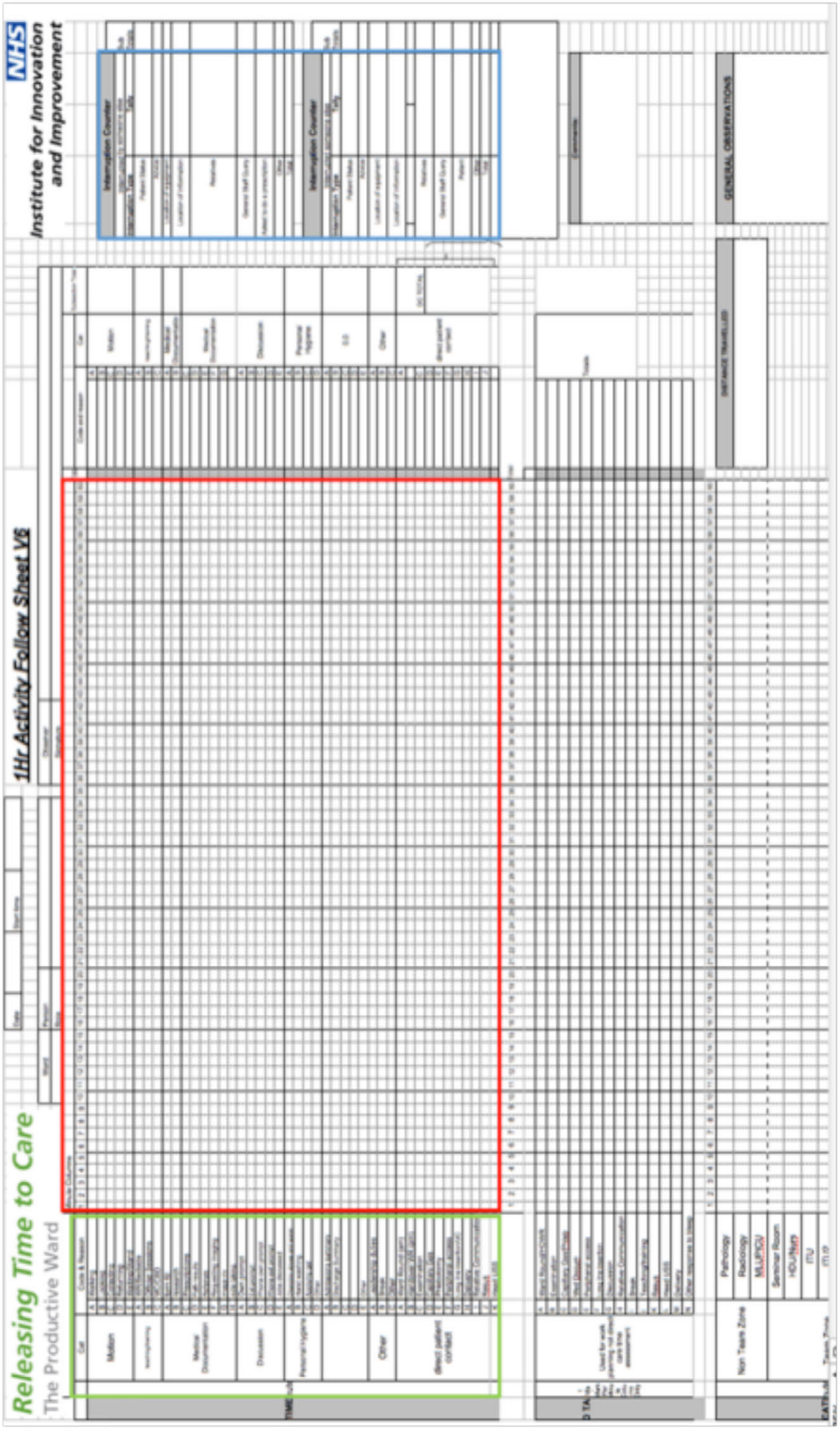
Appendix 1: Standardised 1 hour activity pro forma

Green box: list of main activity categories (e.g. direct patient contact) and their sub-categories (e.g. ward round, examination, phlebotomy etc.); red box: documents the activity occurring at every minute for each hour; blue box: records the number, type and source (external or self-prompted) of each interruption



Appendix 2: Raw data for comparison between registrars and SHOs

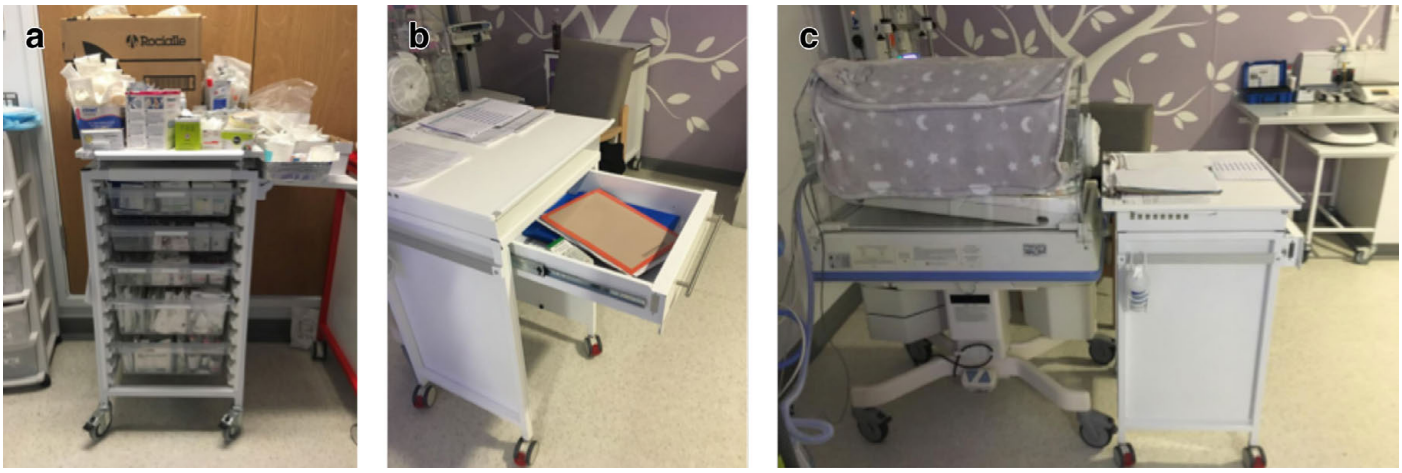
Supplementary Table 1. Comparison of the activity between registrars and SHOs in 2019.

Activity category	$\bar{x}$ time taken (minutes) over 12 hour shift		$\bar{x}$ percentage of 12 hour shift		*p* value
	Registrar	SHO	Registrar	SHO	
'Wasted' time, i.e. unnecessary motion	43.00 ± 11.31	52.33 ± 12.29	5.97 ± 1.57	7.27 ± 1.71	0.46
Teaching/training	19.00 ± 1.41	37.33 ± 53.80	2.64 ± 0.20	5.19 ± 7.47	0.68
Medical documentation	151.25 ± 3.89	217.67 ± 15.83	21.01 ± 0.54	30.23 ± 2.20	0.01
Discussion	151.25 ± 47.02	59.83 ± 17.90	21.01 ± 6.53	8.31 ± 2.49	0.05
Personal hygiene	3.75 ± 1.77	8.33 ± 5.69	0.52 ± 0.25	1.16 ± 0.79	0.37
Other (including breaks)	98.00 ± 24.75	70.17 ± 20.53	13.61 ± 3.44	9.75 ± 2.85	0.26
Direct patient contact (including ward round)	245.25 ± 12.37	264.00 ± 74.23	34.06 ± 1.72	36.67 ± 10.31	0.76
Interruptions	8.50 ± 4.95	10.33 ± 3.82	1.18 ± 0.69	1.44 ± 0.53	0.67

Supplementary Table 2. Comparison of the interruptions to registrars and SHOs in 2019.

	$\bar{x}$ over 12 hour shift 2019		*p* value
	Registrar	SHO	
Externally prompted interruptions	9.50 ± 3.54	7.33 ± 1.15	0.37
Self-prompted interruptions	0.50 ± 0.71	5.00 ± 1.00	0.01

Appendix 3: Images of NICU unit



Supplementary Figure 1. Image showing the practical design of the NICU used in this study to illustrate how this helped to reduce wasted time. (a) All equipment for clinical procedures was stored in one location, resulting in less time looking for it. **(b)** Trolley with medical notes. **(c)** Each patient has their own trolley at the bedside containing their notes, making them easy to find.

