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Editor's Message

Covid-19: A year into the pandemic, what has changed from the first, to the second, and the third waves?

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It has been over 16 months since the first case of SARS COV 2 was identified in Wuhan, China[1]. Soon after, the virus spread to the rest of the world and was declared a global pandemic[2]. When the virus first hit, many countries were unprepared. Limited knowledge of the virus combined with shortage of specialized equipment and proper personal protective equipment lead to rapid spread of the virus and an influx in hospitalization and death[3]. We started hearing new phrases such as limiting spread and quarantine, and states of emergency were declared all over the world. Many restrictions were put in place to limit spread within and between communities. Scientists and clinicians started conducting research to better understand the disease and target the virus. Hospitals became more familiar and prepared to deal with the new virus and as result developed more efficient treatment plans. Overall, the numbers of new cases/deaths were decreasing, and it looked like we had succeeded in withstanding the pandemic. This initial outbreak would later be known as the first wave.

The second wave started few months later. Despite the notable decrease in the spread over the summer, the second wave was more aggressive, and was associated with a big spike in daily cases and death numbers[4]. Several factors contributed to rapid spread during the second/third waves including public, medical, viral and societal factors. The effect of the first wave was felt by everyone, even those who were not directly infected by the virus. Many people lost their jobs and had to depend on social assistance. This had negative impacts on individual mental health[5] as well as the economic and financial burden on different governing bodies6. Therefore, when cases were decreasing during the summer, many countries started to ease restrictions and allow in person gatherings. Meanwhile, the virus itself was evolving and new variants were emerging. The new variants were spreading faster, leading to a surge in cases admitted to hospitals and an increased demand for intensive care unit beds[7,8]. Despite the experience gained from dealing with the first wave, hospitals were overwhelmed, and once again we were facing a shortage in resources. Regardless of the early signs and many reports predicting a second wave[9], lower case numbers coupled with the roll out of the vaccines lead to people becoming negligent and letting their guards down. Despite the period of case decline between the second and third waves, the numerous predominant variants with high attack rates resulted in the spike in daily cases that we are currently seeing.

Several vaccines have been approved in different parts of the world early in the second wave[10]. Some countries achieved faster vaccination rates and as result public and societal measures were relaxed. However, despite the ongoing vaccination efforts it remains unclear how effective the different vaccines are in protecting against the new variants that are emerging[11]. Similarly, the duration of immunity achieved by different vaccines is yet to be established, with reports already suggesting a booster dose might be required for some types[12]. Finally, concerns have emerged recently about potential side effects of some of the approved vaccines, slowing vaccination rates and in turn increasing the potential of being infected by the virus.

Despite the increase in daily cases and the spread of the new variants, health care workers and scientists continue to fight the spread of the virus courageously. It remains to be seen how long this pandemic will persist, however, it is certain that we are better equipped at this stage than when it started.

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Review Article

The revolution of reconstructive microsurgery: Dr. Fu Chan Wei and the Chang Gung Memorial Hospital

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Introduction

Dr. Fu Chan Wei (Chinese: 魏福全) is a household name in the world of plastic surgery, particularly in the field of reconstructive microsurgery. The mere mention of Dr. Wei's name brings to mind countless contributions and surgical advancements, including the fibula osteoseptocutaneous flap, mandible reconstruction, toe-to-hand surgery, among others1. After creating a globally sought-after microsurgery fellowship training program at Chang Gung Memorial Hospital located in Taipei, Taiwan (Figures 1, 2), Dr. Wei went on to establish the Reconstructive Microsurgery Center and has since cultivated it into a world leading microsurgery center with impressive cumulative case volume and research productivity[1,2].

This article explores Dr. Wei's journey to becoming one of the most recognized plastic surgeons of our time, and the process in which he developed the infamous Reconstructive Microsurgery Center at Chang Gung Memorial Hospital. By navigating through his story, we hope to catch a glimpse of the makings of a legend who continues to revolutionize plastic surgery today.

The Road to Microsurgery

Dr. Wei was born in Tainan, Taiwan, and earned his medical degree from Kaohsiung Medical College in 1972[3,4]. From 1973 to 1979, Dr. Wei completed his surgical residency at Kaohsiung Medical College and Mackay Memorial Hospital, followed by a plastic surgery residency at Chang Gung Memorial Hospital, where he served as surgical chief resident[5]. It was during his time at Mackay Memorial Hospital and Chang Gung Memorial Hospital that Dr. Wei met Dr. Samuel Noordhoff, an American plastic surgeon who became Dr. Wei's mentor and greatly impacted his career trajectory[1,4]. Deeply inspired by Dr. Noordoff's compassion and dedication to his patients, Dr. Wei followed in his footsteps and embarked on fellowship training in microsurgery at the University of Toronto followed by a second fellowship in hand microsurgery at the University of Louisville[4,5].

Himself a remarkable individual, Dr. Noordhoff came to Taiwan as a medical missionary and after serving as Mackay Memorial Hospital's superintendent for 16 years, subsequently assumed the role of the inaugural superintendent of Chang Gung Memorial Hospital where he founded the plastic surgery division[4]. Dr. Noordhoff would later go on to establish the Noordhoff Craniofacial Foundation in 1989, a non-profit organization aimed to provide care to patients with cleft palate and craniofacial deformity, and ultimately be remembered as the father of plastic surgery in Taiwan[6,7]. Upon closer examination, one can see many parallels in the leadership and mentoring styles of Dr. Noordhoff and Dr. Wei – both extremely dedicated to supporting further advancement of trainees to create stellar pupils who would continue on and amplify their impact[1,7]. It is likely the possession of this unique attribute led to their respective successes.

Major Contributions: Past and Present

Among the many innovative contributions Dr. Wei has made to plastic surgery, one of the most well-known is his introduction of the fibula osteoseptocutaneous flap in 1986[1,8]. Since then, Dr. Wei and his team continued to refine this technique and extend its application to reconstruction of the mandible and extremities[9,10,11]. With Chang Gung Memorial Hospital being a primary referral center for mandible reconstruction, this subsequently led to the development of simultaneous placement of osseointegrated implants in the fibular osteoseptocutaneous free flaps for mandibular reconstruction[12]. Lastly, Dr. Wei also significantly contributed to the advancement of the toe-to-hand surgery where he pioneered the trimmed-toe transfer technique to improve the overall appearance and function of the reconstructed thumb, introduced the second toe wraparound flap, and developed simultaneous multiple toe transfers[13,14,15].

More recently, Dr. Wei has turned his focus to vascular composite allotransplantation (VCA) and currently acts as the chief of the Center of VCA at Chang Gung Memorial Hospital[3]. Since its establishment in 2011, Dr. Wei and his team have been working towards lowering the risks of immunosuppression to make VCA routine practice at Chang Gung Memorial Hospital. Current research efforts have been focused

on inducing VCA tolerance through different means including adipose-derived stem cells and regulatory T cell adoptive cell therapy[16,17]. Additionally, novel VCA animal models are being established where Dr. Wei and his team recently developed a novel syngeneic face subunit transplantation model in C57BL/6 mice that can be used for future research applications[18]. It is with great interest and excitement that we continue to follow Dr. Wei's research on VCA and await innovative translational findings.

Chang Gung Memorial Hospital and the Infamous Microsurgery Fellowship

Shortly following the establishment of the Microsurgery Fellowship at Chang Gung Memorial Hospital in 1984, Dr. Wei oversaw the development of the Reconstructive Microsurgery Center at the same institution which houses a 24-bed Microsurgical Intensive Care Unit (MICU)[1,19]. The MICU is staffed by highly specialized nurses skilled in flap monitoring as well as physical therapists who work together to provide comprehensive care to patients, undoubtedly playing a crucial part in the center's ability to perform more than 1000 microsurgical cases annually with a success rate of 98%[19,20].

