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Editor's Message

Covid-19: The impact of the ongoing pandemic on the healthcare system

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Two years have passed since the first case of Covid-19 was identified in Wuhan China[1], yet the world remains unable to control the spread of the virus. Several vaccines were urgently developed, and billions of doses were administrated world-wide[2]. Many developed countries achieved high vaccination rates while developing countries are lagging due to hesitation and logistic and financial restriction[3]. The discrepancies in vaccination rate and high mutation ability of the virus continues to stall the efforts to control and end the pandemic. Currently, a wave of the omicron variant is spreading world-wide with data suggesting that two doses of either mRNA vaccine are insufficient to protect against it[4]. As the hospitals get ready for another wave of increased hospitalization with further restrictions imposed on access, it is important to examine the effect of the pandemic on the health care system as a whole. The financial burden of the pandemic on the health care system started with the shortage of personal protective equipment and sanitization and the cost associated with providing adequate isolation and testing for suspected and confirmed cases[5]. Furthermore, the imposed restrictions meant decreased access to hospitals and cancelation of elective surgeries. In private health care systems, this meant decreased income for small and independent centers and resulted in bankruptcies and closure of these practices[6]. In addition to financial and resource exhaustion, the pandemic negatively impacted the physical and mental health of health care workers. Many frontline health workers were infected, hospitalized and died during the pandemic while many others suffer from anxiety, depression, and post-traumatic stress disorders[7].

In addition to the direct impact of the pandemic, other aspects of the health care system have been negatively affected and are predicted to have catastrophic effects. Despite medical advances, cancer remains one of the leading causes of death worldwide. Naturally, several studies investigated the effect of the ongoing pandemic on cancer care and outcomes. Preliminary data suggests that cancer patients are more vulnerable to the virus and display severe symptoms requiring hospitalization. However, the effect is not limited to patients currently diagnosed in cancer. Data suggests that the pandemic has caused a delay in detection given the delayed access to many diagnostic services to limit exposure to Covid-19. Additionally, many clinical trials have been paused or delayed in treatment development[8]. Heart disease is another leading cause of death in Canada and the world that has been heavily impacted by the pandemic. Patients with cardiovascular comorbidities tend to have severe infection presentation. Similarly, international data demonstrates a significant decrease in diagnostic cardiac procedures including echocardiographs and angiograms[9]. This delay in diagnosis results in severe and acute presentation, causing further strain on the health care system and is associated with decreased survival rates and quality of life for patients.

As we enter the third year of the Covid-19 pandemic, the health care system suffers from the direct and indirect impacts. While it is important to continue the direct efforts to control the spread and implement prevention measures, the indirect effects should not be ignored. The physical and mental health of healthcare workers should be considered a priority and support should be readily available. Similarly, the delayed access to diagnostic and interventional services should be addressed to avoid increase in prevalence of high mortality conditions including cancer and cardiovascular disease and to avoid further strains on the healthcare system.

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Review Article

A lens into the past: The history of cataract surgery

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Abstract

Cataract surgery may be one of medicine's greatest achievements, providing treatment for an otherwise blinding condition. These surgeries are among the most common operative procedures performed worldwide and are also among the most successful. The advancements that have been made in cataract management exemplify the progress that has been made in the field of surgery as a whole. Moreover, the story of the evolution of cataract surgery is fascinating. From humble origins with cataract couching to the use of ultrasonic energy in phacoemulsification, each milestone in the advancement of cataract surgery has had innovative physicians at its forefront, striving for better patient visual outcomes. This article seeks to review these major milestones, including couching, extracapsular cataract extraction, intracapsular cataract extraction, and intraocular lens implantation. Procedural steps of modern-day phacoemulsification and recent advancements that may be incorporated into future practice are also reviewed.

Introduction

Cataract surgeries represent one of the most common surgical operations performed in Canada and worldwide. It is estimated that globally, over 10 million cataract surgeries are performed each year[1]. This number appears to be increasing, as the number of cataract surgeries performed in Ontario more than doubled between 1992 and 2004[2]. Needless to say, it is probable that many of us have had or will have exposure to cataract surgery at some point or another. Should one's first exposure to this procedure be as a patient, it is possible that the history of the technique holds little interest. For some, the complexities of eye-surgery in its entirety would be preferred to be left a mystery. However, the current technique exemplifies the tremendous advancements that have been made in surgery, and the story of the evolution of this technique is fascinating. Even within the past 50 years, the procedure has transformed dramatically and improves visual outcomes of millions. Medical therapy has little to no value in the management of cataracts, leaving surgery as the only option to reverse cataract-induced vision loss. Modern day cataract surgeries are relatively safe procedures with success rates of 90-95%[3]. Thus, at the very least, this story of advancements in cataract surgical management does generally have a happy ending. Let us take a step back and review the steps taken to develop such a procedure.

Anatomy of the eye and lens

To appreciate the history of cataract surgery, a review of basic ocular anatomy is required. The primary function of the eye is to convert light into nerve impulses, which requires light to be focused on the retina. To do this, the eye uses two refractive structures. Light first enters the eye through the cornea, which forms an anterior "window" into the eye and is responsible for 2/3 of the eye's refractive power. The lens is responsible for the remaining 1/3 of refraction. Cataracts involve the opacification of the lens with resultant decrease in visual acuity.

As shown in Figure 1, the lens is suspended in the eye by fibers called zonules. The lens itself consists of three distinct layers. The innermost layer is called the nucleus. Nuclear cataracts are the most common and result from opacification of the nucleus[4]. The middle layer of the lens constitutes the lens cortex. Patients with diabetes are at increased risk of developing cortical cataracts[5]. A third type of cataract is the subcapsular cataract, which effects the portion of the lens just interior to the capsule, the outermost layer of the lens. As we will later see, modern day cataracts involve the removal of the nucleus and cortex, while the capsule remains behind to house the new synthetic lens implant. However, there were several techniques utilized prior to the modern procedure.

Couching

As one may expect, the origins of cataract surgery are far from the slick procedure utilized in today's practice. After all, phacoemulsification handpieces did not exist in 600 BC, when the medical record of cataract surgery begins[6]. Rather, surgeons initially relied on a technique called couching, which originated in India. In this technique, a needle or other sharp object is used to dislodge the lens, such that the cataract no longer

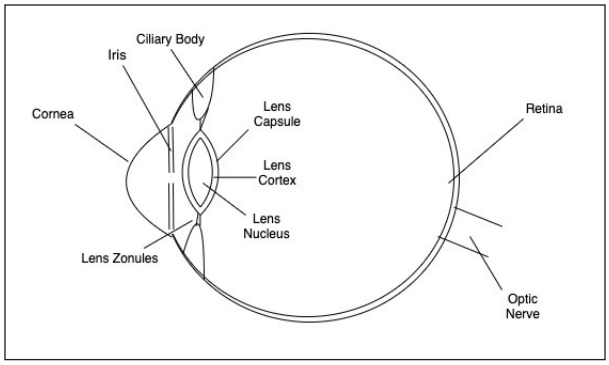

Figure 1. Schematic of the eye.

obstructs the pathway of light into the eye (Figure 2). The dislodged cataract then remains in the vitreous cavity. While this procedure has obvious shortcomings, it provided a treatment for an otherwise imminent cause of blindness. Individuals would be able to see the faces of their families again, albeit from a short distance. As one would expect, the technique was associated with a myriad of complications, including infections that would result in blindness shortly after the procedure in a percentage of patients[7]. Due to a lack of access to modern surgical techniques, couching is unfortunately still used in some developing Nations[8].

Extracapsular Cataract Extraction

There is some evidence that extracapsular cataract extraction (ECCE) began as early as 600 BC by an Indian physician named Shashruta[9]. However, it is more widely accepted that the first ECCE was done in Paris by the French surgeon Jacques Daviel in 1747[10]. As the name suggests, extracapsular cataract extractions involve removal of the cataract while sparing the lens capsule. This technique was a significant advancement from couching, and at the time of Jacques Daviel had a success rate of approximately 50 %[11]. However, this technique was still far from ideal. Daviel's procedure involved a massive corneal incision (greater than 10 mm). For reference, modern-day cataract surgeries involve 1-3 mm incisions. Daviel would then puncture the lens capsule and extract the lens by curettage[12]. Further advancements were made to this technique by German physician Albrecht von Graefe, who carried out the procedure using a much smaller scleral incision. Looking retrospectively, one can't help but admire the steady hands that these medical pioneers must have needed in order to perform such surgeries with the equipment of their time. After all, modern cataract surgeries are done under microscopy to maximise precision and safety. The extracapsular technique was replaced briefly by intracapsular cataract extraction (ICCE) for some time in the 19th century before re-emerging in the 1970s[13]. Intracapsular extractions, which involved the removal of the whole lens – M&M shell and all – had only temporary popularity. The standard of care quickly reverted back to ECCE with the emerging concept of intraocular lens replacement.