Research Article

The effects of long-term blood-thinner usage on the operative complications and patient-reported outcome measures of elective lumbar microdecompression surgery

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Abstract

Aims An increasing number of patients who undergo lumbar microdecompression surgery also have a history of blood-thinner usage secondary to cardiovascular and other co-morbidities. This study aimed to investigate how long-term blood-thinner usage in patients before operation affects surgical and patient-reported outcome measures (PROMs) of elective lumbar microdecompression surgery.

Methodology Surgical outcomes were retrospectively compared in 26 patients who were on blood-thinners (BT) and 30 patients not on blood-thinners (NBT) who underwent elective lumbar microdecompression surgery.

Results There were no statistically significant differences in the rates of venous thromboembolisms, wound complications, dural tears, neurological complications, blood transfusions or bleeding complications between BT and NBT groups. The NBT and BT group had similar improvements in postoperative pain and functional scores. In addition, even when patients continued blood-thinner use intraoperatively, long-term pre-operative blood-thinner usage did not correlate with increased incidence of operative complications or lower levels of patient improvement postoperatively following elective lumbar microdecompression surgery.

Conclusions This study's results show that patients with long-term blood-thinner use are not at higher risk of important postoperative complications than patients not on blood thinners, even if they continue blood-thinner use intraoperatively. Additionally, patients taking blood thinners have similar improvements in pain and functional abilities post-operatively to patients not on blood thinners.

Introduction

Degenerative lumbar spinal changes commonly cause severe back pain and reduced functional capacity.[1] Many patients undergo elective lumbar decompression surgery, with or without spinal fusion as part of the procedure. Because patients are typically older, cardiovascular disease and, subsequently, blood-thinner usage is becoming more prevalent among people undergoing lumbar decompression surgery.[2] There is little literature on how the use of blood-thinners affects the incidence of bleeding complications, blood transfusions, wound complications, dural tears, neurological complications and venous thromboembolisms (VTEs) in those who undergo surgery. If pre-operative blood-thinner usage correlates with increased levels of operative complications or decreased postoperative patient improvement, this will be an important discussion point for surgeons conducting and patients undergoing elective lumbar decompression surgery. This study investigates how long-term blood-thinner usage in patients before operation affects surgical and patient-reported outcome measures (PROMs) of elective lumbar microdecompression surgery at a large tertiary hospital.

Methods

Medical notes of patients who had elective posterior lumbar microdecompression surgery with or without spinal fusion, between 1 January 2013 and 1 January 2018, under the same surgeon at University Hospitals Plymouth NHS Trust (Plymouth, UK), were collected and retrospectively analysed. Ethical approval was not required for this study.

Emergency, revision and paediatric cases were excluded owing to lack of follow-up and possible variation in surgical procedures. Patients with at least a 6-month history of pre-operative blood-thinner usage were included. In this time frame, 26 patients on blood-thinners (BT group) fit the criteria. Thirty patients with no pre-operative blood-thinner usage (non-blood-thinner [NBT] group) were then chosen from the remaining eligible candidates through a random number generator. Complication rates and PROMs were analysed and compared between the BT and NBT patient groups. Complication rates and PROMs were then further analysed in n=22 patients in the BT group with relevant data, according to whether the patient stopped their blood-thinner use immediately before the operation (BTstop) or continued taking blood thinners intraoperatively (BTnstop).

Demographic data and co-morbidities were recorded and analysed for any confounding. Complications were dural tears, blood transfusions, wound healing complications, VTEs, bleeding complications and neurological complications. The definition of 'excessive blood loss' depended on the surgeon's clinical judgement and quantification. The Visual Analog Score (VAS) for leg and back pain and the Oswestry Disability Index (ODI) for functional ability were the PROMs selected for assessment pre-operatively and postoperatively.

Statistical analysis Statistical analysis was conducted using SPSS 25.0 (IBM, Armonk, NY, USA) and GraphPad (GraphPad Software, La Jolla, CA, USA). A p value <0.05 was considered statistically significant.

Results

Demographic data and co-morbidities are shown in **Table 1**. Twenty out of 26 (76.9%) patients in the BT group were on antiplatelet monotherapy (aspirin or clopidogrel), one out of 26 (3.8%) patients in the BT group was on aspirin and clopidogrel, and five out of 26 (19.2%) were on warfarin.

Table 1. Demographic data and possible confounders.

	BT ($n = 26$)	NBT ($n = 30$)	p value ($\alpha = 0.05$)
Age, years (mean ± SD)	68.69 ± 7.63	56.83 ±13.85	
Sex (%)			0.224
Female	69.2	53.3	
Male	30.8	46.7	
BMI >25 (%)	69.2	80.0	0.353
Previous smoking history (%)	26.9	43.3	0.201
Hypertension (%)	53.8	16.7	0.003
Diabetes (%)	34.6	6.7	0.009
Osteoporosis or osteopaenia (%)	7.7	6.7	0.882
Osteoarthritis (%)	23.1	13.3	0.342
Cardiac disease history (%)	73.1	6.7	0.000
History of cancer (%)	0.0	6.7	0.180
Previous lumbar surgery (%)	3.8	6.7	0.640
Psychiatric illness (%)	11.5	16.7	0.584
Neurological or cerebrovascular disease history (%)	44.0	23.3	0.145
Use of immunosuppressant medications (%)	15.4	10.0	0.543
Use of intraoperative haemostatic agents (%)	19.2	30.0	0.353
Length of hospital stay (%)			0.271
<1 day	42.3	41.4	
1–5 days	42.3	55.2	
>5 days	15.4	3.4	
Underwent microdecompression surgery with spinal fusion (%)	42.3	50.0	0.565
Number of spinal levels operated upon (%)			0.983
1 level	73.1	73.3	
2 level	26.9	26.7	
Two patient follow ups (%)	42.3	43.3	0.938
Time to final follow up, months (mean ± SD)	4.27 ± 2.79	4.22 ± 2.27	

Table 1 shows the complication rates for the BT and NBT patient groups. Although there was a difference in the proportion of patients with hypertension, diabetes or history of cardiac disease **(Table 1)** between the two groups, these confounders would be clinically expected in the BT group.

Two (7.7%) patients in the BT group had excessive intraoperative bleeding, whilst no cases of excessive bleeding were observed in the NBT patient group **(Figure 1a)**. During surgery, there were no incidences of VTE complications in both the NBT and BT groups (data not shown). A total of 7.7% of the BT and 10.0% of the NBT group had blood transfusions during surgery **(Figure 1b)**. One (3.8%) patient in the BT group had prolonged oozing as a wound complication **(Figure 1c)**. In contrast, two (6.7%) NBT patients had wound healing complications; one had a superficial wound infection and the other had excessive swelling **(Figure 1c)**. One (3.8%) patient in the BT group and three (10%) in the NBT group had dural tears, but no cerebrospinal fluid (CSF) leakage **(Figure 1d)**. Five (19.2%) patients in the BT group had neurological complications **(Figure 1e)**, none were linked to dural tears. In comparison, nine (30.0%) of patients in the NBT group developed neurological complications **(Figure 1e)**; one had a headache after a dural tear.

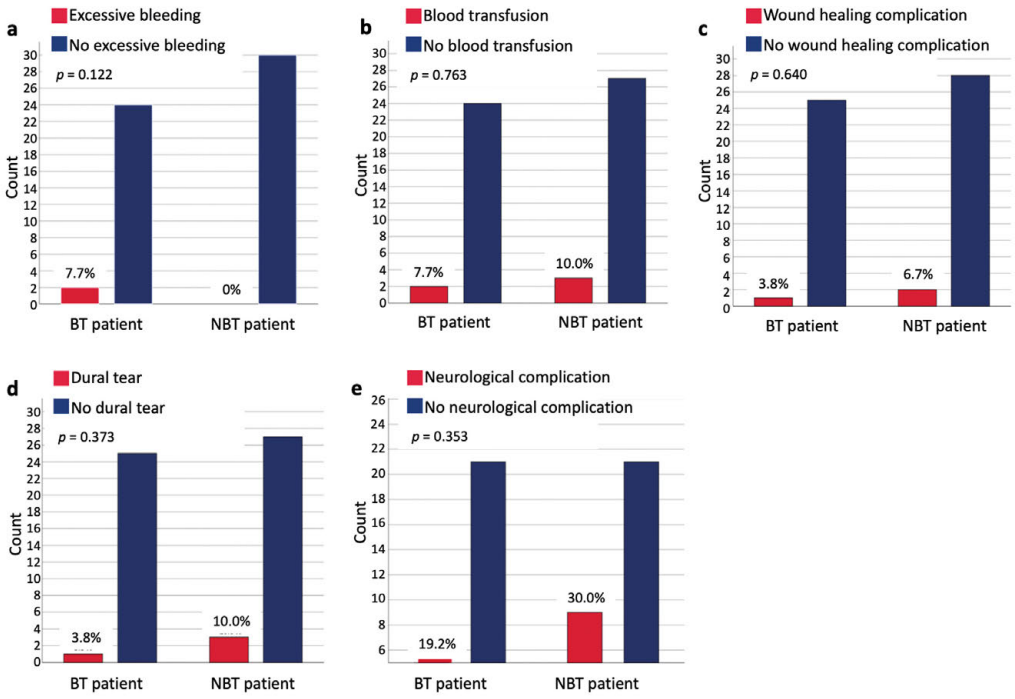

Figure 1. Complication rates for the BT versus NBT group. Rates of bleeding complications **(a)**, blood transfusions **(b)**, wound healing complications **(c)**, dural tears **(d)** and neurological complications **(e)** in patients in the BT and NBT group who underwent elective lumbar microdecompression surgery.