Given the influential history of Dr. Wei and the division of plastic surgery at Chang Gung Memorial Hospital, it is no surprise that the Microsurgery Fellowship is highly sought after by candidates worldwide. Each year, 80-90 applicants apply for eight total spots in the fellowship program, making it extremely competitive[19,21]. Once accepted, each fellow partakes in one-on-one teaching with a senior surgeon following a brief meeting with Dr. Wei who helps to individualize the fellowship experience19. Morning case study discussion meetings, pre-surgery discussions, and skills refinement by performing at least two free flaps per week make up the training model[19,21]. In addition to clinical duties, the Chang Gung Memorial Hospital provides extensive opportunities for fellows to engage in cutting-edge research[19].

The Chang Gung Microsurgery Fellowship program has trained 1312 fellows and visiting scholars from 71 countries between its inception and 2016. This is effectively fulfilling the program's goal of spreading Taiwan's medical advancements worldwide and help increase the calibre of the next generation of surgeons[21]. To take it one step further, in 2015 Dr. Wei transformed the clinical research microsurgery fellowships into the International Master of Science Program in Reconstructive Microsurgery, effectively situating the program globally so dissemination of microsurgery research and knowledge can reach areas of the world most needed[21].

Conclusions

As we travel through Dr. Fu Chan Wei's journey in becoming the influential figure he is today, we notice several themes that have remained pillars throughout his incredible career. Seemingly inspired by Dr. Noordhoff, Dr. Wei appears to have placed making global impact on those who need it most at the forefront. This, combined with his passion for teaching and cultivating the next generation of surgeons, has helped revolutionize reconstructive microsurgery. As echoed by countless former students, his compassion, courage, humility, and most importantly connection to humanity are unparalleled, and may be pearls we all should take with us as we progress through our own journeys.

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Case Report

Insulin desensitization in a patient with gestational diabetes mellitus and the role of continuous positive airway pressure (CPAP) in the management of elevated morning blood glucose

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Abstract

A 31-year-old lady with gestational diabetes started to develop an allergic reaction to all types of insulin injections. It seems that the allergy was related to one of the preservatives in the injections. Different approaches were attempted without significant improvement. She was then admitted for 12 hours for insulin desensitization. Desensitization protocol was administered under strict supervision. There were no significant complications. Patient symptoms improved significantly afterwards. Also, the persistent elevation of the morning blood glucose triggered investigations for obstructive sleep apnea. Continuous Positive Airway Pressure (CPAP) therapy was helpful to reduce the morning blood glucose to the target range.

Case

This 31-year-old lady, Gravida 2 Para 1, had a history of gestational diabetes. During her last pregnancy, Gestational diabetes was managed with diet and exercise, and the patient did reasonably well with no fetal related or maternal complications. After her first delivery and the postpartum period, her blood glucose levels and hemoglobin A1c both within normal ranges. The patient became pregnant again, and screening for gestation diabetes was done around the ninth week of pregnancy, which was positive for gestational diabetes. During her first visit to the gestational diabetes clinic, her vitals were normal, and her physical examination was unremarkable except for being obese with a Body Mass Index (BMI) of 33.

Initially, the patient was managed with a diet, including caloric restriction and exercise, from gestational week nine to eleven. Her morning blood sugars were elevated above the target range. Postprandial readings were mildly elevated most of the time too. There was no evidence of increased ketones. Gestational week eleven, Insulin NPH (Isophane Insulin, Novolin NPH) was started at a low dose. The postprandial blood glucose measurements began to fall within range but not the morning readings. Insulin NPH (Isophane Insulin, Novolin NPH) dosing was increased by the diabetes education center for three consecutive visits without significantly improving morning blood glucose readings. Gestational week seventeen, Metformin (Glucophage) 250 mg orally twice daily was added and increased later to 500 mg orally twice daily. Increasing the dose of Insulin NPH (Isophane Insulin, Novolin NPH) and adding Metformin (Glucophage) did not help with elevated blood glucose readings. The patient was adherent to the diet and exercise recommendations.

As the patient's Body Mass Index (BMI) was high and she also described snoring during sleep, she was tested for obstructive sleep apnea with a level III sleep study. The study revealed evidence of increased upper airway resistance and at least mild obstructive sleep apnea as multiple diminutions of flow were not scored as events due to lack of desaturations. It was determined that if a level I polysomnogram would have been done, it would probably show some arousals matching the periods of the flow diminutions, giving a higher index into the moderate severity range. Around the twentieth week of gestation, the patient was started on Continuous Positive Airway Pressure (CPAP) therapy, automatic setting 4 to 20, and then optimizing treatment accordingly. Soon after the patient began Continuous Positive Airway Pressure (CPAP) therapy, morning blood glucose improved to fall back within the target range.

While escalating the dose of Insulin NPH (Isophane Insulin, Novolin NPH), the patient started developing a delayed reaction at the injection site. She developed a small, around 1 centimetre in diameter, erythematous papule at the site of Insulin NPH (Isophane Insulin, Novolin NPH) injection. A process of elimination was

used to identify the cause, and the patient was started on loratadine empirically. Avoiding alcohol swabs did not make any difference. Dry injection (i.e., inserting the needle without injecting any medications) did not produce any a reaction. Injecting normal saline solution did not create a reaction either. It was suspected that the patient reacted to the insulin component or the preservative used. The type of insulin was changed, and the following types were used:

- Humulin N (Insulin NPH, Isophane Insulin, Novolin NPH)
- Humulin R (Insulin Regular, Novolin Toronto)
- Lantus (Insulin Glargine)
- NovoRapid (Insulin Aspart)
- Levemir (Insulin Detemir)
- Humalog (Insulin Lispro)

The lowest reaction was with Insulin NPH (Isophane Insulin, Novolin NPH),the first type of insulin used, which still caused the patient a great deal of discomfort. The patient reported that the reaction was worse with higher doses of insulin.

Insulin desensitization was offered to the patient around gestation week twenty-four, and she was interested. After discussing the potential benefit and potential complication with the patient, she provided verbal and written consent and subsequently, arrangements for admission to the hospital were made. A protocol was created for the desensitization procedure, which was implemented in the medical inpatient unit. Please see Appendix A for details. Since the patient reported a delayed reaction, up to 3 hours after injection, the patient was monitored for 4 hours after completing all the protocol steps and then discharged home. This is to ensure she did not develop any reactions after the desensitization procedure. This is important to determine the dose that produced a reaction and resume desensitization at the lowest dose that did not produce a reaction. There were not any significant complications.

The patient reported significant improvement in her symptoms. The appearance of any reaction after Insulin NPH (Isophane Insulin, Novolin NPH) injections was rare, and when it occurred, it was delayed by more than 6 hours. When there was a reaction, it was mild and only lasted for a few hours and disappeared spontaneously without any management. The patient was happy with the results. The desensitization made it possible to increase the insulin doses without significant reactions. This was helpful in the third trimester, mainly when the patient needed more calories and higher insulin doses. There were no further complications during the pregnancy, and the patient's blood glucose was well controlled. She had an uneventful delivery of a healthy 8.5 pounds baby boy.

Discussion

Treatment of obstructive sleep apnea in patients with diabetes:

Obstructive sleep apnea can be a factor for uncontrolled Diabetes. Unfortunately, it is usually missed as a cause of difficulty in controlling blood glucose. Other factors make it challenging to investigate the disorder and treat it, as the availability of sleep labs and the cost of purchasing a positive pressure ventilation device. The hormonal disturbance caused by obstructive sleep apnea and interrupted sleep leads to increased insulin resistance. This has been demonstrated in multiple cross-sectional studies[1-5].The association between obstructive sleep apnea and Type II Diabetes has also been demonstrated in multiple studies, especially when the obstructive sleep apnea is moderate or severe[6-10]. The severity of obstructive sleep apnea has also been linked to higher hemoglobin A1c[11-13].

The mechanism of glucose metabolism dysregulation caused by sleep disordered breathing is not fully understood. It is suspected that increased sympathetic activity in patients with sleep disordered breathing plays a role in glucose dysregulation. Sympathetic nerve activity was monitored, and it was noted to be elevated compared to normal subjects[14-15]. The increased sympathetic activity has a direct effect on insulin secretions, glucose synthesis and incretins secretions. Other suggested mechanisms include systemic inflammation and activation of the hypothalamic-pituitary-adrenal axis.