Intraocular Lens Replacement

Sir Nicholas Harold Lloyd Ridley, an English ophthalmologist, takes much of the credit for the origins of intraocular lens (IOL) replacement. But how did Ridley see what so many others had missed? Some of the credit must be given to a medical student, Stephen Perry, who asked Ridley if he "intended to replace the extracted part of the eye" [14]. Later in his career during the second world war, Ridley was tasked with treating many British Royal Air Force pilots who had sustained ocular injuries[15]. These injuries were predominantly shards of glass embedded in the eyes of pilots after bullets shattered the canopies of their planes. Ridley noted that the glass, made of polymethyl methacrylate (PMMA), was inert in the eye. Thus, the same materials would be used by Ridley to insert the first intraocular lens in 1949[15].

Eureka! We now have our first successful IOL replacement. Well, not quite. Although inert, the major pitfall of PMMA lenses was that they were rigid, and therefore required large corneal incisions in order to implant. In today's practice, most IOL replacements are foldable acrylic or silicone lenses, which allow them to be delivered through a small corneal incision. An option in current IOL implants is the use of multifocal lenses, which emerged in the 1990s to 2000s and allow for the correction of both presbyopia and ametropia. Toric intraocular lenses are commonly inserted today for correction of astigmatic refractive errors[16].

Modern Phacoemulsification

Modern-day phacoemulsification is an efficient procedure done under microscopy. Phacoemulsification procedures utilize ultrasonic energy in combination with mechanical force to break up cataracts and permit aspiration. This technique was introduced in 1967 by Charles Kelman, an American Ophthalmologist[17]. The technique continues to be the standard of care for cataract management. In modern procedures, after anaesthetic is applied and the eye is sterilized, the physician makes a small incision (paracentesis) and main corneal incision. A viscous substance called viscoelastic, so named for its high viscosity and elastic properties, is delivered into the eye. The capsule of the lens in removed via continuous curvilinear capsulorrhexis, and hydrodissection is used to detach the lens from the surrounding cortex. The cataract is broken up mechanically and with ultrasound, and irrigation and aspiration

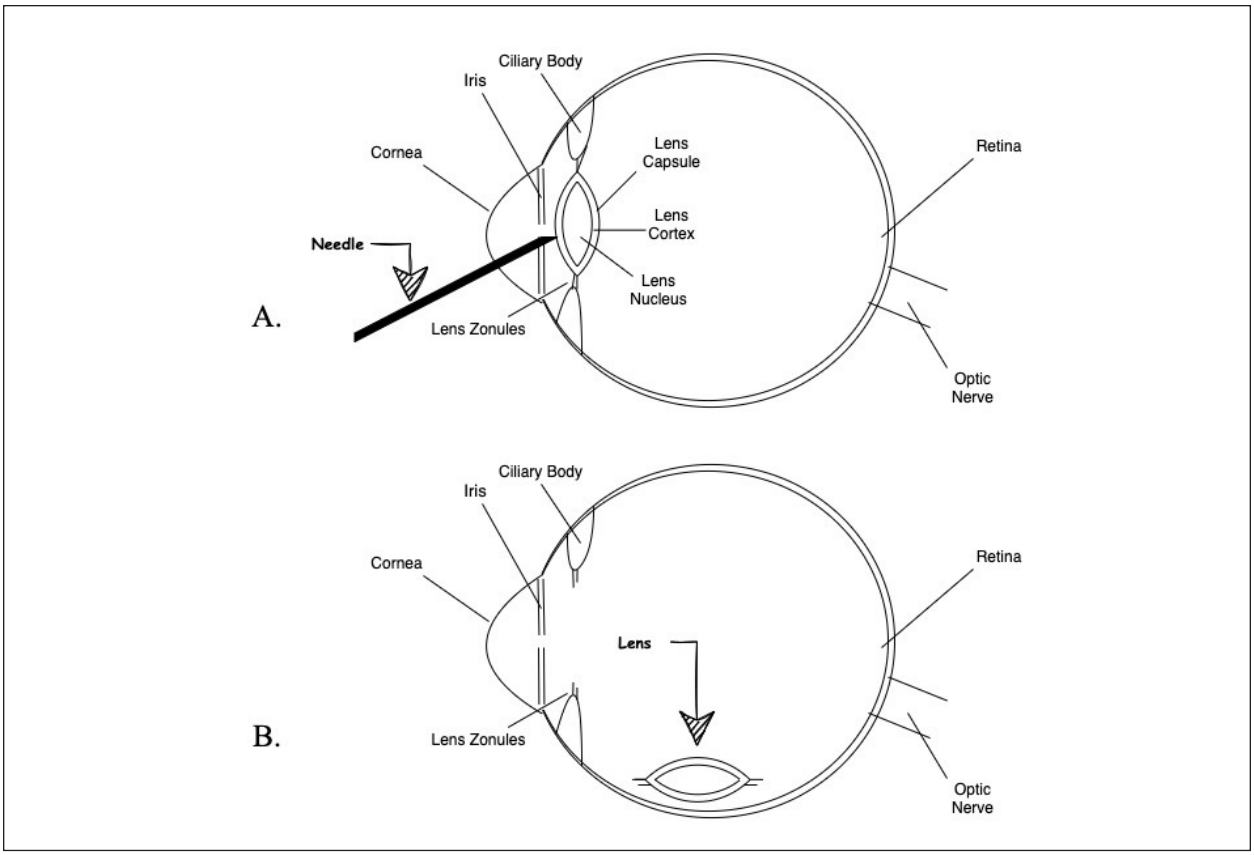

Figure 2. Diagram demonstrating couching techniques for cataract management, showing lens dislodgement with a needle (A) and post-operative lens position (B).

are used to remove the remaining cortex. Viscoelastic is again used to create space for the new synthetic lens. Finally, the synthetic, foldable lens is delivered and aqueous solution is used to induce corneal swelling and seal the incisions. Sutures are usually optional in this procedure but may be used depending on patient characteristics and surgeon preferences.

Alas, our story has reached its end. However, such a rapidly evolving technique will surely continue to undergo various changes and advancements. Let us now take a brief look at some recent advancements that may find their way into practice in the near or distant future.

A Lens into the Future

Cataract surgery continues to be an area of medicine that undergoes constant innovation, with regular emergence of new techniques that may be safer, faster, or more precise. One such example is the femtosecond laser, the use of which has increased in recent years. The femto laser is most commonly used for capsulorrhexis, as some surgeons report it offers more precision and better patient experience[18]. However, others report the technique as costly and unnecessary. Only time will tell whether this technique will become part of the standard of care for cataract management. Another technique increasing in popularity is intraoperative wavefront aberrometry, which allows surgeons to take refractive measurements (both pseudophakic and aphakic) during surgery[19]. These measurements aid in power selection and positioning of the IOL implant and may offer improved patient post-operative visual acuity. One limitation of this technique is the additional time during surgery to make these measurements, which may contribute to delayed uptake of this technique.

Conclusion

Cataract surgery may be one of medicine's greatest breakthroughs, offering a cure for an otherwise blinding condition. From couching to phacoemulsification, the journey through various techniques for cataract surgical management is unique, and exemplifies the innovation and ingenuity of physician-pioneers. There is no doubt that current procedures will continue to undergo improvements and adjustments as new technologies become readily available. As physicians and medical learners, perhaps all that is required is a keen eye.

Acknowledgements

Dr. Rishi Gupta for inspiring this work.

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Case Report

Anterior urethral trauma in a 5-year-old boy

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Case

A 5-year-old boy presented to his local emergency department following a straddle injury after falling from the monkey bars at his school playground. Although he was able to void spontaneously, he experienced ongoing penile discomfort, dysuria, gross hematuria and several hours of persistent urethral bleeding. He was urgently transferred from the peripheral community hospital to our tertiary care centre for assessment of possible urethral trauma. He was otherwise healthy and on no medications.

At our centre, he had a normal appearing urinary meatus and minimal active bleeding. The exam was limited by his physiologic phimosis. His primary and secondary surveys were otherwise unremarkable, and his vitals were within normal range. An abdominal examination was benign, and his bladder was non-palpable. Testicular exam revealed normal testicles which were descended bilaterally with no obvious edema. No perineal bruising was appreciated. Bruising was noted on the left inner thigh.