Both NBT and BT groups had statistically significant improvements in their VAS for leg (VASleg; $p<0.0001$ for NBT; $p = 0.0001$ for BT; data not shown) and back (VASback; $p<0.0001$ for both groups; data not shown), and in ODI scores ($p<0.0001$ for NBT; $p = 0.0105$ for BT; data not shown). Seven of 22 (31. 8%) patients in the BT group were confirmed to not have stopped their blood-thinner use pre-operatively (BTnstop group), while 15 (68.2%) did stop (BTstop group). A greater incidence of excessive intraoperative blood loss in BTnstop patients was statistically significant ($p = 0.030$; **Figure 2a**). Neither the BTstop nor BTnstop group had any VTE complications (data not shown). In addition, there were no statistically significant differences in the rate of intraoperative transfusions ($p=0.563$; **Figure 2b**), wound complications ($p=0.484$; **Figure 2c**), dural tears ($p=0.484$; **Figure 2d**) or neurological complications ($p=0.519$; **Figure 2e**) between patients in the BTstop and BTnstop groups.

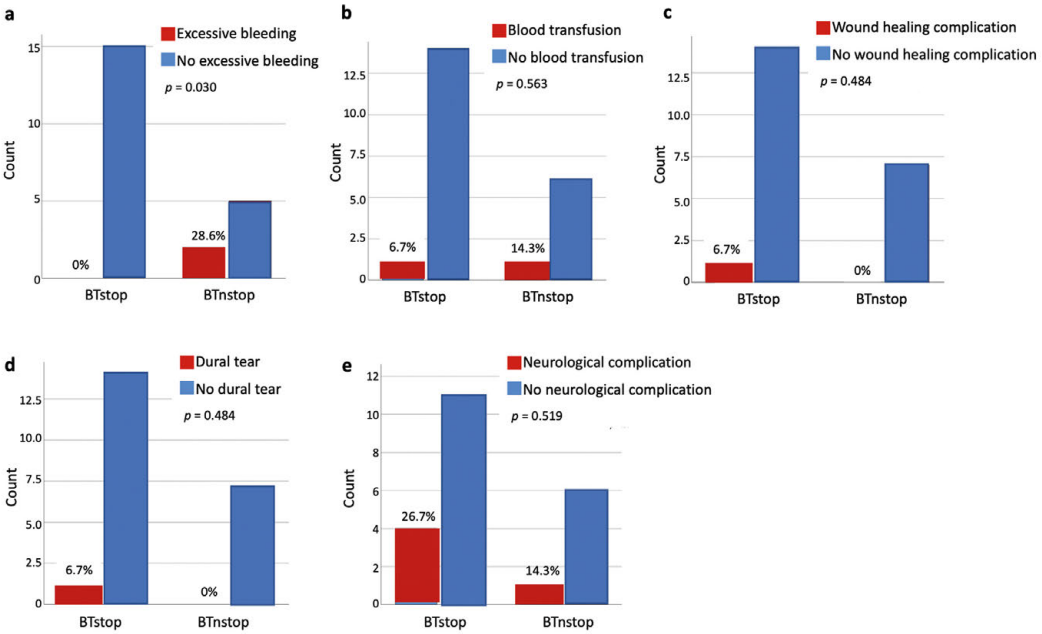

Figure 2. Complication rates for the BTstop versus BTnstop group. Rates of bleeding complications **(a)**, blood transfusions **(b)**, wound complications **(c)**, dural tears **(d)** and neurological complications **(e)** in patients in the BTstop and BTnstop groups who underwent elective lumbar microdecompression surgery.

Discussion

While spinal surgery itself can result in nerve injury, this study focussed on neurological complications secondary to incidental durotomies or bleeding complications, specifically spinal haematomas. Dural tears must be checked for CSF leakage.[3] Unrepaired tears cause minor symptoms, such as postural headaches, or progress into concerning conditions, such as CSF fistulas or epidural abscesses.[3] Furthermore, multiple case reports suggest that incidental durotomies in spinal surgery may contribute to the formation of spinal haematomas.[4,5] A subdural or epidural spinal haematoma is a severe bleeding complication because it causes spinal-cord compression.[6] Patients present with sudden severe pain, sensory deficits, motor weakness and bladder/bowel dysfunction; if the haematoma is not decompressed quickly, these symptoms will become irreversible.[6] Researchers have suggested that patients on blood-thinners undergoing orthopaedic procedures are vulnerable to developing sudden spinal hematomas.[6] However, in this study, patients in the BT group did not have a higher incidence of dural tears, haematomas or neurological complications as compared with those in the NBT group. This may be because the surgeon conducting the procedure is a widely experienced consultant in lumbar decompression surgery whose expertise may have greatly reduced the risk of an accidental durotomy, as compared with a training surgeon. Additionally, none of the dural tears had CSF leakage, which is associated with a higher incidence of neurological or bleeding complications as compared with dural tears without CSF leakage.[5]

Blood transfusions are associated with wound healing complications due to their immunomodulating effects.[7] Thus, haematomas and excessive intraoperative blood loss can, indirectly, contribute to the formation of surgical-site infections and other wound-healing problems. However, current literature on intraoperative aspirin (the commonest antiplatelet therapy) suggests that increased intraoperative blood loss does not necessarily correlate with increased morbidity. A randomised controlled trial (RCT) demonstrated a 7.2% absolute risk reduction for postoperative VTE following major noncardiac surgery with intraoperative aspirin use.[8] In spinal surgery, Goes et al found that intraoperative aspirin use did not increase bleeding risk or blood transfusion requirements.[2] Moreover, it was found that, even though intraoperative aspirin use increased bleeding risk by 50%, this did not correlate with increased patient mortality or morbidity.[8]

In terms of PROMS, VAS and ODI are frequently used together because pain severity strongly correlates with functional ability.[9,10] An equivalence RCT found that PROMs become less reliable after 12 months.[11] For longer follow-up, objective measures, such as reoperation rates, should be considered.[11]

The findings of this study align with those from previous studies. Most patients in the BT group were taking aspirin, and no significant differences were observed in any of the complication rates assessed between the BT and NBT groups, despite increased intraoperative blood loss in BTnstop patients. Additionally, long-term blood-thinner usage did not correlate with reduced postoperative improvement. This study is only a small retrospective investigation of one medical centre. In addition, it did not consider blood-thinner dosages or the effects of other blood thinners, such as heparinoids. Hence, larger prospective studies investigating all blood-thinners and elective lumbar microdecompression surgical outcomes are needed to further determine how safe and satisfactory this operation is for patients on blood-thinners.

Conclusion This study investigated whether patients with a history of long-term blood-thinner usage prior to operation were at more risk of complications of lumbar microdecompression surgery as compared with patients who were not taking blood thinners. This study also investigated whether postoperative PROMs regarding pain and functional ability were affected by long-term blood-thinner usage. The findings show that patients in the BT group were not at higher risk for VTEs, dural tears, neurological complications, or wound complications, including surgical site infections. Patients in the BT group who continued their blood-thinner perioperatively had more intraoperative blood loss, but there was still no statistically significant difference in bleeding complications, including epidural haematomas or intraoperative blood transfusions between the BT and NBT group. Both patients in the BT and NBT group had improvements of the same magnitude in postoperative pain and function. Future randomised, large prospective studies should further investigate the relationship between long-term blood-thinner usage and surgical outcomes.

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Contribution statement Madhumita Kolluri is responsible for the integrity of the work as a whole.

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Research Article

Kidney conundrum: comparing survival outcomes between patients who received live and deceased donor transplants

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Abstract

Aims This research aimed to review patients listed for kidney transplantation between 1 January 2011 and 31 March 2014 in Cardiff and determine if they had received a transplant at 1, 3 or 5 years post-listing. The difference in survival rate in patients who received a transplant from a live versus deceased donor at 5 years was also compared.