Sleep-disordered breathing has been linked to Gestational Diabetes too. Pregnant women with obstructive sleep apnea have a 50% increased risk of developing Gestational Diabetes than pregnant women without obstructive sleep apnea. The risk of other disorders like preeclampsia and eclampsia is also higher in pregnant women with obstructive sleep apnea[16]. A higher micro-arousal index and higher desaturation index were associated with more elevated fasting blood glucose in pregnant women[17].

Some studies demonstrated a favourable impact of Continuous Positive Airway Pressure (CPAP) therapy on obstructive sleep apnea and gestational Diabetes[18-19]. Other studies did not reveal any difference in fasting blood glucose values or hemoglobin A1c values, mainly in patients with type II diabetes[21-23].

The common problem with all these studies is that they are not appropriately powered to demonstrate a reliable outcome. Several variables affect the results of studies investigating the effect of positive airway pressure on glycemic control. The method used in diagno-

sis, the severity of the sleep disorder, concomitant existence of other sleep disorders, adherence to positive airway pressure therapy, and positive airway pressure effectiveness in treating obstructive sleep apnea are all factors that can impact the results of such studies. Other variables include the length of the treatment period and how the effect on glucose metabolism was measured.

Generally, it does not seem that there is strong evidence of better glycemic control with Continuous Positive Airway Pressure (CPAP) therapy in patients with obstructive sleep apnea and gestational diabetes[21]. The effect of CPAP on glycemic control in gestation diabetes is still under investigation[20].

Treatment of obstructive sleep apnea during pregnancy:

According to multiple prospective cohort studies, the prevalence of obstructive sleep apnea in pregnancy is estimated to be between 3.6 and 26.7%24-25.The safety of positive pressure ventilation during pregnancy has been established in various studies, too 26-27. Untreated obstructive sleep apnea has been associated with multiple maternal morbidities, including eclampsia, cardiomyopathy, and pulmonary embolism 28-29. It does not seem that there is any measurable effect of obstructive sleep apnea on the fetus. However, some cohorts show a signal toward retarded fetal growth and maybe intrauterine fetal death. Hence, the general recommendation is to treat obstructive sleep apnea with positive pressure therapy during pregnancy 30-31. In the case describes-above, the patient did not have any significant symptoms other than the elevated blood glucose, which, in my opinion, was an indication to start treatment.

Insulin desensitization:

The desensitization procedure is very well established for multiple medications. For example, the Acetyl Salicylates desensitization protocol is well established across all hospitals in Nova Scotia, as it is frequently used for patients who will require treatment of cardiovascular events[32]. Also, a similar protocol has been established for different antibiotics. There is a published insulin desensitization protocol in previous case studies[33-34]. There is also a case report of insulin desensitization in a pregnant lady[35]. In this case, the protocol is very similar except for monitoring and intravenous administration of Dextrose 5% in water during the procedure to prevent any significant hypoglycemia.

Before attempting desensitization, it is essential to rule out other causes and establish a cause-effect relationship between insulin and the allergic reaction.

Hypersensitivity to preservatives, especially protamine, seems to be more common than hypersensitivity to injectable insulin. Due to the unavailability of injectable insulin without preservatives, we could not determine if the allergic reaction is due to the insulin or the preservatives.

By attempting different insulin formulations, some of the potential allergens were excluded. For example, the patient developed a reaction to Lantus (Insulin Glargine). Lantus (Insulin Glargine) does not contain protamine. It was determined then that the patient either has hypersensitivity to insulin or another preservative like Metacresol, Glycerine or Zinc. Phenol was excluded using the same process of elimination.

Monitoring was an essential part of the protocol. It focused on monitoring for allergic reactions and included hypoglycemia and frequent glucose monitoring to avoid any potential complications.

Conclusion

Gestational Diabetes is considered one of the high-risk conditions due to its multiple effects on the mother and the fetus. Adapting different treatment modalities like Continuous Positive Airway Pressure (CPAP), when appropriate, might mitigate using high doses of insulin and other hypoglycemic agents, which might have their side effects. CPAP therapy is considered safe during pregnancy.

Insulin desensitization is useful in the treatment of insulin hypersensitivity in gestational Diabetes. Precautions to avoid severe hypersensitivity reactions, hypoglycemia, and hyperglycemia are necessary. Close monitoring is critical to ensure the safety of the procedure.

Patient Consent

The case report was discussed with the patient. The patient had the opportunity to read the content of the case report. The patient provided verbal and written consent to publish the case in any medical journal without any preservations. The patient consented to publish any related data, images, photos, records, or any other materials when applicable. The patient understands that the Material will be published without the patient's name attached; however, complete anonymity cannot be guaranteed. Somebody somewhere may recognize the patient. The Material may show or include details of the patient's medical condition or injury, and any prognosis, treatment, or surgery that the patient has, had, or may have in the future. The article may be published in a journal that is distributed worldwide. The article, including the Material, may be the subject of a press release and may be linked to social media and/or

used in other promotional activities. Once published, the article may also be available on other websites. The text of the article will be edited for style, grammar, and consistency before publication. The patient will not receive any financial benefit from the publication of the article. This includes publication in English and translation, in print, in digital formats, and in any other formats that may be used. The article may appear in local editions of journals or other publications. The patient can revoke the consent at any time before publication, but once the article has been committed to publication, it will not be possible to revoke the consent. The patient has had the opportunity to comment on the article, and I am satisfied that the comments, if any, have been reflected in the article.

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Appendix A

Insulin Desensitization Protocol in Gestational Diabetes:

Insulin preparation:

Insulin NPH (Isophane Insulin, Novolin NPH) was used during the whole protocol. The hospital pharmacy prepared different concentrations. Doses less than 1 ml in volume were diluted with normal saline solution, so the end volume in 1 ml.

Patient preparation and monitoring:

The patient was advised to administer the usual night dose of Insulin NPH (Isophane Insulin, Novolin NPH) at the same time it was initially prescribed. The patient was advised not to administer any Insulin NPH (Isophane Insulin, Novolin NPH) the morning of the procedure and arrive 1 hour before the procedure's scheduled start time. Basal vital signs were measured, and baseline blood glucose measurements were obtained using both an intravenous sample and capillary sample at the same time. Dextrose 5% in water was started intravenously at 75 ml per hour and continued to be infused for one hour after the last dose of insulin was injected.

Vital signs were measured hourly. Blood glucose was measured hourly unless it was less than five or more than ten mmol/L. If the blood glucose was less than five or more than ten mmol/L, glucose was checked every 30 minutes. SPO2 was continuously monitored. Inspection of the site of injections was done hourly. If the blood glucose is lower than 4, 10 ml of Dextrose 25% in water should be injected. If the blood glucose value is more than 12, the infusion rate should be decreased to 25 ml per hour.

Questions about the following were also asked hourly to monitor for hypoglycemia or hypersensitivity reaction:

- Sweating
- Irritability or nervousness
- Tremors
- Confusion
- Tachycardia
- Feeling hungry
- Light-headedness or blurring of vision
- Nausea
- Skin rash
- Chest tightness
- Shortness of breath
- Itching
- Wheezing
- Swelling

Insulin injection procedure:

1. Intradermal 1 ml of normal saline solution was injected as a reference. The site was marked "S" for saline.
2. Intradermal 0.001 units of Insulin NPH (Isophane Insulin, Novolin NPH) injected 1 cm away from the previous injection and marked "1".
3. The dose was multiplied by 10 for the subsequent injections until a dose of 1 unit was reached. The same procedure of spacing and marking was used. The dose of 1 unit of Insulin NPH (Isophane Insulin, Novolin NPH) was also injected intradermally.
4. Doses of more than 1 unit were injected subcutaneously.
5. Monitoring for skin reaction was done hourly before each subsequent injection. If there is a reaction, the last dose that did not produce a reaction was used. The site was marked with the same number of the dose that did not produce a reaction.
6. Once 1 unit of Insulin NPH (Isophane Insulin, Novolin NPH) was injected, each dose was double that of the previous dose. E.g., 1 unit, 2 units, 4 units, until the desired dose of Insulin NPH (Isophane Insulin, Novolin NPH) required for glycemic control is reached.
7. The patient should be monitored for 4 hours after the last injection.
8. The patient should start the initially prescribed dose of Insulin NPH (Isophane Insulin, Novolin NPH) within 12 hours after completing the desensitization protocol.