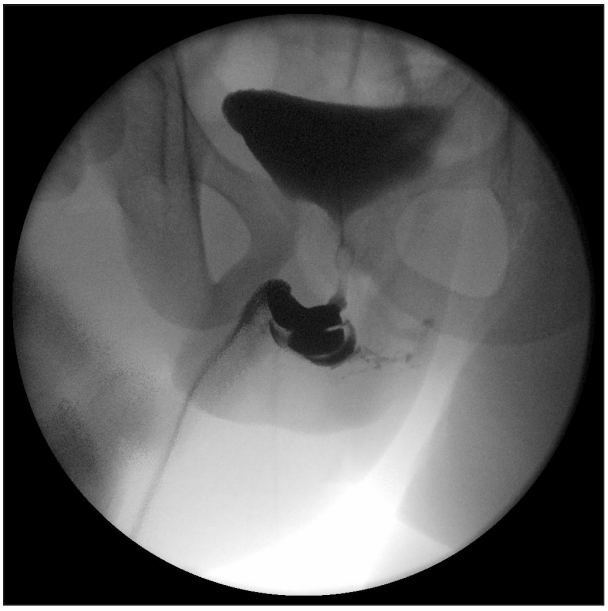

Figure 1. Voiding cystourethrogram at the time of presentation, demonstrating contrast extravasation around the membranous urethra in keeping with an incomplete tear of the bulbar urethra.

Due to ongoing bleeding per urethra, he was urgently brought to the operating suite for retrograde urethrogram (RUG) and cystoscopy to evaluate for a possible urethral injury. At that time, he was found to have extravasation of contrast at the membranous urethra on RUG (Figure 1). Contrast entered the bladder easily and a ventral defect was identified with urethroscopy at the bulbo-membranous urethral junction without any defect to the posterior urethra. Cystoscopy revealed a normal bladder. A 12-French suprapubic catheter was placed under direct visualization. An 8-French urethral catheter was inserted over a wire without difficulty to tamponade ongoing urethral bleeding. Antibiotics and an anti-spasmodic (oxybutynin) were initiated. His urethral catheter was removed the following day. He demonstrated no signs of infection or further urethral bleeding post-operatively and was discharged home with the suprapubic catheter in place to straight drainage.

A cystogram on post-operative day 14 revealed opacification at the ventral aspect of the bulbous urethra. This was interpreted by the radiologist to be an opacification of the Cowper's gland rather than a traumatic pseudodiverticulum (Figure 2). He voided without pain during the voiding cystourethrography. A trial of voiding was given by clamping the suprapubic catheter. However, the patient developed severe dysuria with voiding and required subsequent unclamping of his suprapubic catheter. Twenty-four days after his surgery, he was reassessed and found to have a normal voiding cystogram with no dysuria or discomfort. His suprapubic catheter was clamped, and he began voiding spontaneously without symptoms.

Two months post-operatively, the patient reported normal voiding without dysuria or hematuria. Uroflowmetry was performed which demonstrated a voided volume of 240 mL. He had a slightly flattened and prolonged voiding curve with a borderline obstructive picture. His post-void residual was 25 mL with a normal stream. Follow-up with repeat uroflowmetry and a post-void residual is booked.

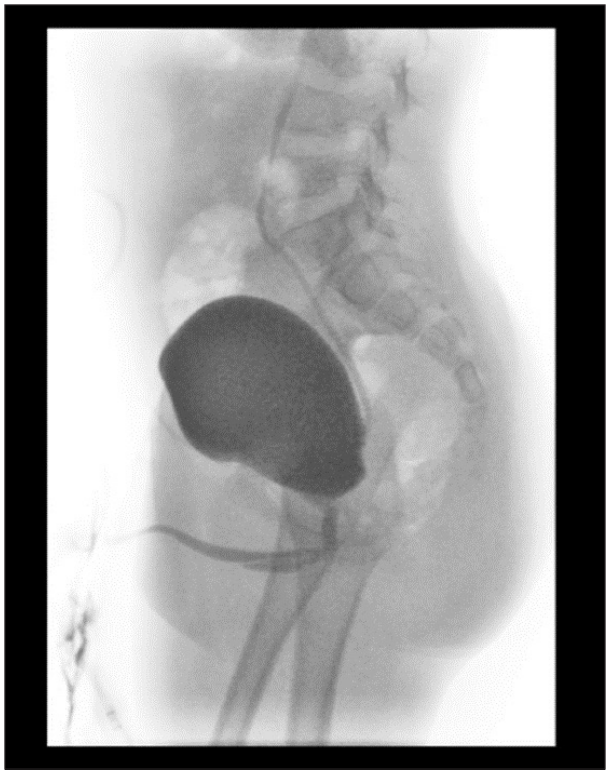

Figure 2. Voiding cystourethrogram on post-operative day 14 demonstrating a shuttle-shaped opacification at the junction between the pubis and membranous urethra which did not impede the flow of urine through the anterior urethra, thought to represent opacification of Cowper's Gland. Right vesicoureteral reflux was also noted.

Discussion

Urethral injuries are classified depending on their location. Anterior urethral injuries include the penile or bulbar urethra and are uncommon, accounting for one third of urethral injuries[1]. However, blunt trauma from straddle injuries often results in this type of crushing injury due to the proximity of the symphysis pubis in males. Posterior urethral injuries are frequently associated with pelvic fractures and have been reported to occur in 0.6-10% of pediatric pelvic fracture cases[2,3]. When urethral injury is suspected, physical exam often reveals blood at the urethral meatus or bruising of the perineal area, and a high riding prostate can be palpated in adult patients. The definitive diagnosis must be achieved by RUG as was done in our case[4-6].

The lack of literature and consensus guidelines for the treatment of straddle injuries in pediatric populations lead us to extrapolate treatment plans from adult data for our patient[1,4,5]. Moreover, posterior injuries are more common and treatment approaches often focus on posterior insults and pelvic fracture management, which was not applicable in this case. Our patient was managed with suprapubic catheterization, which is currently the recommended treatment approach for incomplete anterior urethral trauma cases[4,5]. The goal of this treatment is urinary diversion to promote healing, prevent abscesses or infection and primarily to decrease the likelihood of stricture formation. Stricture formation is very common from straddle injuries with urethral trauma and significant damage to the corpus spongiosum may require urethral reconstruction[1,5]. Urethroplasty for stricture repair has demonstrated good long-term success rates in 15 children investigated by Baradaran et al., including 7 straddle injuries to the bulbar urethra with no reported cases of urinary incontinence or erectile dysfunction[7].

Surveillance for stricture formation is vital and should be assessed three months after the initial injury to ensure adequate tissue healing[1]. Due to the ongoing urethral bleeding, we elected to leave a urethral catheter in overnight to tamponade the bleeding, but planned to use the suprapubic catheter for long-term diversion.

Primary realignment has also been a proposed treatment, and despite quicker times to symptom-free spontaneous voids having been documented with this approach, it appears to serve a better role for complete injuries or penetrating trauma[8,9]. While literature is scant for this type of injury, there is a growing consensus to avoid primary realignment due to worse outcomes, which are thought to be related to increased iatrogenic trauma at the time of the repair[10,11]. Small scale studies have documented suprapubic catherization to have lower rates of stenosis, with rates as low as 11% for incomplete disruptions compared to 67% when treated with primary realignment[10]. Although there remains a role for primary realignment, the higher rates

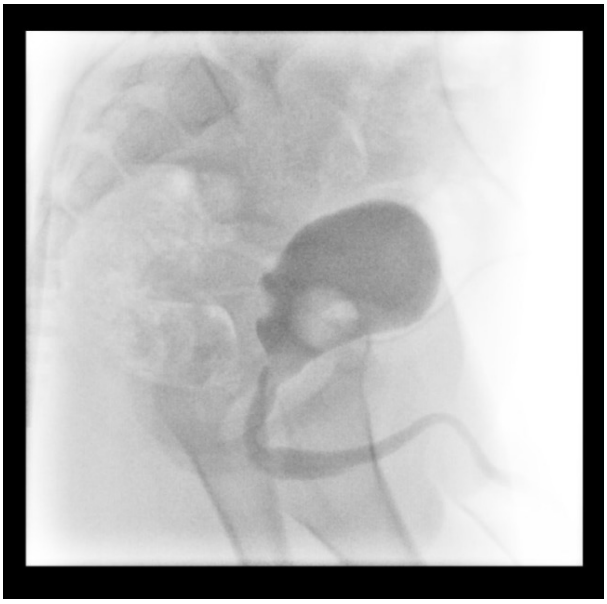

Figure 3. Normal Voiding cystourethrogram on post-operative day 24.

of impotence and incontinence observed with this treatment option make it less favorable than cystotomy, which has been shown to have satisfactory outcomes historically[12,13].

In summary, in treating incomplete anterior urethral trauma in pediatrics, we found that an approach mimicking the recommended treatment for the same injury in adults resulted in a good outcome in the early post-injury period. Our case highlights the role of short-term urethral catheterization to tamponade ongoing hematuria if necessary. Due to the rarity of pediatric urethral trauma, it is important to report approaches and outcomes in these patients to help guide clinical decision-making. Prolonged urinary diversion to ensure appropriate healing time may be longer for children in comparison to adults based on this case, however more evidence is needed to support this observation. Long-term follow up will require monitoring for complications such as incontinence, impotence and most importantly voiding dysfunction related to stricture formation from the urethral injury.