Methods Data were obtained from the kidney transplant list during the time period specified, removing any patients who were listed for multi-organ transplant. Data were then analysed to assess type of transplant and survival outcomes.

Results Of the 364 patients listed, 40% had been transplanted within 1 year, 67% by 3 years and 73% by 5 years. Of those who had been transplanted, survival rate was 90%, and of those who had not, survival rate was 68%. Recipients of live donors had a mortality rate of 1.5% if they received a transplant 5 years post-listing, whilst those of deceased donors had a mortality rate of 11%.

Conclusions Currently, live donor transplants result in a higher survival rate if received within 5 years of being listed than deceased donor transplants. This may be due to the reduced time on dialysis and may change with the introduction of the opt-out donation system across the UK as the donor pool will increase. Future studies could be carried out to explore the effect of this new system.

Introduction

Over the past 8 years, the number of patients requiring a kidney transplant has been declining (from 287 in 2011 to 253 in 2019). Alongside this, the number of kidney donors has been increasing: when comparing 2017–2018 with 2016–2017, deceased donors increased by 10%, while living donors increased by 1%.[1] This is likely due to the introduction of the opt-out system in Wales and campaigns across the UK increasing awareness about organ donation. This article reviews the patients listed for kidney transplant at 1, 3 and 5 years post-listing to see if they received a transplant and compares the survival differences between recipients of live and deceased donor transplants, assessing the benefits and limitations to these patients. This is particularly important as the introduction of the opt-out system to England in 2020 means that kidneys from many more deceased donors are likely to become available.

Methods

This study retrospectively analysed the outcomes of patients being treated in Cardiff on the NHS Wales Kidney Transplant list between 1 January 2011 and 31 March 2014. Patients requiring multi-organ transplants were excluded. Patient outcomes at 1, 3 and 5 years post-listing were recorded and categorised as one of the following: active (still waiting), removed, transplanted (deceased donor), transplanted (live donor), or died.

There are two main types of donor: living and cadaveric. The recipient mortality rate at 5 years post-listing for the two different types of transplantation was compared. Patients were also grouped demographically by sex and age bracket (discrete variable) and their outcomes were compared to see if there was a difference in transplant rates between groups. Patients who were still listed at the 5-year mark were explored further to find out if there was a reason for them not being transplanted during this time.

Results

A total of 364 patients were included and, of these, 40% (146) had been transplanted within 1 year, 67% (244) by 3 years and 73% (267) by 5 years post-listing **(Figure 1)**.

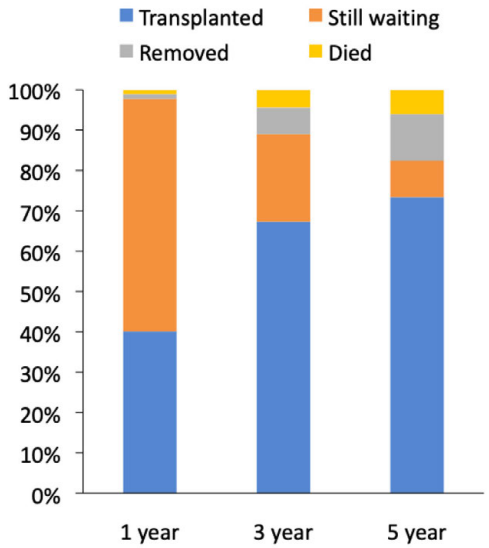

Figure 1. Proportional transplant outcomes of patients requiring a kidney transplant at 1, 3 and 5 years post-listing.

Of those who had been transplanted within 5 years of being listed, survival rate at the end of the 5 year period (post-listing) was 90% and of those who had not been transplanted during this time, survival rate was 68%. When distinguishing between deceased and live donor transplant recipients, it was found that those who had live transplants had a better survival outcome, with a mortality rate of only 1.5%. The mortality rate amongst deceased donor recipients

was 11% and the mortality rate amongst those not transplanted was 32% **(Figure 2)**. Of total live transplants, 75% occurred within the first year post-listing, compared with 55% of total deceased transplants.

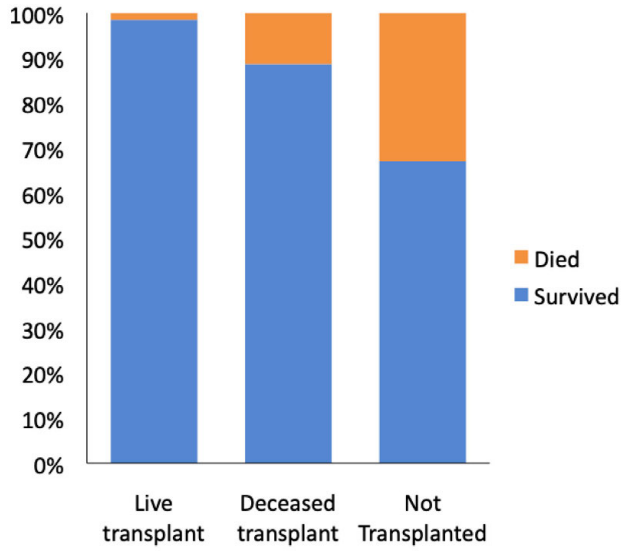

Figure 2. Overall survival rate at 5 years post-listing, grouped by live donor recipient, deceased donor recipient and not transplanted.

Further analysis considered the demographics of those listed, focussing on sex and age at listing. Although the total number of males listed (*n*=253) was over double the number of females (*n*=111), the proportional 5-year outcomes (transplanted, removed, still waiting or died) were very similar between the two groups. Outcomes were slightly more varied with age at listing, with the highest proportion of transplantation occurring amongst those aged 20–39 years (80% of those listed in this age bracket were transplanted by 5 years) and lowest amongst those aged 70–79 years (64% of those listed in this age bracket were transplanted by 5 years). The highest proportion of individuals removed from the transplant list was in the 70–79 years age bracket (27% of those listed in this age bracket were removed by 5 years). The median age at listing of those who received a live transplant was 50 years and, for those who received a deceased transplant, it was 54 years.

Discussion

These findings show that, for patients with renal disease, live kidney transplants lead to a higher survival rate than deceased donor transplants. One reason for this may be because such transplants tend to occur sooner post-listing, whereas waiting times for cadaveric transplants are generally longer, meaning more time is spent on dialysis, which is known to worsen outcomes.[2] Specifically, in this study, the mean time spent on dialysis pre-listing was 237 days for patients who received a live transplant, whereas it was 360 days for patients who received a deceased transplant.

Another possible reason why patients who received a deceased transplant had a higher mortality rate could have been because, on average, they were older at listing and older recipients are known to have a higher risk of graft failure.[3] A likely explanation for why older patients (aged 70–79 years) were least likely to be transplanted in the 5 years post listing is because they are more likely to become unsuitable for transplant due to other health issues and comorbidities, such as diabetes or cardiovascular disease.[4]

Although it has the most optimal outcome, live transplant is not always an option for patients because they may not have someone who is willing or suitable to donate. It is also important to consider that although a live transplant prolongs the life of the recipient and improves their quality of life by removing their need for dialysis,[5] it involves an unnecessary surgical procedure for the healthy donor, which carries its own set of risks that the donor would otherwise not have had, such as increased cardiovascular disease risk.[6] In the case of cadaveric donors, concerns regarding the donor's health are not an issue. Hence, the transplant list and cadaveric donors still play a very important part in the treatment for end-stage renal disease and allocation is a very complex process, which tries to optimise the available kidneys whilst providing the best-matched graft for each individual.

This study focussed on survival as a measure of successful transplantation but it is also important to consider the patient's quality of life and, whilst a transplant may not always extend a patient's life, it provides a much better quality of life than they would have had on dialysis,[7] so may still be the most desirable treatment option.

Conclusion Overall, at 5 years post-listing, there is a higher rate of recipient survival with live kidney donors than with deceased donors. Further research is required to determine the balance between waiting longer for a potentially closer-matched live kidney donor and the risk of spending longer on dialysis. This is particularly important with the expansion of the opt-out organ donation scheme to England in 2020 (as well as in Wales), as it will result in a significant increase in deceased kidney donors becoming available across the UK.

Acknowledgements With special thanks to Mr Michael Stephens, Consultant Transplant Surgeon, UHW, Cardiff, UK.

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Research Article

Genetic testing in retinitis pigmentosa: detection rate and phenotype–genotype associations

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Abstract

Aims This study aimed to determine the detection rate of pathogenic DNA variants associated with retinitis pigmentosa and examine the phenotypic variability in patients with similar genotypes.

Methods Out of 49 individuals who had undergone genetic testing for retinitis pigmentosa, 34 were assessed to identify clinical presentation related to the condition. The specifics of genetic testing were also assessed, including the genetic panel used and the number of genes tested. These data were used to form a database upon which detection rate and trends in phenotype–genotype associations could be examined.