Original Research

Deferred consent model for an observational study in a pediatric emergency department

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Abstract

Background: A limited amount of literature has been published regarding the use of deferred consent for studies involving children. We aim to inform future studies by reporting the results of an observational study in a pediatric emergency department which employed a deferred consent model.

Methods: Over a 14-month period, prospective data was collected on children who presented to the emergency department of the IWK Health Center (Halifax, NS, Canada) and the Alberta Children's Hospital (Calgary, AB, Canada) with blunt abdominal trauma. At presentation in Halifax, parents were offered the option of deferring consent until they could speak to a member of the study team. In Calgary, parents had to decide to consent or not at the time of assessment.

Results: A total of forty potential study participants were approached over the study period. All 8 of the participants in Halifax consented to be enrolled, with 25% choosing to defer consent. In Calgary, where there was no option to defer consent, only 53% provided consent for study enrolment.

Conclusions: A deferred consent model should be considered when designing observational studies in the pediatric emergency department setting. Based on the results of our small study, deferred consent is feasible, an acceptable option for parents, and aided our ability to maximize enrolment. Further research is required to validate our findings.

Introduction

Conducting prospective research studies in the pediatric emergency department (ED) setting is a time-sensitive and resource-intensive endeavor. Particularly in the setting of pediatric trauma research, potential study participants present to the ED infrequently, and at all times of the day. Despite this challenge, key data must be collected at the time of presentation in order to produce valid results[1,2]. Given this, consenting and enrolling participants on an ongoing basis for prospective studies in the ED usually requires research staff to be present around the clock to maximize recruitment and minimize selection bias. However, the feasibility of maintaining such staffing at all times is limited by resource availability. We present the results of a study that used a deferred consent model. This model provided a more feasible approach to recruiting study participants for our observational study in the ED while maintaining research ethics standards[2-4].

Deferred consent has been used successfully in several studies in the United Kingdom and Australia[1,5]. This has yielded positive results from both a participant and an investigator perspective. In the pediatric ED there is a conflict between the requirement for informed consent prior to data collection, which may not be feasible in emergencies, and the need for high-quality prospective evidence to guide clinical decision making[1]. There is also uncertainty regarding the validity of informed consent when it is obtained in the stressful environment of a pediatric emergency; in this case, parents or guardians are unlikely to fully process the study information provided, and so are unlikely to give consent that is fully informed[6]. This is a situation unique to the pediatric ED, and this clinical area has a paucity of published data on obtaining consent. Additionally, the need for initiation of emergent investigations and treatment without delay often leaves little time to obtain consent[7]. In certain cases, obtaining informed consent before starting management could even compromise patient care, particularly in circumstances when a parent or guardian is not initially present[1]. Deferring consent to participation in an observational study avoids delaying emergency interventions while still ensuring fully informed consent to the use of patient data[2].

We designed an observational study to assess the feasibility of running a larger multicenter study which would collect data on clinical predictors of significant injury after pediatric blunt abdominal trauma. The aim of this paper is to present and describe the impact of our deferred consent model using results from this observational study. To our knowledge, this model represents a novel consent process and may serve as a blueprint for future research in the pediatric ED.

Materials and Methods

The authors collected data over a 14-month period on children less than 18 years of age who presented to the ED of either the IWK Health Centre, Halifax, NS, Canada (IWK) or the Alberta Children's Hospital, Calgary, AB, Canada (ACH) with blunt abdominal trauma. The IWK employed a deferred consent model, while the ACH did not. Consent was required to permit collection of clinical variables related to the traumatic event and to allow the study team to follow-up with the parents via telephone in order to rule-out missed injuries should the child be discharged from the ED. The study protocol was approved by the Offices of Research Ethics at the IWK and ACH.

Participants at both sites were flagged by registration or triage staff in the ED for inclusion in the study and a Data Collection Form was placed on each participant's chart. The Data Collection Form was completed by the emergency physician in order to obtain the time-sensitive data regarding their clinical assessment of the trauma. The registration clerk or nursing staff gave the potential participants' parent(s)/guardian(s) an Information and Consent Form (ICF) to review while waiting in the ED. After reviewing the ICF, they could choose to provide written consent to participate or not to participate in the study. At the IWK, parent(s)/guardian(s) were also provided with a third option to defer consent until speaking to a member of the study team (Figure 1). For those who wished to speak to a study team member before giving consent, or for those potential participants who had a completed Data Collection Form without an ICF, a member of the study team contacted them via telephone within four days to obtain informed consent.

For participants who declined to be included in the study, all data collected by the emergency physician on the Data Collection Form, except for the date and time of assessment, age, and gender of the patient, were destroyed. The patient's electronic medical record was not accessed by the study team if consent was not obtained.

For each participant who did consent to inclusion in the study, data from their initial clinical assessment by the emergency physician were inputted into a secure research database. Further clinical data regarding each participant's injury were collected by the study team from the participant's electronic medical record to determine the clinical significance and possible predictors of the injury.

Results

A total of forty children were approached over the 14-month study period: 8 at the IWK, and 32 at the ACH.

Of the eight sets of parent(s)/guardian(s) that reviewed the ICF at the IWK, 6 (75%) provided written consent immediately, and 2 (25%) wished to defer con-

If you are **too busy to decide now or want more time to think about it**, one of the study team members will contact you within 4 days to ask if you are willing to include you/your child's information in the study. **If you decide you want to wait to consent, you do not need to complete this form.**

I have read or had read to me this information and consent form and have had the chance to ask questions which have been answered to my satisfaction before signing my name. I understand the nature of the study and I understand the harms and benefits. I understand that I have the right to withdraw from the study at any time without affecting my care in any way. I have received a copy of the Information and Consent Form for future reference. I freely agree to participate in this research study.

_____
Name of Participant (printed)

_____	_____	_____
Parent/Guardian Name (printed)	**Parent/Guardian Signature**	**Date**

PLEASE CHECK ONE:

☐ **Yes,** I wish to participate ☐ **No**, I do not wish to participate ☐ I would like **more information**

☐ ***Do you wish to receive a lay summary of the results of the study? If so provide your address:***

Email or postal address_____

Figure 1. Excerpt from Information & Consent Form at the IWK Health Centre.

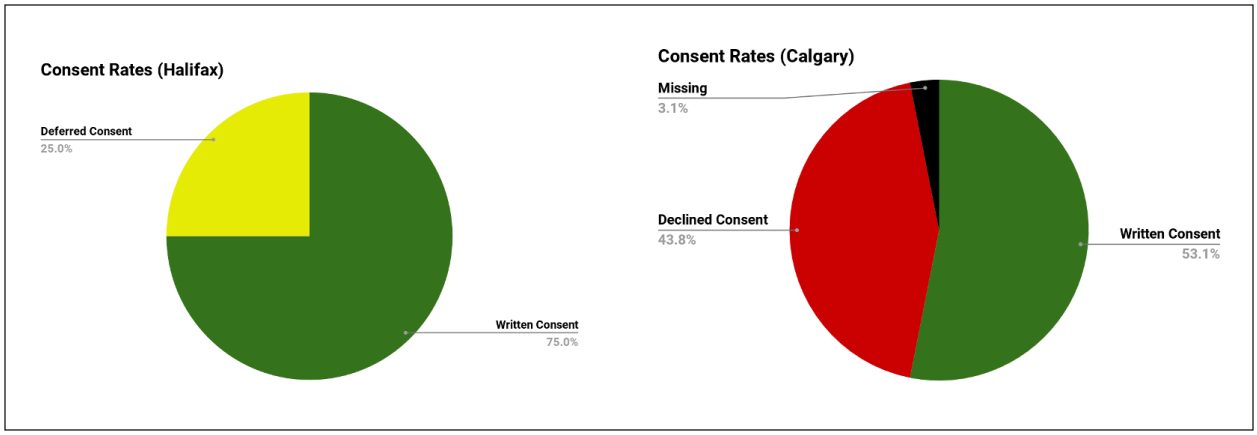

Figure 2. Consent Rates at the IWK Health Centre (Halifax) and the Alberta Children's Hospital (Calgary). The Halifax study site offered a deferred consent option to participants, whereas the Calgary site did not.

sent. After speaking with a study team member via telephone, both participants' parent(s)/guardian(s) ultimately provided consent. No participants denied consent at the IWK, where the deferred consent model was employed.