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Review Article

Amphetamines in the treatment of adult attention-deficit/hyperactivity disorder (ADHD) and cocaine use disorder (CUD): The role of pharmacists

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattentiveness, hyperactivity, and impulsivity. This review paper outlines the role that pharmacists can play in monitoring amphetamine use, to reduce the possibility of medication abuse by those with ADHD and/or Cocaine Use Disorder (CUD). Because individuals with ADHD also struggle with impulsivity, they are more likely to abuse substances, particularly illegal stimulants (such as cocaine), in an effort to self-medicate. This article also reviews the pharmacokinetics of amphetamine derivatives as well as the evidence for their use to manage ADHD and CUD. Neuropharmacologically, the proposed mechanism of action of amphetamines in the treatment of CUD is also detailed. Finally, the implications of these findings for pharmacy practice are discussed. The primary findings and principal conclusions are that amphetamines have been found to improve both ADHD and CUD symptomatology, primarily through increasing DA release from nerve terminals in the central nervous system, as well as increasing the release of NE and serotonin. Pharmacists can play an important role in monitoring use of these medications by working in collaboration with family physicians and psychiatrists to ensure that ADHD/CUD patients are taking their amphetamines as prescribed.

Background on ADHD and CUD

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattentiveness, hyperactivity, and impulsivity[1]. The symptoms of ADHD include restlessness, the urge to be "going" nonstop, impatience, talking very fast, being forgetful, losing things easily, an inability to focus, and difficulties sustaining attention on important daily life tasks[1]. Roughly 80% of children with ADHD will continue to meet diagnostic criteria for the disorder into their adolescent years and approximately 60% will maintain the core symptoms of the disorder into their adult years[2]. Amphetamine derivatives are used in ADHD because they help with maintaining focus by increasing levels of dopamine and norepinephrine in brain pathways involved in attention, reinforcement, and reward; however, this means they also have a high potential for dependence and abuse.

Cocaine Use Disorder (CUD) is defined as a pattern of cocaine use that leads to clinically significant impairment or distress evidenced by at least two of the following symptoms in a 12-month period: (1) cocaine is used in larger amounts or over a longer period than intended, (2) the patient displays a desire or unsuccessful attempts to control/cut down their use, (3) the patient spends significant amounts of time trying to acquire cocaine, use cocaine, or recover from its effects, (4) the patient craves cocaine, (5) the patient is significantly impaired in the domains of work, school, and/or home due to their cocaine use, (6) the patient continues using cocaine despite persistent/recurring interpersonal issues due to their cocaine use, (7) the patient reduces/stops important social/occupational/recreational activities due to cocaine use, (8) the patient uses cocaine in situations where they are in physical danger, (9) the patient continues using cocaine despite knowing that they have a physical/psychological problem caused or exacerbated by cocaine use, (10) the patient displays tolerance to cocaine, and (11) the patient displays symptoms characteristic of stimulant withdrawal when they are not using cocaine[1].

Pharmacists can play a central role in monitoring amphetamine use to reduce the possibility of it being abused, both in individuals with ADHD as well as in individuals with comorbid ADHD and CUD. The issue of proper stimulant use is very relevant in modern society because there are great personal and societal costs associated with stimulants, such as adverse health effects, premature deaths, and higher crime rates in certain communities[3].

Because patients with ADHD struggle with impulsivity, they are statistically more likely to abuse substances, particularly illegal stimulants (of which co-

caine is the most common), but also prescription stimulants (of which the amphetamine derivatives are the most common), in an effort to self-medicate[4,5]. Given that amphetamines are quite effective in the treatment of ADHD[6], they have also been investigated for the treatment of CUD, which is another disorder linked to deficient dopamine transmission, like ADHD. Comorbid ADHD and CUD worsens the prognosis, and these patients have poorer long-term outcomes in many life domains[5].

Patients who misuse cocaine may be self-medicating latent/undiagnosed ADHD, therefore assessment of these patients for ADHD is very important – in patients with comorbid ADHD and CUD, treating their ADHD could dramatically improve their psychosocial functioning and help to address the underlying factors contributing to their cocaine abuse[5]. Individuals who have higher baseline ADHD symptomatology have been found to be at a much higher risk for misusing cocaine and other illegal stimulants[5]. This epidemiological association underscores the importance of diagnosis and formal testing in all patients who abuse stimulants, whether they are stimulants that are available by prescription or illegal stimulants such as cocaine.

This review paper will examine the evidence for the potential role of interdisciplinary collaboration between pharmacy, medicine, and other healthcare disciplines in treating patients with comorbid ADHD and CUD. Furthermore, an association between ADHD and CUD has been established in the literature and has a neurophysiological basis, which will also be discussed.

Pharmacokinetics

When ingested via the oral route, amphetamines have a bioavailability of roughly 75%[7]. The immediate-release (IR) formulations require one to three hours to reach their peak effect; their duration of action is roughly four to six hours[8]. Extended-release (ER) or sustained-release (SR) formulations of amphetamines typically last longer in the body, with a duration of action of approximately ten hours[8]. Because of their pharmacokinetic properties (both the longer duration of action and the slower/lower peak plasma level), ER and SR formulations also have a lower potential for abuse[8].

Evidence for Amphetamines in CUD

Mooney and colleagues (2009) found that the use of amphetamine analogues can lead to significant reductions in cocaine use as well as cravings. Chronic cocaine use has been found to deplete dopaminergic, serotonergic, and noradrenergic pathways in the brain, leading to psychiatric symptoms that include increased impulsivity, depression, and anhedonia[9]. Amphetamine derivatives can help to target these symptoms and are associated with reductions in cocaine use as well as cocaine cravings[9,10,11]. However, it is only the SR or ER amphetamine derivatives that have been found to be effective for treating CUD, not the IR formulations, which need to be taken multiple times a day (due to their shorter duration of action) and are more likely to be abused[8,9]. Levin and colleagues (2015) conducted a randomized clinical trial showing that ER amphetamine salts (in addition to Cognitive Behavioral Therapy) are effective in the treatment of individuals with comorbid ADHD and CUD. The ER amphetamine salts were found to improve ADHD symptoms in addition to reducing cocaine use, further supporting the theory that individuals with ADHD are more likely to use cocaine as a form of self-medication to address their underlying ADHD symptoms[5].

While the role for amphetamine derivatives has been well established in the treatment of patients with comorbid ADHD and CUD, adding psychotherapy (e.g., Cognitive Behavioral Therapy) to amphetamine-based pharmacotherapy could also confer additional clinical benefit to help patients achieve and maintain cocaine abstinence, although more research is needed in this domain[10]. Patients with co-occurring ADHD and CUD that achieve cocaine abstinence at the beginning of treatment while treated with amphetamines (to address their core ADHD symptoms) appear to have better outcomes in achieving/maintaining CUD remission; this is likely due to an improvement in ADHD symptoms[11]. These findings support the self-medication theory of stimulant abuse in patients with ADHD. Several well-designed large-scale studies examining amphetamine derivatives in the treatment of ADHD and comorbid CUD have shown promising results[4,10,11].

Mechanism of Action

Amphetamine's mechanism of action is on the monoamine neurotransmitters dopamine (DA), norepinephrine (NE), and serotonin[6]. It is considered an indirect-acting sympathomimetic and is associated with increases in blood pressure, heart rate, body temperature, and cardiac output, in addition to reducing appetite[6]. Amphetamines are weak reuptake inhibitors of DA and serotonin, and moderate reuptake inhibitors of NE[6]. Amphetamines enter NE neurons via the norepinephrine transporter (NET) and are taken into storage vesicles by the vesicular monoamine transporter (VMAT). By moving into NE storage vesicles, amphetamines displace NE into the cytoplasm of presynaptic neurons. Subsequently, there is movement of NE into the synaptic cleft. No action potential is needed for this release of NE into the synapse; the movement is triggered by amphetamine molecules moving NE out

of their storage vesicles in the presynaptic neuron. The NE in the synapse then stimulates adrenergic receptors on postsynaptic neurons.

In regard to DA, amphetamines block the ability of the dopamine transporter (DAT) to clear DA from the synapse, leading to increased synaptic DA concentrations. Amphetamines also bind to VMAT, leading to DA transfer reversing so that higher concentrations of DA end up moving into the synapse from storage vesicles[6].

Amphetamines block NET and SERT (the serotonin transporter) as well, leading to higher concentrations of NE and serotonin in the synapse in addition to increasing synaptic DA levels[6]. Regular cocaine use depletes dopaminergic and noradrenergic systems in the brain and can have lasting effects on impulse control. Since amphetamines target these systems in the brain, they can improve some of the psychiatric symptoms experienced by CUD patients.

In terms of the brain regions they affect, amphetamines lead to increases in DA and NE in the prefrontal cortex and the striatum. Amphetamines are highly reinforcing, primarily due to increased DA release in the synapses within the mesolimbic (reward) pathway of the brain, which includes the nucleus accumbens (part of the ventral striatum)[5]. The nucleus accumbens is a central part of the brain's reward circuit and is implicated in both ADHD and CUD.