Results Of the 34 unrelated individuals, 21 were clinically diagnosed as having retinitis pigmentosa, whilst 15 were positive for a pathogenic variant associated with the disease. The corresponding detection rate was 71.4%. Unexpected trends in phenotype–genotype associations were noted.

Conclusions The significant heterogeneity present at both a phenotypic and genotypic level mean prognostic counselling for retinitis pigmentosa can be challenging. Traditional diagnostic tests must be used in conjunction with genetic testing to delineate an exact clinical diagnosis.

Introduction

Inherited retinal dystrophies represent a highly heterogenous group of disorders.[1] This, combined with the significant phenotypic overlap between similar conditions, means that the exact cause and associations between an individual's genotype and phenotype is yet to be clearly defined.[1]

This study focused on individuals diagnosed with retinitis pigmentosa, the most common cause of peripheral retinal dystrophy. Pathologically, changes occur in rod photoreceptor cells, with central vision subsequently being affected once the cone system becomes involved.[2] Systemic retinitis pigmentosa syndromes also exist, including Usher syndrome type I, where individuals are born with hearing loss, with visual disturbances becoming apparent in childhood. In contrast, types II and III of Usher syndrome are characterised by vision and hearing loss in later life.[3]

Diagnostic testing for retinitis pigmentosa includes optical coherence tomography (OCT), which reveals the presence of cystoid macular oedema.[4] In addition, fundus autofluorescence (FAF) can highlight hallmark 'bone spicules' present within the retina for the majority of patients[5] **(Figure 1)**.

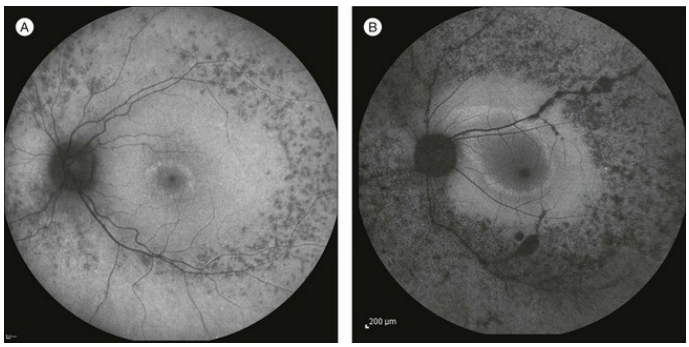

Figure 1. Fundus autofluorescence of the eye. (a) Fundus autofluorescence of the left eye in a patient with early retinitis pigmentosa. **(b)** Fundus autofluorescence of the left eye in a patient with more advanced retinitis pigmentosa. Both images show a central ring of hyper-fluorescence and a peripheral region of hypofluorescence, indicating the presence of hallmark 'bone spicules'. Reprinted from Gregory-Evans et al[6] with permission from Elsevier.

Furthermore, electrodiagnostic testing (EDT) is used to measure the electrical response of the retina to a light stimulus. Patients with retinitis pigmentosa present with reduced rod and cone amplitudes with a delay in their onset.[7]

This study aimed to determine the detection rate of pathogenic DNA variants associated with retinitis pigmentosa and examine the phenotypic variability in patients with similar genotypes.

Methods

Forty-nine patients who had undergone genetic testing for retinal dystrophies were identified by the Bristol Genetics Laboratory, and their medical notes were requested. Individuals were classed as positive if they carried a pathogenic variant known to cause retinitis pigmentosa and negative if no pathogenic variants were identified. Individuals with a variant that was felt to be insufficient alone to cause the disease, but was known to be implicated in retinal disease, were classed as 'inconclusive'. Of the 49 individuals identified, 34 individuals were included in the detection rate analysis (n=8 were excluded because their medical records were unavailable; n=2 were excluded because they were related to another individual in the study; and n=5 were excluded because their genetic test results were unavailable).

Results

Of the 34 unrelated individuals included, 21 individuals were clinically diagnosed as having retinitis pigmentosa, whilst 15 individuals were

positive for a pathogenic DNA variant that was associated with the disease. Five individuals had a negative genetic test for retinal dystrophies, and one had inconclusive results. The percentage of causative variants identified (the detection rate) was 71.4%. This was calculated by dividing the number of individuals with a positive genetic test result (15), by the total number of unrelated individuals (21).

Table 1 shows the 15 individuals who were positive for a pathogenic variant associated with retinitis pigmentosa. Individuals who were similar for a particular pathogenic variant were more likely, although not guaranteed, to develop resembling phenotypes, despite differences in their zygosity.

Table 1. Genotype of the 15 individuals who were positive for a pathogenic variant associated with retinitis pigmentosa.

Individual number	Genetic test results	Zygosity
1	*RDH12*	Compound heterozygous
2	*RDH12*	Heterozygous
	PROM1	Homozygous
	PITPNM3	Heterozygous
3	*CNGA1*	Compound heterozygous
4	*CNGA3*	Heterozygous
	CLRN1	Heterozygous
5	*RP1*	Heterozygous
	GPR179	Heterozygous
6	*TOPORS*	Heterozygous
7	*EYS*	Compound heterozygous
8	*USH2A*	Compound heterozygous
9	*USH2A*	Compound heterozygous
10	*USH2A*	Compound heterozygous
11	*USH2A*	Compound heterozygous
12	*RPGR*	Homozygous
13	*NR2E3*	Homozygous
14	*PDE6B*	Compound heterozygous
15	*RHO*	Heterozygous

All individuals were tested using the Manchester Retinal Dystrophy Panel. Panels varied from testing 105 to 176 genes.[8]

The data are colour-coded to indicate individuals who were similar for a particular pathogenic variant.

***RDH12* genotype–phenotype associations** Loss of function in the *RDH12* gene has been associated with autosomal recessive retinitis pigmentosa.[9] Individuals 1 and 2 presented at a similar age (45 and 47, respectively). Both had extensive bone spicule pigmentation bilaterally. Nonetheless, significant differences were evident on visual field testing: individual 2 had reduced visual fields concentrically, but visual fields in individual 1 were immeasurable due to little vision being maintained.

Interestingly, individual 2 was positive for two further pathogenic variants in the *PITPNM3 and PROM1* genes.

***USH2A* genotype–phenotype associations** Defective forms of the *USH2A* gene are associated with Usher syndrome and autosomal recessive retinitis pigmentosa (RP12).[10] Despite large differences in phenotypic presentation **(Table 2)**, individuals 8–11 were all clinically diagnosed with autosomal recessive retinitis pigmentosa.

Table 2. The differences in phenotypic presentation between individuals 8-11, who had a pathogenic variant of the *USH2A* gene.

Individual number	Hearing ability	Visual acuity using the Snellen Chart[a]	OCT changes	Fundal examination	Visual field changes	EDT changes
8	Normal	6/7.5 bilaterally	ND	No significant change	Bilaterally constricted	ND
9	Requires hearing aids	6/5 bilaterally	Retinal layer atrophy	Bilateral bone spicules	Bilaterally constricted	Macula dysfunction bilaterally[b]
10	Normal	6/36 bilaterally	Intra-retinal oedema and retinal layer atrophy	Bilateral bone spicules	Bilaterally constricted	Reduced rod and cone amplitudes with a delay in their onset[c]
11	Requires hearing aids	6/7.5 bilaterally	ND	Bilateral epiretinal membranes[d]	Bilaterally constricted	Reduced rod and cone amplitudes with a delay in their onset[c]

[a]A test of visual acuity that consists of a series of letters, positioned in decreasing size. A patient's visual acuity is stated as a fraction. The numerator is the distance from the chart (6) and the denominator is the last line of letters a 'normal eye' would be able to read at 6 metres. For example, 6/6 indicates normal vision i.e. the patient can read the line of letters at 6 metres that a 'normal eye' would be able to read at 6 metres. A patient with poor visual acuity e.g. 6/36 indicates they are able to read at 6 metres what a normal person could read at 36 metres.[11]

[b]Not a classical finding in retinitis pigmentosa.

[c]Classical finding in retinitis pigmentosa.

[d]Fibrous tissue that develops on the surface of the macula.

ND, no data; RP, retinitis pigmentosa.