Of the 32 sets of parent(s)/guardian(s) that reviewed the ICF at the ACH, 17 (53%) provided written consent immediately, 14 (43%) denied consent and 1 (3%) did not complete the form. No participants were able to defer consent as this study site did not employ the deferred consent model (Figure 2).

Discussion

The ED presents many barriers to conducting prospective research. One of the major difficulties was obtaining informed consent prior to the collection of time-sensitive data. ED visits are often an incredibly stressful time for pediatric patients and their families, particularly in the setting of trauma. Reading a consent form and making an informed decision about research participation can be overwhelming in this environment and can lead to a default response of denied consent. Deferred consent provides an opportunity for participants and their families to review study information in a less stressful setting, thereby allowing them to be better informed prior to their consent decision.

Our data demonstrates that a deferred consent model is feasible and ethical. Deferred consent was offered to the 8 potential participants identified at the Halifax site. Of those approached, 6 consented to participate in the study immediately, while the 2 participants who chose to defer consent agreed to participate after speaking with a member of the research team. At the Calgary site, 32 potential participants were identified, each of whom was approached by a research assistant at the time of assessment to either confirm or deny consent. Of those approached, 17 consented to participate in the study immediately, 14 declined to participate in the study, and in one case the form was not completed. At the Calgary site, potential participants and their families did not have the option to defer consent until they were able to speak with a member of the study team. Though we appreciate that this is a small sample size, it is possible that the Calgary site would have seen an improved participation rate had they provided the option for deferred consent. We do acknowledge that we did not explicitly survey participants to gauge their level of satisfaction with the deferred consent process. This would be valuable information to include in a future study.

Another advantage of the deferred consent model is that it reduces the incidence of missing or incomplete consent forms. The protocol approved by the Research Ethics Board at the Halifax site allowed a study team member to contact a participant's guardian within four days should their Data Collection Form be collected with an incomplete or missing ICF. Forms can be easily misplaced or left incomplete in the setting of a busy ED; the deferred consent model helps limit the number of participants missed as a result of this. The Calgary site did not employ the deferred consent model and had to exclude one participant due to an incomplete ICF. The data for this patient would have likely been included at the Halifax site, as deferred consent could have been obtained by contacting the potential participant's guardian within four days of presentation.

The deferred consent model provides a more feasible option when it is not possible to have study team members constantly available to obtain patient consent. This model can minimize the resources required to conduct emergency department research, leading to exciting observational research opportunities.

Finally, though not addressed in our study, the question has been raised as to whether consent is re-

quired at all in the context of observational prospective clinical data collection in the pediatric ED for the purpose of research. In this study, aside from any data obtained from the tool used by the emergency physician to systematically document clinical findings, all data used by the researchers would have ultimately been available from participants' electronic health records. Had we opted to perform this study retrospectively using electronic health records, waiver of consent would have been permitted. However, systematic collection of clinical variables (such as abdominal exam findings) that were to be examined for the purpose of a developing a clinical decision tool would have been limited in a retrospective study. Undoubtedly, the general principles of ethics in research, including doing good (beneficence), doing no harm (non-maleficence), assuring confidentiality and minimizing risk to participants, must be upheld in all research. There is ongoing debate surrounding how to uphold these principles while balancing them with the feasibility of obtaining informed consent and the need for quality prospective research to guide clinical decision making, particularly in the setting of acute care, but that is beyond the scope of this paper[8].

The main limitation of our study is the small number of participants recruited through the Halifax site where the deferred consent model was used. It would be beneficial to use the deferred consent model at a site better staffed to identify potential study participants. This would help to determine whether potential participants would utilize the deferred consent option, and whether this would result in increased consent rates.

Conclusion

When designing observational studies to be conducted in the pediatric emergency department setting, researchers should consider the use of a deferred consent model when approaching children and their parents for recruitment. While some may see deferred consent as aa shortcut and cost-cutting measure, our experience demonstrates that it is, in fact, a feasible option acceptable to parents at a stressful time, and that it may help to increase consent rates. Further research is required to determine the validity and acceptability of using a deferred consent model in a larger study.

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Original Research

Reducing Medical Student Performance Anxiety through the Pre-clerkship Residency Exploration Program (PREP)

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Abstract

Background: Medical students face numerous stressors during their pre-clerkship years, including selecting a specialty for residency. For those interested in specialties with limited integration into the traditional pre-clerkship curriculum, or students with broad interests at the end of pre-clerkship studies, a two-week Pre-clerkship Residency Exploration Program (PREP) could be a useful tool to reduce career-decision-making anxiety. This study assessed whether PREP, an elective for second-year medical students, can effectively reduce performance anxiety and stress related to the transition into a clinical learning environment and career decision making.

Methods: Eighty second-year medical students participated in PREP (2018-2019), and completed pre- and post-program surveys that assessed, on a Likert-scale, their level of performance anxiety during clinical electives, and anxiety surrounding future career decisions (i.e., clerkship, specialty selection, residency match). A modified version of the Test Emotions Questionnaire (TEQ) assessed student emotions regarding the Canadian Residency Matching Service (CaRMS) process.

Results: Sixty-nine students completed both surveys. Performance anxiety was low at baseline and unchanged at the end of PREP (p-value = 0.29). However, there was a significant decrease in stress surrounding exposure to enough specialties to make an informed career choice (p-value < 0.001). Furthermore, there was a significant decline in participant anxiety regarding CaRMS as indicated by the TEQ anxiety-subscale (p-value < 0.001).

Conclusions: PREP may serve as an effective tool to expose medical students to a high volume of specialties and reduce the stress associated with transitioning into a clinical learning environment and making career-related decisions.

Introduction

It is well established that medical students face higher than average levels of anxiety, burnout, and stress which can impact their learning and performance[1–4]. Among common stressors for medical students is selecting a specialty to pursue for residency and as a career. To reduce this stress, pre-clerkship medical students are increasingly exploring options to gain more clinical exposure before reaching their clinical years. Researchers from many specialties have identified earlier clinical exposure as a key way to increase interest in their field[5–7]. While the majority of studies have focused on this recruitment lens[5–7], there remains an absence of literature on the impact of earlier pre-clerkship exposure on the stress and anxiety of medical students facing career decisions.

Undergraduate medical students identify the transition to clerkship as a highly stressful time as they anxiously anticipate what lies ahead[8]. Medical students often aim to reduce this anxiety by spending more time in clinical environments, particularly in the context of confirming their competencies and career interests[9]. Medical schools in North America have sought to minimize the anxiety of this transition through programs which focus on clinical skills and stress management[10,11]. Additionally, changes to undergraduate medical curriculum such as adjusting course content, scheduling, and increasing elective time have been associated with significantly decreased levels of depression, anxiety, and stress. For instance, Slavin and colleagues implemented additional electives for first and second-year students for a total of 12 days per year, with the intent to provide additional opportunity to explore areas of interest[3]. The study found that compared to those without this increase in exposure, students who took part in the additional elective time were less anxious and showed a progressive reduction in their stress levels over the course of the electives[3].