Implications for Pharmacy Practice

The pharmacy model of care that could be implemented when pharmacists are monitoring patients receiving treatment for comorbid ADHD and CUD has parallels to the role that pharmacists currently play in methadone maintenance treatment. Firstly, it is important that pharmacists establish a strong therapeutic pharmacist-patient relationship with ADHD/CUD patients, based on a foundation of mutual respect, empathy, compassion, and understanding[12]. Pharmacists should treat substance use disorder patients as they would all other patients.

In community pharmacy practice, pharmacists can play an important role in monitoring amphetamine use by working in close collaboration with family physicians and psychiatrists to ensure that ADHD/CUD patients are taking their amphetamines as prescribed. As part of this collaboration, there should also be regular communication between pharmacists and physicians so that there is safe, seamless, uninterrupted treatment for ADHD/CUD patients, especially when they are transitioning from inpatient to outpatient institutions and when they are switching pharmacies[12]. Thorough documentation is also important to ensure that pharmacists are able to collaborate effectively with other healthcare providers who are treating their ADHD/CUD patients[12]. Pharmacists can also educate patients (e.g., using behavioral approaches)[3] regarding the adverse effects of stimulants, in order to reinforce the benefits of using stimulants as prescribed and the consequences of stimulant abuse. Pharmacists should also ensure that they keep up to date on the clinical knowledge and research surrounding both ADHD and CUD, as well as any relevant clinical practice guidelines that are published when they are treating this specific patient population[12]. Lastly, pharmacists must keep a close eye out for early renewal requests for amphetamines in ADHD/CUD patients as well as attempts by these patients to get their amphetamines prescribed by multiple physicians, as these could be subtle but important signs that amphetamines are being misused.

Because patients generally have good relationships with pharmacists, pharmacists are among the most readily accessible and highly trained healthcare professionals, and the fact pharmacists work long hours (which include weekends/holidays), pharmacists are in an excellent position to ensure that patients with comorbid ADHD/CUD are taking their prescription stimulants properly. Management of ADHD and CUD must be targeted using a multimodal approach, which includes medications, education, and behavioral interventions. Pharmacists have an integral role to play in this targeted multimodal approach because they are a key player in complete and comprehensive therapeutic interventions for any given patient. Pharmacists play a vital role in continuation of patient care and in improving long term outcomes for patients suffering with these chronic and often difficult-to-treat disorders.

Conclusions

In patients with comorbid ADHD and CUD, these neuropsychologically linked disorders can be addressed together and in a safe manner. Pharmacists can have an important role in overseeing treatment adherence and minimizing the risk of diversion (of stimulant medications from those with ADHD to others) or abuse of amphetamine derivatives[5].

This paper focused on reviewing the literature linking ADHD and CUD, their treatment individually and comorbidly, and the role that pharmacists can play in monitoring the treatment of these patients. This is an important topic that is generally poorly understood and historically understudied. In typical clinical practice, clinicians avoid prescribing stimulants for patients with cocaine abuse problems due to the fear of them abusing prescription stimulants such as amphetamines, even though there is substantive evidence that treatment with amphetamines can improve both conditions (ADHD and CUD)[4,5,9,10,11]. In conclusion, amphet-

amines have been found to improve both ADHD and CUD symptomatology primarily through increasing DA release from nerve terminals in the central nervous system, as well as increasing the release of NE and serotonin[4,9]. However, their use in patients with CUD must be monitored closely due to their high potential for abuse.

Acknowledgements

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EDUCATION

A medical student's guide to flexible nasal pharyngoscopy

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Abstract

Flexible nasopharyngoscopy (FNP) is a specialized skill commonly used by otolaryngologists as an important component of the head and neck examination. FNP can be diagnostic and therapeutic for many head and neck pathologies. Mastering this skill facilitates the effective performance of other specialized skills and procedures such as fibreoptic nasal intubations and flexible bronchoscopies. During otolaryngology rotations and electives, medical students are exposed to a high volume of FNP. Often, they are also asked to perform this procedure in clinic and on-call. There is currently no widely available simulation tool for medical students to practice using FNP, and medical students at our institution do not receive any formal training prior to performing FNP. The following is an introductory guide for medical students to become proficient at performing FNP while on their otolaryngology rotation.

Introduction

Background

Flexible nasopharyngoscopy (FNP) is also called fiberoptic nasoendoscopy, flexible nasolaryngoscopy, and flexible fiberoptic nasopharyngolaryngoscopy[1]. After the advent of fibreoptic technology in the 1950s, Hirschowitz was the first to use it for the purposes of clinical endoscopy in the early 1960s[2]. This procedure has evolved into a well-tolerated, low-risk, and integral part of the head and neck examination. It can be successfully performed in adults, cooperative children, and even neonates[3].

Types of endoscopes

Undergraduate medical students identify the transitio-Trans-nasal endoscopy can be performed using rigid or flexible endoscopes. Rigid nasal telescopes can provide endoscopists with a high-definition view of the nasal cavity, post-nasal space, and nasopharynx. Flexible nasal endoscopes are typically 30 cm in length and can 'bend' or 'flex' to maneuver into the lower pharynx. Various scope sizes are available, with diameters ranging from 1.9 mm (pediatric) to 6 mm (adult). Typical scope tip diameters are 2.7mm for pediatric scopes and 4mm for adult scopes.

Optical FNP uses a portable light source and requires users to look through the eyepiece or connect to an external camera. Distal chip FNP uses a separate light source located on the tower and projects the image onto a screen.

Diagnostic use

FNP offers a detailed and direct examination of the nasal cavity, sinuses, pharynx, and larynx. Visualizing these structures may be otherwise difficult by direct visualization or mirror laryngoscopy[4]. The indication for FNP is as an adjunct to a comprehensive head-and-neck physical examination for a wide variety of clinical presentations. In the nasal cavity, FNP can be used to diagnose pathologies such as polyps or adhesions and localize sources of bleeding in acute epistaxis. It can also be used for functional evaluation of swallowing, breathing, or voicing complaints originating from the pharynx and glottis, including those with impending upper airway compromise. FNP is a routine part of the initial workup for patients with suspected head-and-neck cancers as well as oncologic surveillance[1].

Therapeutic uses

Some endoscopes are equipped with side ports or working channels that enable the surgeon to perform endoscopic procedures using a wire and grasper inserted through the endoscope. The working channel provides access for application of topical anesthetics and suctioning of blood or secretions to improve visualization. This helps to retrieve foreign bodies and perform biopsies. FNP provides adequate visualization for targeted treatments of the larynx; such as performing vocal cord injections in patients with vocal cord paralysis[4]. More recently, FNP has paved the way for office-based laser procedures, which can be used in the treatment of a variety of laryngeal pathologies, including (but not

limited to) recurrent respiratory papillomatosis and early vocal cord dysplastic lesions.

Contraindications

FNP is a low-risk procedure and carries no absolute contraindications. Acute epiglottitis and croup have been cited as potential contraindications, as manipulation of the pharynx may induce laryngospasm1. The only reported relative contraindication is coagulopathy, though it is commonly used in these settings on a case-by-case basis. Vascular lesions such as telangiectasias or angiofibromas may also be traumatized by the scope and result in hemorrhage[4].

Risks

FNP is a well-tolerated procedure with rare complications. The most common adverse effects are sneezing, gagging, mucosal tearing, and bleeding secondary to local abrasion[1,4]. Serious complications and anatomical damage such as severe epistaxis, perforation, and laryngospasm are reported but are rare[5]. With training and practice, these risks can be minimized, making FNP a safe procedure.

Procedure

Preparation

1. Obtain consent from the patient for the procedure, thoroughly explaining the benefits, risks, and what to expect. The procedure lasts approximately 30 – 60 seconds, it is not painful but may be slightly uncomfortable. Simple verbal consent is sufficient, similar to a patient consenting to any means of physical examination.

2. FNP is considered an aerosol-generating medical procedure (AGMP), and all necessary precautions should be followed according to local infection control practices. Wearing gloves is recommended for this procedure.

3. Gather the instruments required for the procedure: tower or handheld scope, lidocaine spray, decongestant, alcohol pad, and water-based lubricant gel (Figure 1).

4. A few minutes before the procedure, local anesthetic can be administered into each nostril to minimize discomfort. Lidocaine spray (10mg/metered dose) is commonly used. Alternatively, 1-2 mL of 4% lidocaine on a cotton ball can be gently inserted into the nasal

Table 1. Anatomy and pathology.