Discussion

Retinitis pigmentosa is the most common cause of peripheral retinal dystrophy.[2] In this study, we investigated whether individuals who had similar pathogenic variants associated with the condition were more likely to develop resembling phenotypes

Two individuals had pathogenic variants of the *RDH12* gene. As mentioned, loss of function in the *RDH12* gene has been associated with autosomal recessive retinitis pigmentosa.[9] Interestingly, one of these individuals (individual 2) was also positive for pathogenic variants in the *PITPNM3* and *PROM1* genes. Köhn et al[12] discovered that mutations within *PITPNM3* caused autosomal dominant retinitis pigmentosa. Consequently, genetic testing detected a variance in inheritance that would otherwise not have been identified using clinic-based methods alone. Zhang et al[13] identified homozygosity for a mutation in the *PROM1* gene in members of a consanguineous family, presenting with retinal atrophy by the age of 40 years. Their severe retinitis pigmentosa was accompanied by macular degeneration.[13] Interestingly, the father of individual 2 had macular degeneration. It is, therefore, possible that variation within the *PROM1* gene was, in fact, accountable for retinitis pigmentosa in individual 2, rather than the *RDH12* gene. This is particularly supported by the fact that the literature has predominantly identified compound heterozygous variants within the *RDH12* gene as contributing to retinitis pigmentosa development,[14] rather than the simple heterozygous variant that was apparent in individual 2.

Four individuals were found to have pathogenic variants of the *USH2A* gene in our study. A previous study reported that Cys759Phe, a missense mutation within *USH2A*, is associated with autosomal recessive retinitis pigmentosa without hearing loss.[15] One of the individuals with a variant *USH2A* gene (individual 10) presented with this exact missense alteration and did not suffer from hearing loss;

thus, these findings suggest that clinical diagnosis was accurate. On the contrary, literature has identified the Ile371PhefsTer3 variant of the *USH2A* gene, which was observed in individual 9, as only being associated with Usher syndrome type II.[16] Interestingly, individual 9 had had hearing loss for the past 15 years, for which no specific cause had been found. This finding highlights the possibility that the clinical diagnosis of retinitis pigmentosa in individual 9 was inaccurate.

In addition, the p.Cys934Trp variant of the *USH2A* gene has been associated with both Usher syndrome type II and autosomal recessive retinitis pigmentosa.[17] Individual 11 was positive for this particular variant and had abnormal hearing tests. The possibility of Usher syndrome in individuals 9 and 11 should, therefore, not be overlooked.

Despite the aforementioned hypotheses, which suggest inaccuracies in clinical diagnosis of retinitis pigmentosa based on *USH2A* gene variants, certain studies suggest that the differences in phenotypic presentation are largely due to the multifactorial nature of *USH2A* gene expression. More specifically, Bernal et al[18] studied 28 patients with Usher Syndrome type II. They identified ten different pathogenic mutations and 17 polymorphisms in the *USH2A* gene. They further observed discordant phenotypes in sibling pairs from two unrelated families.[18] Furthermore, Liu et al[19] reported clinical differences in monozygotic twins with Usher syndrome type II and suggested that variation in the expression of the *USH2A* gene is not determined simply by genetic factors. More specifically, the environment and the effects of genetic background, including modifier genes, can all lead to an atypical presentation of Usher syndrome.[19]

Conclusion Due to the significant heterogeneity present in the individuals included in this study, at both a genotypic and phenotypic level, the results suggest that traditional clinic-based methods of assessing retinitis pigmentosa cannot always provide accurate prognostic and diagnostic information. Future focus must be placed on the development of retinitis pigmentosa-specific gene panels. This will enable both an earlier diagnosis and a more definitive characterisation of the disease.

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Research Article

Teaching ophthalmology: mastering the slit lamp examination

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Abstract

Aims Slit lamp examination forms the cornerstone of all ophthalmic consultations but remains a complex skill to master. With the demand on ophthalmologists rising year on year due to an ageing population, a highly trained multidisciplinary team is required to help relieve pressure on the eye clinic. Hence, we decided to evaluate the efficacy of a camera-based slit lamp to teach slit lamp biomicroscopy to a range of healthcare professionals.

Methods Ten volunteers from the eye clinic were recruited onto our training programme (four ophthalmic technicians, an orthoptist, an ophthalmic nurse, a charge nurse, an assistant practitioner, a trainee assistant practitioner and a specialty training 1 [ST1] trainee). Participants were given 30 minutes of structured teaching, including on how to perform anterior and posterior segment examination using the slit lamp and how to use a 90D lens with the camera. Participants completed questionnaires to compare their level of experience, confidence and familiarity with the operations of a slit lamp before and after the programme and results were compared.

Results After training, participants showed improvements in experience, confidence and familiarity in use of the slit lamp. They were also able to label anatomical landmarks of images captured by the slit lamp more accurately following training. Our study demonstrated that the innovative new technology used by the camera-based slit lamp simplified the complex skill of mastering slit lamp examinations.

Conclusions Use of a camera-based slit lamp may be of great benefit, not only to ophthalmologists, but also to allied health professionals. Since a highly trained multi-disciplinary team is crucial to help relieve pressure on the eye clinic, we hope that our teaching programme will help to encourage other allied health professionals to master slit lamp examinations.

Introduction

Despite being introduced over half a century ago, slit lamp examination continues to form the cornerstone of all ophthalmic examinations.[1] The slit lamp biomicroscope illuminates the eye providing a magnified image of ocular structures, making it important for the detection of diabetic and hypertensive complications, such as retinopathy and diabetic macular oedema.[2] However, being able to conduct slit lamp examinations remains a complex skill to acquire.[3] It has been said that "you can't treat a problem if you can't identify it"; thus, teaching people to perform slit lamp biomicroscopy remains vital to allowing health professionals to treat patients to the best of their ability.[4]

Ophthalmology consultations account for 10% of all outpatient appointments, the highest of any specialty.[5] An increasing demand is being placed upon ophthalmologists year on year due to an ageing population.[6] With demand on eye services suspected to rise by 40% over the next 20 years, it is necessary to have a highly trained multidisciplinary team to help relieve pressure on the eye clinic.[7] A new curriculum has been published by the Royal College of Ophthalmologists to encourage the training of a highly skilled ophthalmic team to certify the best care for our patients.[7] Nurses are required to perform post-operative cataract examinations and routinely perform the majority of intra-vitreal injections in many eye units across the country. Optometrists are qualified to use slit lamps to examine patients with glaucoma and age-related macular degeneration, and provide them with healthcare advice and glasses.[8] Therefore, as healthcare providers continue to take on more roles and responsibilities in the eye department, it justifies the need to train allied health professionals how to use a slit lamp, which is an essential tool in the eye clinic.

The eye clinic in the Great Western Hospital, Swindon (UK), was recently allocated funding from Health Education England (HEE) to purchase a camera-based slit lamp teaching unit.[9] It allows multiple people to view through the slit lamp simultaneously by projecting the microscope image onto a large screen. We decided to evaluate the utility and efficacy of this system as a novel teaching tool. Our aim was to enhance training methods currently implemented to teach slit lamp biomicroscopy and encourage other allied health professionals to master slit lamp examination.

Methods

Ten volunteers were recruited from the eye clinic into our training programme. Participants included four ophthalmic technicians, an orthoptist, an ophthalmic nurse, a charge nurse, an assistant practitioner, a trainee assistant practitioner and a specialty training 1 (ST1) trainee. All participants were inexperienced in the use of a slit lamp. Ethical approval was not required for this study; consent for participation was provided by the study participants.

Firstly, participants completed a slit lamp teaching questionnaire (see **Appendix 1**). This consisted of four questions to subjectively measure their level of experience, confidence and familiarity with the operations of a slit lamp, in addition to their basic understanding of eye anatomy. A Likert scale was used to rank the questions, ranging from 1 to 5, where 1=strongly disagree, 2=disagree, 3=neutral, 4=agree and 5=strongly agree. Participants were then asked to label captured images from the slit lamp to objectively test their ability to recognise anatomical landmarks. The questionnaire was internally validated by two consultant ophthalmologists.

My supervisor and I then trained the participants for 30 minutes using a wide range of videos and photos taken with the slit lamp teaching

camera (Mediworks S390L; Mediworks, Shanghai, China) and stored in a library on the Great Western Hospital database. Training covered how to perform anterior and posterior segment examination and how to use a 90D lens with the camera. Participants then practiced on each other **(Figure 1)** and support was provided if they found the process challenging. Having completed the structured teaching programme, participants then completed a post-test questionnaire that was identical to the one they had completed before teaching, and the scores were compared with baseline scores.