Many institutions have explored the use of intensive electives, workshops, or skills sessions to help students interested in surgical specialties explore different fields prior to entering clerkship. For instance, the University of Toronto established the Surgical Exploration and Discovery (SEAD) program in 2012, which allows

first-year medical students to rotate through seven core surgical specialties to help students identify or solidify their interests[12]. The success of the SEAD program for surgically-minded medical students has been replicated at a number of Canadian medical schools since its founding and has expanded to include additional surgical subspecialties[13,14]. Despite its demonstrated efficacy in helping pre-clerkship medical students identify specialties of interest and gain early exposure to the clinical environment, there has yet to be a similarly structured program to expose students to underrepresented areas of medicine.

Specialty interests at the beginning of medical school are strongly associated with residency match by graduation, despite limited clinical exposure and a lack of student confidence in pursuing their identified interests[15,16]. We implemented the Pre-clerkship Residency Exploration Program (PREP) at Dalhousie University (2018) to allow second-year medical students to experience electives, workshops, skills sessions and lifestyle presentations in over 15 different specialties before transitioning to clerkship training.

This study may help support the implementation of intensive pre-clerkship elective programs to reduce the stress of entering clerkship and making future career decisions. In this study, we evaluated the effectiveness of PREP in reducing student anxiety about their clinical performance in clerkship and making career decisions.

Methods

PREP

A group of second-year medical students at Dalhousie University designed and implemented PREP. This occurred with significant support from the Department of Undergraduate Medical Education (UGME), Student Affairs (including Dalhousie Medicine's career counselor), and department heads or staff physicians from all specialties included in the program. The founding members spent several months in consultation with the aforementioned parties to determine the program structure and goals, selection criteria, and which specialties would be included. At our institution, the first two years are primarily non-clinical, with some opportunities for time-limited electives and observerships. Departments initially contacted were those with limited exposure in the pre-clerkship curriculum. This was followed by specialties with direct-entry in the Canadian Residency Matching Service (CaRMS) match. Participating departments needed to have capacity and interest in accommodating the 40 students annually. Where specialties were unable to accommodate 40 students due to administrative burden or department size, student preference was used to divide participants into sub-groups (e.g., 20 students participated in adult hematology, and 20 in pediatric hematology).

Participants rotated through a combination of electives, skills sessions, and workshops over a two-week period. Two groups of 20 students (40 total) rotated through alternating schedules. Across both groups, pairs of students completed each of their ten half-day elective rotations through a combination of the following medical specialties: anesthesia, cardiology, endocrinology, general internal medicine, ophthalmology, pathology, radiation oncology, physical medicine and rehabilitation, hematology, neurology, nephrology, pediatric hematology, medical oncology, and neonatology. PREP students also completed skills sessions that included basic procedures (e.g., suturing, intravenous (IV)/intraosseous (IO) insertion), advanced procedures (e.g., endoscopy/bronchoscopy, femoral line insertion), trauma exercises (e.g., primary surveying, airway management), and ultrasound practice. Specialty-specific workshops involving career discussions and additional skills exposure were also included for physical medicine and rehabilitation, ophthalmology, anesthesia, radiology, and pathology. The specialties and workshops offered were consistent for both cohorts of the program. Finally, all participants attended lunchtime presentations and discussions from staff and residents from various specialties which focused on career decisions, CaRMS, and the lifestyle of their specialty.

Participants

Participants were 80 pre-clerkship medical students (male = 28, female = 52), composed of two years of consecutive cohorts of 40 students at the end of their second year of undergraduate medical training. Students were recruited for the program online via email and social media in addition to receiving an in-class presentation describing PREP and its purpose. Participants were selected using a blinded randomized lottery. A third party used an online randomization software system to select participants from the 133 applicants (60% of students) and place the remaining students on a waitlist. The only exclusion criterion was the inability to attend all of the program sessions during the two-week block of the program. The Nova Scotia Health Authority Research Ethics Board approved the ethics for this study (File No. 1023087).

Measures

We used a sixteen-item Likert-scale questionnaire to assess participant anxiety regarding their performance in a clinical setting. To assess performance anxiety at baseline, students completed a questionnaire on their most recent elective experience prior to PREP and

selected the number that best reflected the degree to which they agreed with the given statement (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). Participants completed the same sixteen questions again at the end of PREP. The first ten questions assessed behavioral, cognitive, and physical markers of performance anxiety. Behavioral items included "I avoided tasks that involved exposure to new clinical scenarios"; cognitive items included " I was worried I would panic or make a fool of myself while on elective"; and physical items included "I experienced trembling in my hands when trying to perform tasks". The remaining six questions specifically assessed student anxiety surrounding the CaRMS process with respect to preparation and performance in clerkship, as well as exposure to a sufficient number of specialties to make an informed decision during the residency matching process.

Additionally, for the second cohort of 40 students, we implemented a modified version of the Test Emotions Questionnaire (TEQ), a subset of the Achievement Emotions Questionnaire (AEQ). This is a standardized survey validated for use with university students to assess the emotions they feel in particular academic achievement scenarios17. We adapted 25 questions from the TEQ to assess the following emotions related to CaRMS, before and after our intervention (PREP): test-related enjoyment, pride, hope, anger, hopelessness, and anxiety. This included items such as, "I worry whether the match will be too difficult", and "Thinking about the match, I feel nervous and uneasy". All items were answered on a Likert-scale.

Procedure

Before beginning PREP, students completed the online questionnaire using Opinio Surveys (Object Planet, Oslo, Norway) together in a classroom. We gave a verbal presentation to explain the nature of the survey and to obtain voluntary consent. Students had the opportunity to decline participation by choosing not to sign the consent form. If students chose not to consent then it did not impact their participation, experience or treatment during or at any time following PREP. The researchers were available for any question clarification if required. At the end of the two weeks, we administered a post-program survey containing the same questions as the pre-program survey, in addition to quality assurance questions pertaining to program feedback and improvement.

Statistical analysis

Cronbach's alpha was calculated to determine the reliability of the two subscales used in the questionnaire (performance anxiety and future-learning anxiety). Cronbach's alpha determines the relatedness of each item used in the measure to indicate its reliability. The closer its value is to 1, the higher the internal consistency of the measure. Wilcoxon Signed-Rank Test was also determined to compare the pre-PREP and post-PREP responses for each question. This test was chosen as a non-parametric alternative to a dependent samples t-test as the assumption of normality was not met. The Wilcoxon Signed-Rank Test compares the average pre- and post-test scores for this study. Dependent samples t-tests were conducted for the TEQ overall, as well as each of the emotion subscales. All data were analyzed using v.25 of SPSS Statistics (SPSS, Chicago, USA).

Results

Descriptive statistics

Twenty-five males (33.8%) and 49 females (66.2%) completed the questionnaires (n = 74). Three students in each cohort of 40 participants who did not complete the questionnaires were program administrators and thus were excluded due to the potential for bias. We analyzed the pre- and post-PREP results for all remaining program participants, with two exclusions due to incomplete response data (total n = 72). Age ranged from 20 – 32 with all participants having at least a bachelor's degree, and a subset of participants having a master's degree or higher.

Performance anxiety

The performance anxiety subscale included 10 items18 (α= 0.79), indicating that the questionnaire was reliable. The median pre-test and post-test scores were 2.00, corresponding with "disagree" on a Likert-scale (pre-test M = 2.31, post-test M = 2.19). The Wilcoxon Signed-Ranks Test showed that post-program performance anxiety was not significantly lower than pre-program performance anxiety (Z = -1.06, p = 0.29). Importantly, though not statistically significant, student responses to "I was worried I would panic or make a fool of myself while on elective" decreased from a median of 4 (agree) to 3 (neutral).

Clerkship and residency selection anxiety

This subscale of the questionnaire included 6 items (a = 0.80). The Wilcoxon Signed-Ranks Test indicated that following PREP, students felt significantly less anxiety towards clerkship and residency decision-making than they did prior to the program (Z = -5.69, p < 0.001). Table 1 summarizes pre- and post-PREP Likert-scale responses of participants related to clerkship, residency, and future career decisions.