	Normal Findings	Abnormal Findings
Nasal Cavity	External and internal nasal valves Nasal septum Turbinates	Fluid (purulence, blood, secretions) Polyps Adhesions Crusting Septal perforations Septal deviations Bony Spurs Mucopurulent debris Sinus drainage Mucosal edema Cerebrospinal fluid (CSF) rhinorrhea
Nasopharynx	Eustachian tube orifices Fossa of Rosenmüller Adenoidal pad	Obstruction Masses
Oropharynx	Base of tongue Tonsils Vallecula	Masses Cysts
Hypopharynx	Piriform sinus Post-cricoid space	Pooling of secretions Fullness Masses Foreign body
Supraglottis	Arytenoid cartilages False cords Epiglottis	Omega-shaped epiglottis Shortened aryepiglottic folds (laryngomalacia)
Glottis	Posterior commissure Anterior commissure True cords	Abnormal or asymmetric vocal cord movements Swelling Edema Masses Mucosal changes

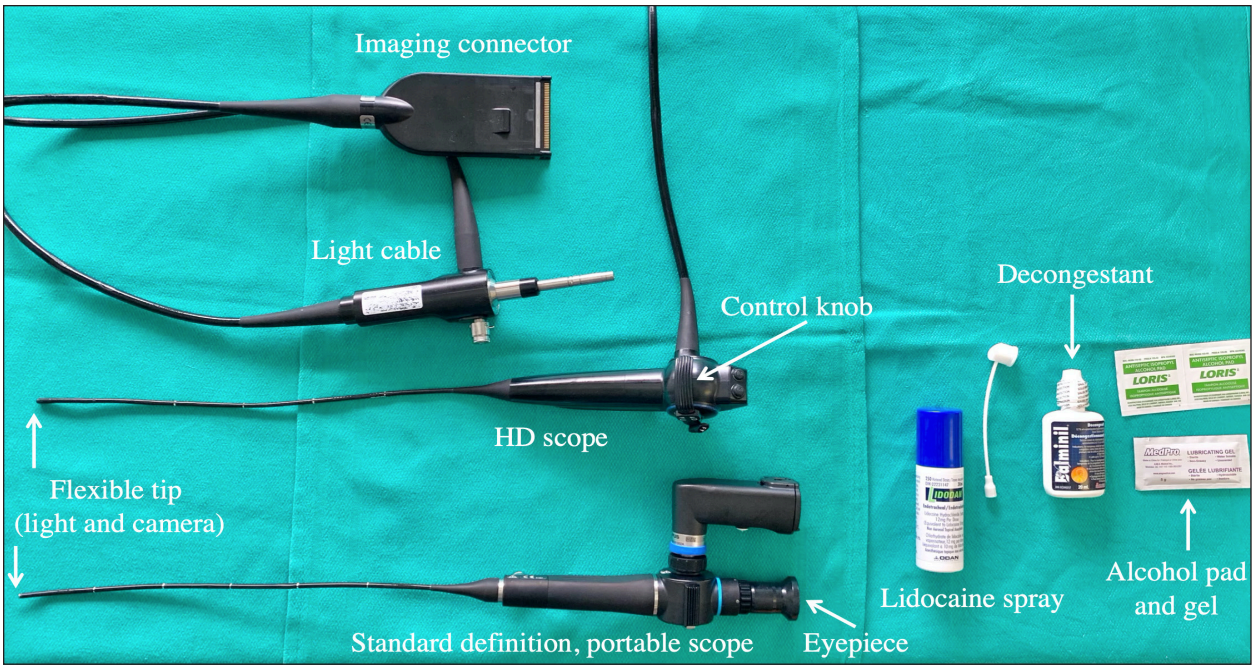

Figure 1. Setup on tray with a tower scope and handheld scope.

cavity, or 4% lidocaine jelly may be applied on the end of the scope. Some surgeons administer a vasoconstrictor such as xylometazoline (Otrivin®) on a cotton ball, or sprayed directly, to help reduce nasal mucosal swelling for easier navigation of the endoscope through the nasal cavity.

a. Application of topical preparations can be surgeon-dependent, as studies have not shown a clear advantage for reducing pain or discomfort with local anesthetic or vasoconstrictor prior to the use of FNP[6].

b. Some patients may prefer to forego the topical anesthetic, as it can create a globus sensation that is uncomfortable for patients; however, normal sensation returns after about 15 minutes.

5. Examine the endoscope.

a. If using a distal chip scope, the video input and light source input will need to be connected to the tower. Simply turn the tower on, ensuring the light source is on as well. The white balance may need to be adjusted by pressing the button when visualizing something white (i.e., gauze or paper).

b. If using an optical scope, ensure the batteries are fully charged (green LED indicator) and that light is on at the tip of the endoscope. Visualize the eyepiece and focus the image appropriately by centering it on an object 2-3 mm away from the tip of the endoscope and turning the focus dial at the eyepiece.

6. Apply anti-fog solution to the tip of the endoscope. Any liquid can suffice, such as decongestant spray or saline. An alcohol swab can also be used to wipe the tip of the scope.

7. Gel can be applied on the end of the scope for patient comfort. Some surgeons may consider the lidocaine lubricant.

8. Position the patient in an upright sniffing position, with the head protruding forward with the neck in slight flexion. This position expands the pharynx in an anterior-posterior dimension, allowing for more complete visualization. It also reduces the risk of inadvertently contacting the mucosa and causing discomfort or gagging. This positioning is critical and can make a significant difference in visualizing hypopharyngeal and laryngeal structures. Placing a pillow behind the patient's shoulders may help them maintain this position. Describe the procedure as it unfolds. Remind the patient to breathe gently through their nose.

9. Hold the body of the endoscope in the dominant hand with the thumb on the control (Figure 2).

10. Pushing the control switch up will steer the tip down, and vice versa. This motion, combined with rotation of the right hand on the endoscope body, will allow ma-

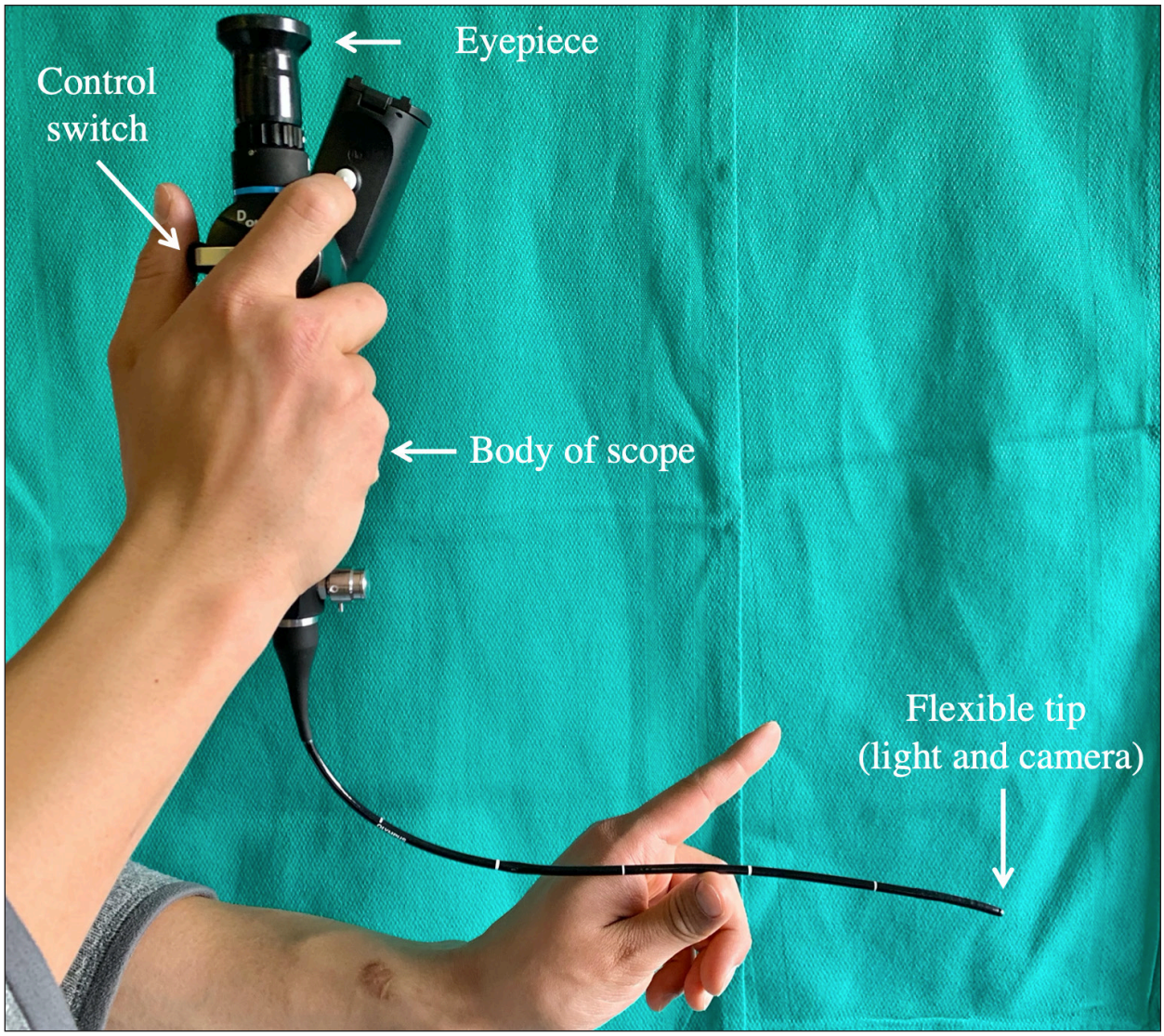

Figure 2. How to hold the handheld scope.

nipulation of the endoscope throughout a 360 degree range. For example, to look leftward, one could angle the tip upward and turn their wrist counter-clockwise, or alternatively, angle downward and turn their wrist clockwise. This skill, simultaneous movement of the control switch, along with rotation of the endoscope, requires some practice to become second nature.