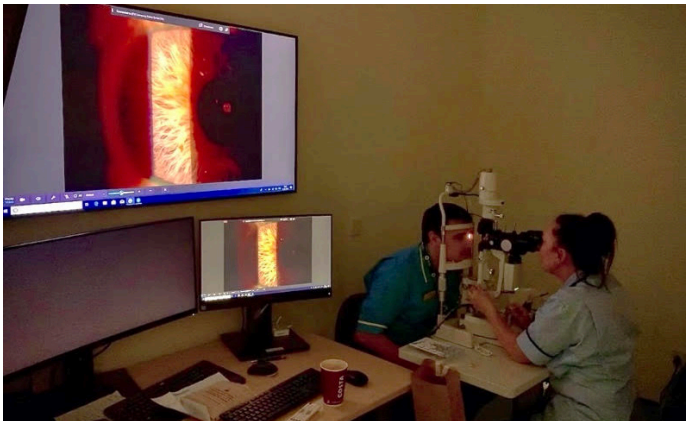

Figure 1. Participants practicing using the camera-based slit lamp on each other. The slit lamp camera is shown to project a large image onto the screen; this image can also be simultaneously viewed down the microscope.

Results

After training, improvements were seen in all four areas for some participants. The increase in knowledge of the operations and functions of the slit lamp was greatest for both the ophthalmic nurse and the ST1 trainee, who both answered the question *'I have a good knowledge of the operations and functions of the slit lamp'* with 'strongly disagree' (1) before training and 'agree' (4) after training (see **Figure 2**). The increase in experience using the slit lamp was greatest for both the assistant practitioner and the ST1 trainee, with the assistant practitioner answering the question *'I have extensive experience in performing slit lamp examination'* with 'disagree' (2) before training and 'strongly agree' (5) after training, and the ST1 trainee answering with 'strongly disagree' (1) before training and 'agree' (4) after training. The increase in confidence using the slit lamp was greatest for the orthoptist who answered the question *'I feel confident at using the slit lamp'* with 'strongly disagree' (1) before training and 'agree' (4) after training. The increase in knowledge of basic eye anatomy was greatest for the ophthalmic nurse who answered the question *'I have a good knowledge of basic eye anatomy'* with 'strongly disagree' (1) before training and 'strongly agree' (5) after training.

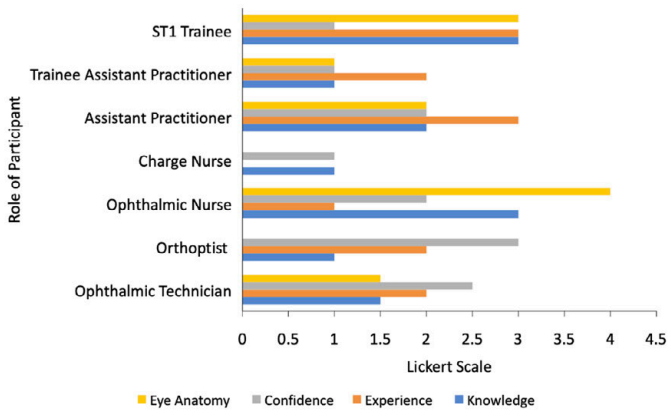

Figure 2. Increase in scores across all questionnaire categories after participation in the teaching programme vs baseline, sorted by participants' role.

In the questionnaire, participants also labelled anatomical landmarks of images captured by the slit lamp. The number of correct labels increased for all participants across all groups after teaching **(Figure 3)**. The ST1 trainee had the greatest change in the number of correctly identified labels, with an increase from three correct labels before training to eight after training.

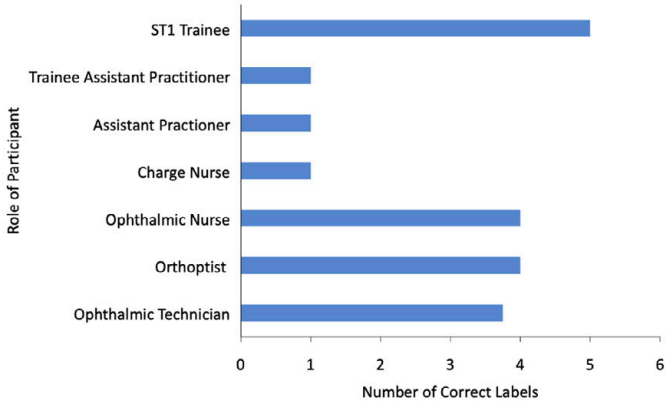

Figure 3. Increase in correctly identified anatomical landmarks of images captured by the slit lamp after participation in the teaching programme vs baseline, sorted by participants' role.

Discussion

Our study suggests that the innovative new technology used by the camera-based slit lamp has simplified the complex skill of mastering slit lamp examinations, potentially making it of great benefit, not only to ophthalmologists, but also to allied health professionals. Nurses, technicians, optometrists and other staff in the eye clinic all saw improvements in all aspects relating to their knowledge of anatomical landmarks and confidence in using a slit lamp. This justifies the need to implement similar training programmes to enhance the efficiency of learning such an essential tool in the eye department for both ophthalmologists and the ophthalmic team alike.

Feedback about the educational material used in this study was thoroughly positive. Nurses who had worked in the health sector for 20 years stated that they *"[couldn't] believe that they had managed to perform a basic slit lamp examination"*, when previously they had presumed this to be an unachievable goal. Despite many years in the profession, many had never had the opportunity to look through a slit lamp microscope and claimed to feel more invested in patients' care due to having a deeper understanding of the clinical aspects. We intend to repeat this study to collate more data and plan to act on the participants' feedback to improve our training programme.

The main limitation of this study was how outcomes were measured. Basing results upon subjective judgements may lead to erroneous conclusions about the programme's effectiveness due to a lack of insight into the participants' abilities and the impact of the programme on their performance.

Conclusions This study, which investigated the slit lamp camera as a useful teaching tool for a range of health professionals, is the first of its kind and we hope its use will continue to be incorporated into teaching in eye clinics at the Great Western Hospital in Swindon. In addition, it is hoped that other hospitals may also introduce programmes to teach health professionals how to use a slit lamp camera to allow better teaching among trainees, as these individuals particularly seemed to benefit from the experience. The greatest increase in the outcomes we measured occurred in confidence, which suggests that a lack of confidence, rather than a lack of knowledge, prohibits clinicians from mastering the use of a slit lamp.

In the future, we hope this may aid in quicker diagnoses of eye clinic patients and better outcomes. It would also be valuable to see the use of such a training programme outside of the eye clinic to teach other clinicians who would benefit from having such a skill, such as accident and emergency doctors, which would help to relieve the pressure on the eye clinic.

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Appendix 1: Questionnaire to subjectively measure level of experience, confidence and familiarity with the operations of a slit lamp, in addition to basic understanding of eye anatomy

The questionnaire was completed by all participants before and after the teaching programme.

The Likert scale was used to rank the questions, ranging from 1 to 5, where **1**=strongly disagree, **2**=disagree, **3**=neutral, **4**=agree and **5**=strongly agree.

Slit Lamp Teaching Questionnaire

What is your job title:

For the following statements please circle the most appropriate response:

I have a good knowledge of the operations and functions of the slit lamp

Strongly **Disagree** **Neutral** **Agree** **Strongly Agree**

I have extensive experience in performing slit-lamp examination

Strongly **Disagree** **Neutral** **Agree** **Strongly Agree**

I feel confident at using the slit-lamp

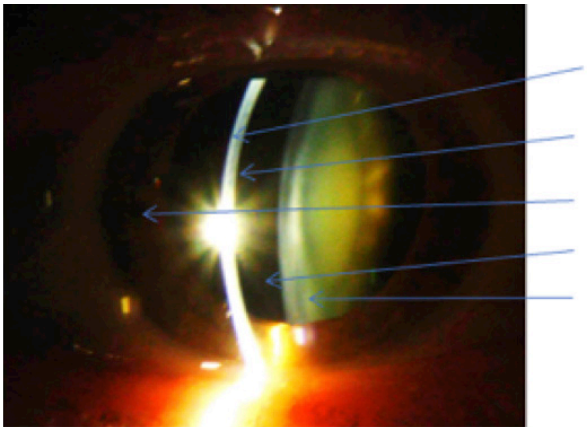
Strongly **Disagree** **Neutral** **Agree** **Strongly Agree**

I have good knowledge of basic eye-anatomy

Strongly **Disagree** **Neutral** **Agree** **Strongly Agree**

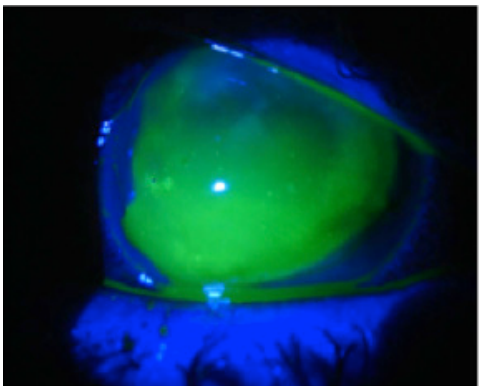
Label the following structures

Answer:



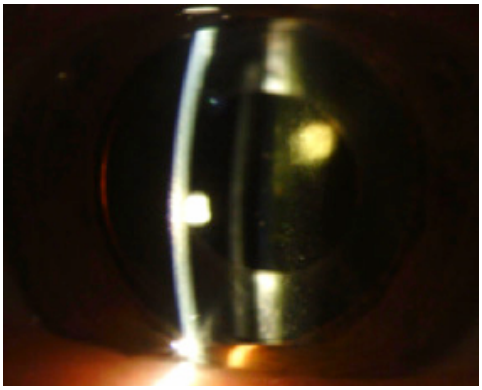
What dye is being used in this picture and what are of the cornea is being stained?