CaRMS-related emotions (TEQ)

Thirty-six students completed the TEQ. The t-test results from our modified-TEQ did not support a significant change in participant emotions towards the CaRMS match immediately after PREP (p-value = 0.151). However, when analyzing the modified-TEQ by subscale, there was a statistically significant decline in both anxiety and hope regarding the CaRMS match after our intervention (p-values < 0.05). CaRMS-related enjoyment, anger, hopelessness, and pride were unchanged (p-values > 0.05). Detailed results from each of the subscales can be found in table 2.

Discussion and Conclusions

Based on the results, participants in PREP did not find a significant change in their overall stress level about performance in electives through participation in the program. Both PREP and previous elective experiences appear to be low-stress environments for clinical learning, as statements pertaining to behavioral, cognitive, and physical anxiety symptoms during electives were, on average, disagreed with by participants. However, when participants looked forward to clerkship, residency, and having enough clinical exposure to make informed career decisions, there was a significant decline in anxieties following PREP compared to before participating. This finding suggests that, though only two weeks in length, an elective with a focus on exploring a high volume of residency options over half-day electives can provide enough exposure to help students feel more comfortable about their transition to a clinical learning environment.

The present results are consistent with past literature on the benefits of early clinical exposure during undergraduate medical education. For instance, Ray et al. (2018) observed that students with early experience in emergency medicine made earlier decisions to pursue the specialty. The authors suggest that by gaining an understanding of the specialty earlier in medical school, students are better able to identify a career path to suit their lifestyle[7].The findings from our independently developed survey, as well as the CaRMS-related TEQ, indicate an association between the opportunity to make this decision sooner and less anxiety during the transition to clerkship and beyond. This is consistent with the positive impact of early electives on medical student stress and anxiety as described by Slavin et al[3].

While our findings regarding a decline in student anxiety following PREP are in line with past literature, the significant decline in CaRMS-related hope at the end of PREP was not anticipated. When the CaRMS-related hope subscale is analyzed by item, it appears that this finding is attributable to a change in attitude to the statement "I start preparing for CaRMS with great hope and anticipation". Prior to PREP, the mean response was "agree" on a Likert-scale, while at the end of PREP, the mean response declined to "disagree"; mean response to the other hope-related items was unchanged. It is possible that this change is related to the amount of career and CaRMS-focused seminars that were delivered during PREP. For many participants, this was their first exposure to the full extent of the application, match, and interview process, and may have left students feeling more overwhelmed than hopeful. Importantly, the TEQ did not indicate a corresponding increase in hopelessness or anger regarding the CaRMS process. Enjoyment and pride were also unchanged, as neither emotions were specifically targeted by our intervention.

This study has a few limitations. Primarily, we implemented the program at a single Canadian medical institution. As such, there may be unique participant characteristics that are not fully generalizable to other classes or institutions. Additionally, the administra-

Table 1. Average pre- and post-PREP anxiety regarding future clinical education and career decisions.

Item on Clerkship and Residency Selection Anxiety score	Pre-Program Response, mean	Post-Program Response, mean	p-value
I am worried that I do not have the skills necessary to perform at the level required for my next year of training	3.39	2.93	0.009
I am concerned that I have not had exposure to enough specialties to make a career decision	3.97	3	<0.001
I do not feel that I have had enough time pre-clerkship to expose myself to enough specialties	4.03	3.2	<0.001
I feel anxious about making career decisions due to lack of information about the specialty	3.69	3.11	0.001
I am worried I will not find a medical specialty that I am interested in before I need to apply for CaRMs	2.82	2.53	0.082
I am worried that I will not have exposure to lesser known medical specialties that will not be in our clerkship rotations	3.83	3.04	<0.001

Table 2. Average pre- and post- PREP scores on the Test Emotions Questionnaire (TEQ) subscales.

TEQ Score	Pre-Program Response, mean	Post-Program Response, mean	p-value
Overall	3.39	2.93	0.009
Enjoyment	3.97	3	<0.001
Anxiety	4.03	3.2	<0.001
Hope	3.69	3.11	0.001
Hopelessness	2.82	2.53	0.082
Anger	3.83	3.04	<0.001

tive and logistic constraints of implementing this type of programming meant only 40 students were able to participate in the program yearly. This limits the ability to assess how the program could affect an entire class of medical students, although this may be feasible at institutions that have the desire and the capacity. Additionally, data could not be collected from non-PREP participants in the class to provide a comparison group for those who participated. Moreover, it is possible that the use of Likert-style questions reduced the ability to capture the full degree of stress and anxiety of the participant sample, as a 5-point scale provides limited potential responses for those that fall in-between options. For example, participants who partially agreed or partially disagreed may have selected neutral options. Student performance anxiety was low at baseline, which could indicate that this sample was generally confident in their abilities or were unwilling to admit it in the context of having classmates analyze their responses. It is also possible that the low-performance anxiety could be attributed to Dalhousie Medicine offering pre-clerkship electives in the first two years of medical school. As such, results from other institutions may differ. Lastly, the TEQ was only implemented for the second year of the program and thus data on only one year's cohort of 40 students was available for assessment.

Overall, the findings of this study are important in showing that PREP is an effective tool for helping pre-clerkship medical students explore various specialty options before entering clerkship. By the end of the two weeks, students gained sufficient exposure to feel less stressed about finding a specialty of interest. It is important to determine whether the immediate effects of PREP remain short-term or continue into clerkship and the residency application process. As such, future studies should aim to follow up with students who participated in the program and include a comparison group of students who do not participate. Data from future years of running the program and expansion of PREP to other medical schools is also warranted. Further research will help support the incorporation of PREP across universities in North America.

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Case Report

A case of heavy menstrual bleeding in an adolescent due to undiagnosed severe hypothyroidism

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Abstract

Heavy menstrual bleeding can be life threatening in both adult and pediatric populations, sometimes requiring emergent resuscitation. Once stabilized, it is important to carefully consider the extensive list of potential causes. Hypothyroidism should be considered in the differential diagnosis of heavy menstrual bleeding. It is important to recognize this early, as hypothyroidism can affect many other body systems, sometimes significantly. This report outlines the case of a 16-year-old female who presented with heavy menstrual bleeding, ultimately determined to be due to severe hypothyroidism. It highlights the importance of investigation, recognition, and treatment of uncommon causes of heavy menstrual bleeding in adolescent patients for pediatricians, emergency physicians, and primary care providers alike.

Introduction

In the adolescent population, the differential diagnosis for heavy menstrual bleeding is wide, including endocrine disorders (e.g. anovulatory bleeding, polycystic ovarian syndrome, thyroid disease), bleeding disorders (e.g. von Willebrand disease, platelet dysfunction, thrombocytopenia, clotting factor deficiencies), infections (e.g. cervicitis), medications (e.g. anticoagulants, depot medroxyprogesterone), trauma, foreign body, pregnancy (e.g. spontaneous abortion, ectopic, gestational trophoblastic disease), and structural uterine disorders (e.g. adenomyosis, myomas, polyps, cancer)[1]. Heavy menstrual bleeding in the pediatric population has also been attributed to Van Wyk-Grumbach Syndrome, consisting of chronic hypothyroidism, precocious puberty, delayed bone age and ovarian cysts[2, 3, 4]. Despite the wide range of etiologies, the most common cause of heavy menstrual bleeding in adolescents is anovulatory bleeding related to an immature hypothalamic-pituitary-ovarian axis[1,3].

Given that heavy menstrual bleeding can be severe and life threatening, it is imperative that after resuscitation, clinicians be able to promptly diagnose and treat the underlying cause. This report outlines the case of a 16-year-old female who presented with life threatening heavy menstrual bleeding and was subsequently diagnosed with severe hypothyroidism as the underlying cause. Hypothyroidism as a cause of heavy menstrual bleeding has been debated[5], though it has been attributed to pseudoprecocious puberty in children[6], and may cause a variety of menstrual irregularities in women of reproductive age[7].