11. The picture will be visible through the eyepiece lens, attached to the control body, or on the monitor if connected to a tower.

Performing the procedure

12. Holding the flexible tip of the endoscope with the index finger and thumb, approach the nose with the little finger resting on the patient's nose or face for stability and pass the tip into the nose. The patient may prefer you enter through a specific nostril if they have experience with this procedure. Otherwise, start with the patient's right nostril, and then the left.

13. Guide entry into the nose with your fingers placed a few centimeters from the distal tip of the endoscope. This can be done in many ways, but the key is to avoid excessive manipulation, as this may increase patient discomfort.

14. Looking up at the nose, enter the nasal vestibule and then direct the tip downward to stay along the nasal floor.

15. Straighten the scope as you advance toward the in-

ferior turbinate.

16. At this point you can assess: the inferior turbinate superiorly, the floor of the nose inferiorly, and the septum medially. The middle turbinate is visible above and more posterior to the inferior turbinate. Note any turbinate enlargement, or any significant septal deviation. If significant septal deviation obstructs passage of the scope, the contralateral side can be approached (Figure 3).

17. Guide the tip of the scope under the inferior turbinate medially and advance deeper into the nose, avoiding the septum. It is more comfortable to contact the turbinate with the scope than the septum. Keep the tip straight until the posterior nasal passage.

18. Examine the area between the inferior and middle turbinates (the middle meatus), and the lateral nasal wall in that area for any masses, mucopurulent drainage, or polyps.

19. As the scope approaches the nasopharynx, you will first notice the choana and the eustachian tube orifices. Carefully examine the nasopharynx for any masses, cysts, or adenoid tissue, paying close attention to the divot immediately posterior to the eustachian tube orifice, known as the Fossa of Rosenmüller. Malignant masses can be found in that location (Figure 4).

20. Passing the scope further posteriorly, point the tip downwards guiding it into the oropharynx. Instruct the patient to breathe through their nose in order to drop the soft palate. Examine the superior surface of the soft palate. As the scope is advanced further, examine the posterior pharyngeal wall, and the lateral pharyngeal walls as well as the tonsils. The base of tongue should be visible, as well as the epiglottis. The vallecula is the space between the base of tongue and the epiglottis. This is best visualized by asking the patient to stick out their tongue. Observe this space for pooled secretions or debris such as food residue (Figure 5).

21. The hypopharynx is the space lateral and posterior to the supraglottis and includes the piriform sinuses and post-cricoid space. These spaces can be expanded with a Valsalva maneuver by asking the patient to "puff out [their] cheeks". Observe these areas for pooled secretions, debris and masses.

22. The structures of the supraglottis should next be assessed. The epiglottis should be at the bottom of your view, the arytenoid cartilages near the top of your view, and the false and true vocal cords anterior-inferiorly.

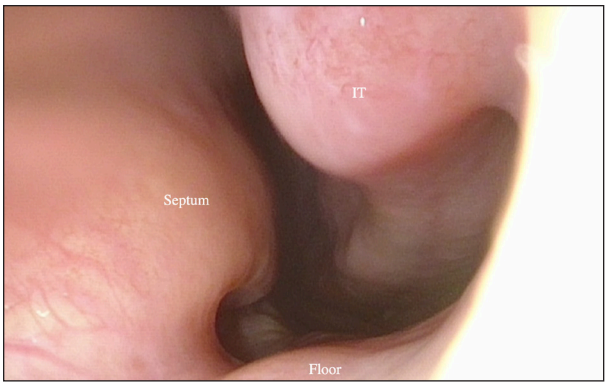

Figure 3. Initial view at the anterior nasal passage. IT: Inferior Turbinate..

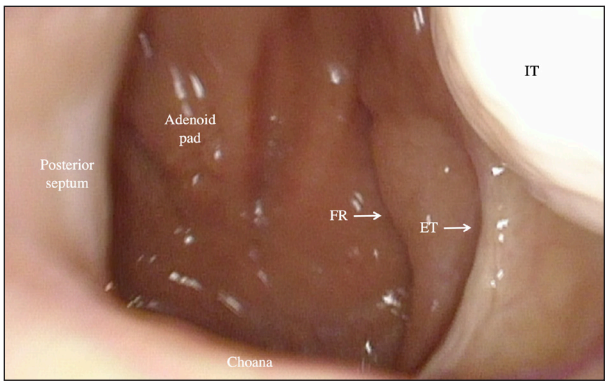

Figure 4. Posterior nasal passage and nasopharynx. NP: Nasopharynx. FR: Fossa of Rosenmuller. ET: Opening of Eustachian Tube.

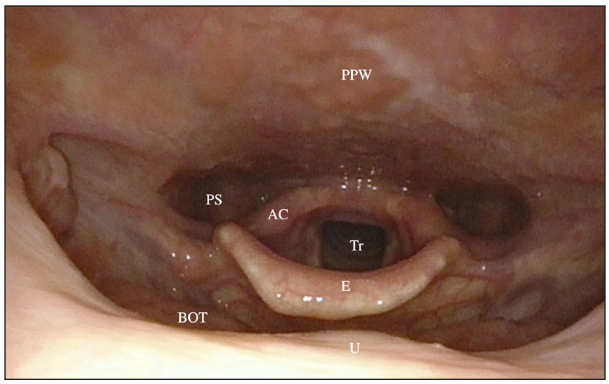

Figure 5. Looking down at the oropharynx. PS: Pyriform Sinus. AC: Arytenoid Cartilages. Tr: Trachea. E: Epiglottis. T: Tongue base.

Examine the aryepiglottic folds on either side, which connect the epiglottis to the arytenoid cartilages (Figure 6).

23. With careful advancement beyond (distal to) the epiglottis, the subglottic space and trachea may be observed (Figure 7).

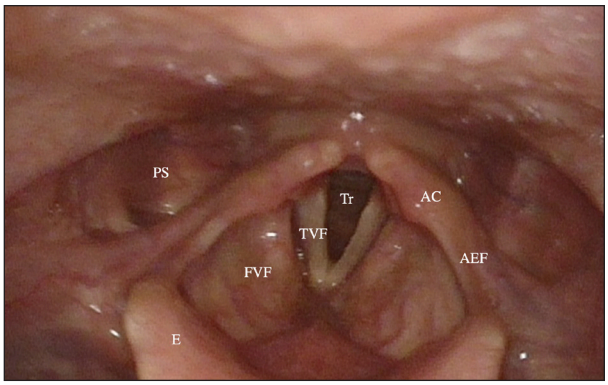

Figure 6a. View of the supraglottic structures with open vocal cords. TVF: True Vocal Fold. FVF: False Vocal Fold..

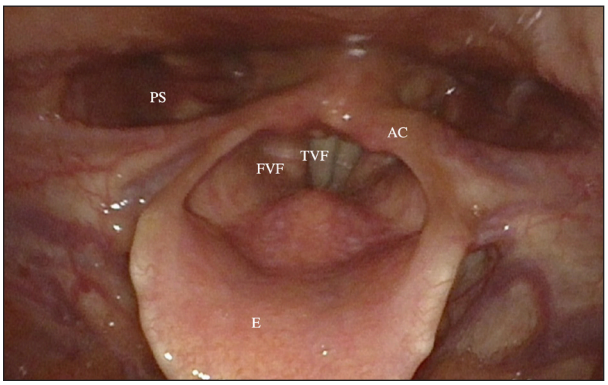

Figure 6b. View of the supraglottic structures with closed vocal cords.

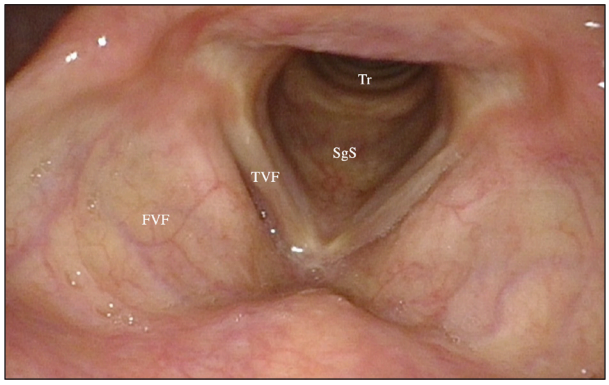

Figure 7. View of the subglottic space and trachea. SgS: Subglottic Space.