Answer:



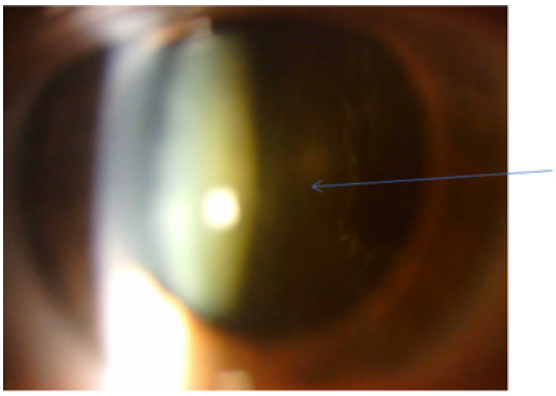
In the below photograph what is the lens status in this patient?

Answer:



In the below photograph state what the arrow is pointing to?

Answer:



Please provide any other additional comments:

Senior Editors, Autumn 2020

Jonathan Bray

I undertook the role of Senior Editor for the *INSPIRE Health Sciences Research Journal* whilst working as an Academic Foundation Doctor in Wales, having just graduated from The University of Bristol. I have a passion for combining academic medicine with my clinical career, and have a particular interest in academic cardiology. The *INSPIRE journal* has been a fantastic opportunity to work with professionals and actively participate in the publication process.

Aarti Jalan

I am a third year medical student at Bristol University and came into medicine with a desire to learn both about clinical medicine and the research that underpins it. INSPIRE has allowed me to gain an insight into how research and publishing functions and an invaluable opportunity to develop skills and collaborate with students from different universities and disciplines. My main interests within medicine include paediatrics and neurology, amongst many others, and my biggest passion outside of medicine would have to be drama.

Viktorija Kaminskaite

I am a fourth year medical student at the University of Exeter and have been involved with the INSPIRE programme in various roles since my first year. Doing a year of medical sciences before transferring to medicine made me fall in love with research, and the central message of INSPIRE of widening student access to research was the reason why I got involved. I have thoroughly enjoyed my time as a senior editor for the journal. My current interests include ENT, obstetrics and gynaecology, and breast surgery. Next year I will be intercalating in MSc Genomic Medicine with a project on thyroid cancer. My interests include music, fitness, painting/drawing and travelling.

Izzy McNally

I am a third year vet student at the University of Bristol and have previously gained a BSc in Biological Science. I developed a keen interest in skeletal pathology research through my BSc and I hope to pursue a career as a specialist veterinary surgeon in this area. Being an editor for *INSPIRE* has given me a great opportunity to hear about research from the other health science professions. Outside of medicine, I enjoy running and cycling.

Weronika Nasterska

Originally from Warsaw, I am a third-year dentistry student at the University of Plymouth. My journey with academic research began with the INSPIRE studentship programme, which I completed in 2019. Since then I have been pursuing further research opportunities and engaging in other research-related activities. I am especially interested in the relationship between dentistry and systemic health and I enjoy exploring immunological perspectives in dentistry. I aspire to combine research with a clinical career.

King-David Nweze

Having completed a summer research project as part of the INSPIRE scheme at the Institute of Translational and Stratified Medicine (ITSMed) in Plymouth, I was convinced that taking the opportunity to be part of the editorial team for INSPIRE's student research journal would be a fantastic opportunity to further broaden my interest in research. I am a third year medical student at the Peninsula Medical School (Plymouth University) and my research interests mainly include clinical neuroscience research. From my experience of working alongside fellow students as a senior editor for the *INSPIRE Health Sciences Research Journal* I have been able to further enhance several personal skills, ranging from critically evaluating research work to teamworking.

Senior Editors, Autumn 2020

Temidayo Osunronbi

I graduated as a medical doctor from the University of Plymouth in 2020 after obtaining an MSc in Neuroscience from the University of Oxford in 2019. I have authored multiple peer-reviewed surgery-related articles in PubMed-indexed journals and presented at various (inter)national scientific meetings. My passion to encourage students' participation in research motivated my decision to join the *INSPIRE Journal's* editorial team. I aim for a career in academic neurosurgery and will commence an academic foundation programme (research) in August 2020. Outside of academic interests, my hobbies are football, cycling and basketball.

Christina Wainer

I am currently a fifth-year dental student at the University of Bristol. Having completed a BSc in Pharmacology at University College London prior to attending dental school, I have a passion for research and I hope to combine this with a clinical career in the future. I have thoroughly enjoyed being a senior editor for the *INSPIRE Health Sciences Research Journal*, and it has been a pleasure to see the growth of the journal during the past year. It has been a great opportunity to participate in the publication process and to contribute to the journal's aim of encouraging readers to have a wider appreciation for the many subfields of medicine, dentistry and veterinary science. In my spare time I enjoy scuba diving, skiing and baking.

Shannon Seet

I am currently a third year medical student studying at Cardiff University. Having not much experience in research studies, I thought joining INSPIRE will allow me to have a chance to explore and gain more understanding within this field. This opportunity has definitely allowed me to be more aware about research topics across the different disciplines and the effort that goes behind research. I am particularly interested in acute medicine, critical care and paediatrics. Aside from medicine, I enjoy binge-watching my favourite TV shows and spending time with my family and friends.

Emily Wales

I am a fourth year postgraduate medical student at Cardiff University. I have previously undertaken a degree in Biomedical Science and graduated with a first class honours. Coming from a research-based degree into medicine, INSPIRE has allowed me to continue my exposure to clinical research and meet like-minded people from other universities. I have a wide range of interests including neurology, surgery and anaesthetics. Outside of medicine, my interests include fitness, being outdoors, painting and cooking.

List of referees, Autumn 2020

Fatima Adamu-Biu, University of Plymouth
Isabel Andrews, University of Bristol
Megan Anley, University of Bristol
Lauren Ashley, University of Bristol
Lelyn Osei Atiemo, University of Bristol
Chelsie Bailey, University of Bristol
Sneha Chotaliya, University of Bristol
Serena Dodhia, University of Bristol
Gabriella Fecci, University of Plymouth
Ella Fisher, University of Bristol
Molly Flint, University of Bristol
Lauren Garratt, University of Bristol
Khadijah Ginwalla, University of Bristol
Clare Goh, University of Bristol
Grace Hosking, Cardiff University
Atchchuthan Kanagasabai, University of Bristol
Aurimas Kudzinskas, University of Exeter
Sara Lam, University of Bristol
Eva Larkai, University of Bristol
Keng Siang Lee, University of Bristol
Qui Lim, University of Bristol
Niamh Mackdermott, University of Bristol
Alice McBride, University of Bristol
Sruthi Murthy, University of Bristol
Ross Morgan, University of Bristol
Ellen Nelson-Rowe, Cardiff University
Brianna Robinson, University of Bristol
Taiwo Mary Oki, University of Bristol
Tushar Rakhecha, University of Bristol
Shaneel Shah, University of Bristol
Teerajet Taechameekietichai, University of Plymouth
Adam Tremlett, University of Exeter
Marisol Vazquez, Cardiff University
Aimee Wilkinson, University of Bristol
Lara Wirt, Cardiff University
Usman Yakubu, University of Bristol

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University of Bristol

www.bristol.ac.uk/medical-school/study/undergraduate/inspire
www.bristol.ac.uk/vet-school/research/inspire

Leads: Elizabeth Coulthard, Associate Professor in Dementia Neurology;
Richard Coward, Professor of Renal Medicine and Consultant Paediatric Nephrologist;
Linda Wooldridge, Chair in Translational Immunology

University of Cardiff

http://cures.cardiff.ac.uk/inspire

Lead: Colin Dayan, Professor of Clinical Diabetes and Metabolism

University of Exeter

https://medicine.exeter.ac.uk/study/ug/medicine/researchopportunities

Lead: Joanna Tarr, Senior Lecturer, College of Medicine and Health

Plymouth University Peninsula School of Medicine and Dentistry

www.plymouth.ac.uk/about-us/university-structure/faculties/health/inspire

Leads: David Parkinson, Professor of Neuroscience;
Vehid Salih, Associate Professor in Oral & Dental Health Research

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