Case Presentation

A 16-year-old female presented to a community emergency department (ED) after three syncopal episodes at home in conjunction with heavy menstrual bleeding. She had undergone menarche five months prior but had no further vaginal bleeding until this presentation. Her initial menses was also heavy; she missed school as a result, but she did not have syncopal episodes. On presentation, she described changing menstrual pads every two hours and passing moderate-sized clots. She denied dysmenorrhea, dyspnea, pedal edema, pleuritic chest pain or skin/nail/hair changes. When asked, she endorsed protracted fatigue, cold intolerance, flat mood and occasional constipation for several years. She did not have symptoms of a bleeding diathesis. There was no family history of autoimmune nor bleeding disorders. She was otherwise healthy, and her only prior surgery was dental work. She was not taking any medications and her immunizations were up to date.

On initial assessment to the community ED, she was normotensive and mildly tachycardic (110 bpm). She weighed 45.5 kg, but due to the nature of her presentation, a height was not obtained. Her lips and conjunctiva were pale, and cardiorespiratory and abdominal exam were unremarkable. She was Tanner Stage II for breast and pubic hair development. No myxedema

or pedal edema was evident. Her mentation was normal, but it was difficult to assess cognition due to the focus on her acute presentation.

Her urine beta-hCG was negative. Her hemoglobin was 64 g/L (normal: 105-150), with no previous for comparison. Her coagulation studies were as follows: platelets 264 x10^9/L (normal: 130-400), international normalized ratio 1.3 (normal: 0.8-1.2), partial thromboplastin time 27.1 (normal: 22.8-29.5) seconds, and fibrinogen 1.3 (normal: 2.2-5.5) g/L. Liver enzymes, lactate dehydrogenase and renal function tests were normal. Her blood smear was negative for schistocytes. Thyroid and von Willebrand testing were sent. An electrocardiogram showed sinus tachycardia with a non-specific T wave abnormality.

She was fluid resuscitated and received two units of packed red blood cells (pRBCs) in the ED and was then admitted to the medical floor. Gynecology at this peripheral centre was consulted. She was started on tranexamic acid 1g intravenous (IV) q6h and conjugated estrogen (Premarin) 25mg IV q6h for three doses. She was also given medroxyprogesterone acetate (Provera) 20mg PO. A pelvic ultrasound was completed and ruled out a structural abnormality of the uterus and ovaries.

Her heavy menstrual bleeding continued, and repeat hemoglobin was 65 g/L, so she was transfused two more units of pRBCs. Her platelets decreased during the first 48 hours to a nadir of 83 x109/L. Hematology at this centre was consulted, and suggested giving DDAVP 13.65mcg IV empirically, as the von Willebrand screen was still pending. She was also transfused with cryoprecipitate and platelets. Her fibrinogen continued to be low (1.9 g/L). During the first 36 hours of admission, she received a total of eight units pRBCs, ten units of cryoprecipitate, one unit of platelets and one dose of DDAVP.

Despite this early management, she continued to experience heavy menstrual bleeding beyond this initial 36 hours. Eventually, she became hypotensive with systolic blood pressure as low as 60 mmHg, though her heart rate remained normal (65-80 bpm). Pediatric Intensive Care and Pediatric Gynecology services at the tertiary care hospital were consulted for management recommendations, transport and monitoring, as despite blood product transfusion and fluid resuscitation, she remained hypotensive. A clear etiology had yet to be established as well. At this point, she was transferred by air to the tertiary care centre's pediatric ED.

Upon arrival, she was persistently bradycardic (40-50 bpm). The remainder of her vital signs were normal. Her vaginal bleeding was minimal. Her initial thyroid studies from the community hospital returned, revealing a thyroid stimulating hormone (TSH) of 856 (normal: 0.3-5) mIU/L; her free thyroxine (T4) and triiodothyronine (T3) were undetectable. Her von Willebrand testing was negative. She was admitted for monitoring. She was stepped down from IV to oral tranexamic acid and started on continuous combined oral contraceptive pill regimen (two pills, each containing 30 mcg of ethinyl estradiol and 150 mcg of desogestrel, for one week, then one pill daily). Internal Medicine and Endocrinology services were consulted. Her thyroid studies were repeated, with a TSH of 510 mIU/L, free T4 of 2.2 (normal: 11.5-22.7) pmol/L, and anti-thyroid peroxidase (anti-TPO) antibodies 8 (normal: <6) IU/mL. Her thyroid gland was noted to be atrophic on physical examination and subsequently on ultrasound. A chest radiograph was completed and ruled out pleural and pericardial effusions. Her electrocardiogram was repeated, with the non-specific T wave abnormality resolved, but persisting sinus bradycardia.

She was started on levothyroxine 75mcg PO daily and was monitored for an additional 24 hours given the bradycardia; however, she remained clinically stable with minimal vaginal bleeding. She was discharged home four days after presentation and her menstrual bleeding had ceased.

Her follow-up TSH six weeks after discharge was mildly elevated 5.6 mIU/L and her free T4 was 16.6 pmol/L. Her TSH was again repeated three weeks after this and was within the normal range (0.91 mIU/L).

Discussion

This case describes a patient who, on initial presentation, had substantial blood loss requiring significant resuscitative efforts for stabilization. In some cases, heavy menstrual bleeding can cause patients to decompensate to the point of hemorrhagic shock. It is important to recognize this quickly and adequately resuscitate the patient. Many hospitals have massive transfusion protocols in place for cases like this, which includes rapid administration of blood products and tranexamic acid. After initial resuscitation, these cases require careful consideration and interdisciplinary care to determine the underlying cause and treat accordingly. In addition, hormonal therapy to treat anovulatory uterine bleeding is essential to assist with cessation of bleeding. In this case, the discrepancy in the patient's vital signs (bradycardia rather than tachycardia in the setting of hypovolemic hypotension) was an important indicator of her undiagnosed hypothyroidism.

Through the combined efforts of specialists including, Gynecology, Emergency Medicine, Internal Medicine, and Endocrinology, this patient was diagnosed with severe hypothyroidism. Hypothyroidism is a common pediatric endocrine condition and may be either congenital or acquired[8]. In many regions, how-

ever, congenital hypothyroidism has been added to newborn screening programs, and delayed diagnosis of hypothyroidism is becoming less common. Early diagnosis of congenital hypothyroidism is important as if left untreated, it can potentially impair neuro-cognitive development in young children[9]. In women of reproductive age, hypothyroidism has been documented to cause a variety of menstrual irregularities[7]. Hypothyroidism can affect steroid metabolism by altering the binding activity of sex hormone binding globulin, then decreasing the plasma concentrations of testosterone and estradiol, while increasing their unbound, free or biologically active fractions. Furthermore, it can delay the luteinizing hormone response to gonadotropin-releasing hormone. In this case, she had evidence of pubertal delay (Tanner stage 2 at onset of menses) and chronic symptoms of hypothyroidism, which suggests that her hypothyroidism was present for a few years and affected her hypothalamic-pituitary-gonadal axis. These changes can contribute to anovulation, a common cause of heavy menstrual bleeding in adolescents1. Additionally, hypothyroidism may cause coagulopathies[7] that can increase bleeding time, activated partial thromboplastin time, activated recalcification time, and clotting time, all of which can also lead to heavy menstrual bleeding[10]. The menstrual irregularities associated with severe hypothyroidism typically resolve with thyroid replacement therapy once TSH levels normalize[11]. It is also important to note that in the pediatric population, rapid treatment of longstanding hypothyroidism is not recommended as there is a risk for behavioural/emotional problems and pseudotumor cerebri, therefore a combination of an oral contraceptive pill and treating the hypothyroidism slowly with a low dose and gradually advancing as tolerated, is suggested[12].

Conclusion

In cases of heavy menstrual bleeding, resuscitation should be initiated immediately to avoid progression to hemorrhagic shock. The underlying cause of the heavy menstrual bleeding should be investigated and diagnosed. Given the broad differential diagnosis of heavy menstrual bleeding in adolescents, diagnosis and treatment may require a multidisciplinary approach. Less common causes of heavy menstrual bleeding in the adolescent population, such as severe hypothyroidism, should be considered, and targeted treatment should begin early but with careful consideration of possible adverse effects.

Consent was obtained from the patient and their legal guardian prior to preparation of this case report.

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