24. The glottis should be observed carefully and systematically.

a. Examine the vocal cords themselves, looking for areas of swelling, erythema, masses or atrophy, scarring, and asymmetry or abnormal-appearing tissue.

b. Next, consider the movement of the vocal cords. Ask the patient to breathe deeply through their nose to observe abduction of the cords. Ask the patient for natural laugh to witness the full extent and speed of their vocal cord movement. Having the patient sustain "EEE" in a regular pitch will result in the adduction of the vocal cords, causing them to pull together. Note any asymmetry in movement between either side. Once completed, withdraw the endoscope gently. Inform the patient that the procedure is complete.

Tips and Tricks

- Always move slowly and gently. Even with the anesthetic spray, sudden movements can cause discomfort.
- Rest the flexible scope on your left thumb and avoid gripping the scope with your thumb and index finger: this can cause a push-pull movement of the scope along the nasal floor, which can be irritating.
- Reassure the patient during the procedure, encourage slow calm nasal breathing.
- If the camera gets fogged up or covered with mucus, ask the patient to swallow if the tip is at or distal to the oropharynx. This should clear the camera lens.
- Be careful when the tip is close to the larynx. Accidentally touching the mucosa with the endoscope will be uncomfortable for the patient and may trigger a cough reflex.

Discussion

With the development of fibreoptic imaging technology, FNP has become a cornerstone of otolaryngology outpatient clinics, allowing for visualization of upper airway structures. In a head-and-neck cancer clinic, many patients will require FNP for disease surveillance, treatment response, or recurrence.

For medical students, understanding the indications and steps of FNP is a useful introduction to the procedure. Performing and interpreting FNP are important skills and require a learning curve, but when done properly and carefully, is a low-morbidity and efficient technique that provides valuable information about the anatomic structures. In addition, these skills are easily transferrable to flexible bronchoscopy, which has an identical control mechanism and is frequently performed by a wider range of medical and surgical specialties such as anesthesia, surgery, and critical care.

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Review Article

Pain mitigation during vaccine injections of the frail older adult population: A systematic review

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Abstract

Background: Adults require disease-appropriate immunizations against a variety of vaccine preventable illnesses. The frail older adult population is at particular risk if not appropriately immunized due to increased vulnerability of morbidity and mortality. Despite this, adult immunization rates continue to be suboptimal, and studies have shown that pain mitigation is an important, modifiable factor in low immunization rates.
Objectives: To determine the effective pain mitigating interventions available for use by the frail older adult population during routine vaccine injections.
Methods: A systematic review of randomized controlled trials and quasi-randomized controlled trials was conducted, evaluating the effectiveness of available pain-relieving interventions during vaccine injections of the frail older adult population. Original articles were searched through MEDLINE via Ovid, EMBASE, the Cochrane Central Database, CINAHL via EBSCOhost, and grey literature until February 2017.
Results: There were no documented trials to investigate the effectiveness of pain-mitigating strategies during vaccine injections of the frail older adult population.
Conclusion: This systematic review demonstrates the need for investigation and further research of pain-mitigating strategies in the immunization of frail older adults. Research in this field may help to improve vaccination rates in this population.

Introduction

Immunizations are widely considered to be one of the most effective and safe public health interventions available, but despite best efforts, vaccination rates remain suboptimal in adults[1]. Immunization schedules are important in adult health for many reasons. As we age, we require several disease-appropriate immunizations to restore waning immunity against vaccine preventable illnesses[2]. Immunizations also protect those who are at increased risk of acquiring various vaccine-preventable diseases due to a range of factors that includes occupation, chronic conditions, and age[3]. Older adults suffer the highest rates of morbidity and mortality of any age group from vaccine-preventable illnesses like influenza[4]. To decrease infection rates in the adult population, current immunization recommendations include tetanus and diphtheria boosters every 10 years and single-dose immunizations against pneumococcal disease and herpes zoster[5]. Depending on individual risk factors, they may also be encouraged to receive additional immunizations against hepatitis A and B, pertussis, and others[6]. Despite the proven benefits from vaccines, fewer than half of Canadian adults are up to date on their vaccinations, and only 38% of Canadians reported they were vaccinated against influenza during the 2017/18 season[7].

Frailty is a syndrome characterized by cumulative declines in functional reserves across multiple physiologic systems during the lifespan[8]. There are several frailty measures in the literature and a lack of consensus on how the syndrome is best measured; however, all definitions indicate that frail individuals are increasingly vulnerable to adverse outcomes compared to their age-matched peers[9]. These adults are a particularly important target population for immunization because of the increased vulnerability to adverse outcomes from vaccine-preventable illnesses. It is estimated that the majority of influenza-related deaths and hospitalizations occur among older adults[10]. Influenza vaccination of the older adult population has been demonstrated to reduce morbidity and mortality[11]. Despite evidence of the effectiveness of immunization, frail older adults, as with other adult age groups, continue to remain under-vaccinated[12].

Although the lack of widespread immunization in adults is multifactorial, it is clear that fear and anxiety of pain from immunizations is an important factor[13]. It has been demonstrated that upwards of 20% of adults express anxiety about procedural pain involving needles, and 8% of adults are intensely fearful[14]. These numbers are likely an underestimation of the percentage of adults affected by a fear of needle pain, as those with a fear of a painful stimulus tend to avoid exposure to it[15]. Studies have indicated that at least 8% of adults avoid the yearly influenza immunization because of fear of pain[16]. The specific prevalence of fear and anxiety of pain from immunizations in frail adults is unknown.

Despite routine immunizations being one of the most common painful medical procedures performed, and although there are effective pain management strategies available, current practice to alleviate immunization pain is not well-documented[17]. Developing and communicating methods to manage the pain associated with receiving immunizations has the potential to improve vaccination rates.

There has recently been work completed on mitigation of pain in immunizations as it relates to healthy adults; however, there is still a significant gap in the literature with regards to frail older adult immunization pain mitigation. The purpose of this systematic review was to evaluate the effectiveness of different pain-relieving interventions for reducing pain during vaccine injections in the frail older adult population.

Case Presentation

Study design

A systematic review of randomized controlled trials (RCTs) and quasi-randomized controlled trials was conducted to evaluate the effectiveness of pain-relieving interventions during vaccine injections in the frail older adult population. This systematic review is registered with PROSPERO (CRD42015023777, available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42015023777).

Search strategy

Detailed search strategies were developed for each electronic database searched. They were based on a search strategy developed for MEDLINE that was revised appropriately for each database. A sensitive search filter to identify geriatric medicine in MEDLINE 18 was modified and used to identify the frail adult population. A MEDLINE search created by Hogan et al17 was modified to identify pharmacological, physical or psychological techniques to reduce pain during vaccine injections. Studies were identified through keyword searches in the following databases from inception to February 2017 (with a truncated update completed in the fall of 2019) with no language restrictions: MEDLINE via Ovid, EMBASE, the Cochrane Central Registry of Controlled Trials, and CINAHL via EBSCOhost. A search of grey literature was conducted using Google and Google Scholar, with the first 100 search items reviewed (sorted by relevance). Systematic reviews, and evidence-based clinical guidelines related to pain reduction or pain management strategies for vaccine injections were hand-searched for additional articles. Two reviewers independently screened the titles and abstracts of search results using pre-established eligibility criteria (Figure 1)[19].

Selection criteria

Two reviewers independently screened titles and abstracts for the following inclusion criteria determined *a priori*: (1) study population included frail older adults with frailty defined as all accepted definitions of frailty (e.g. frailty index, phenotype) and age greater than 65; (2) randomized control trial or quasi-randomized control trial; (3) vaccine(s) administered via intramuscular or subcutaneous routes in any setting (e.g. hospital or community); (4) pain-mitigating treatment interventions included any pharmacological, physical or psychological technique; (5) determination of acute pain experienced during the vaccine injection was done via self-report using any age-appropriate pain assessment tool with established validity and reliability.

Risk of bias in individual studies and across studies

Bias assessment of individual studies was planned using the Cochrane risk of bias tool and across studies using GRADE methodology[20,21].

Results

Figure 1 summarizes the screening and selection process. All studies were excluded by examination of title or abstract. No studies were identified that included frail older adults in the population being studied.

Discussion

To our knowledge, this is the first systematic review to address the effectiveness of pharmacological, physical, or psychological pain-relieving interventions for reducing pain during vaccine injections in the frail adult population. We found no studies that examined pain mitigation in this population with any of the three treatment modalities.

Although immunization rates of frail older adults have been widely demonstrated to be below target, and

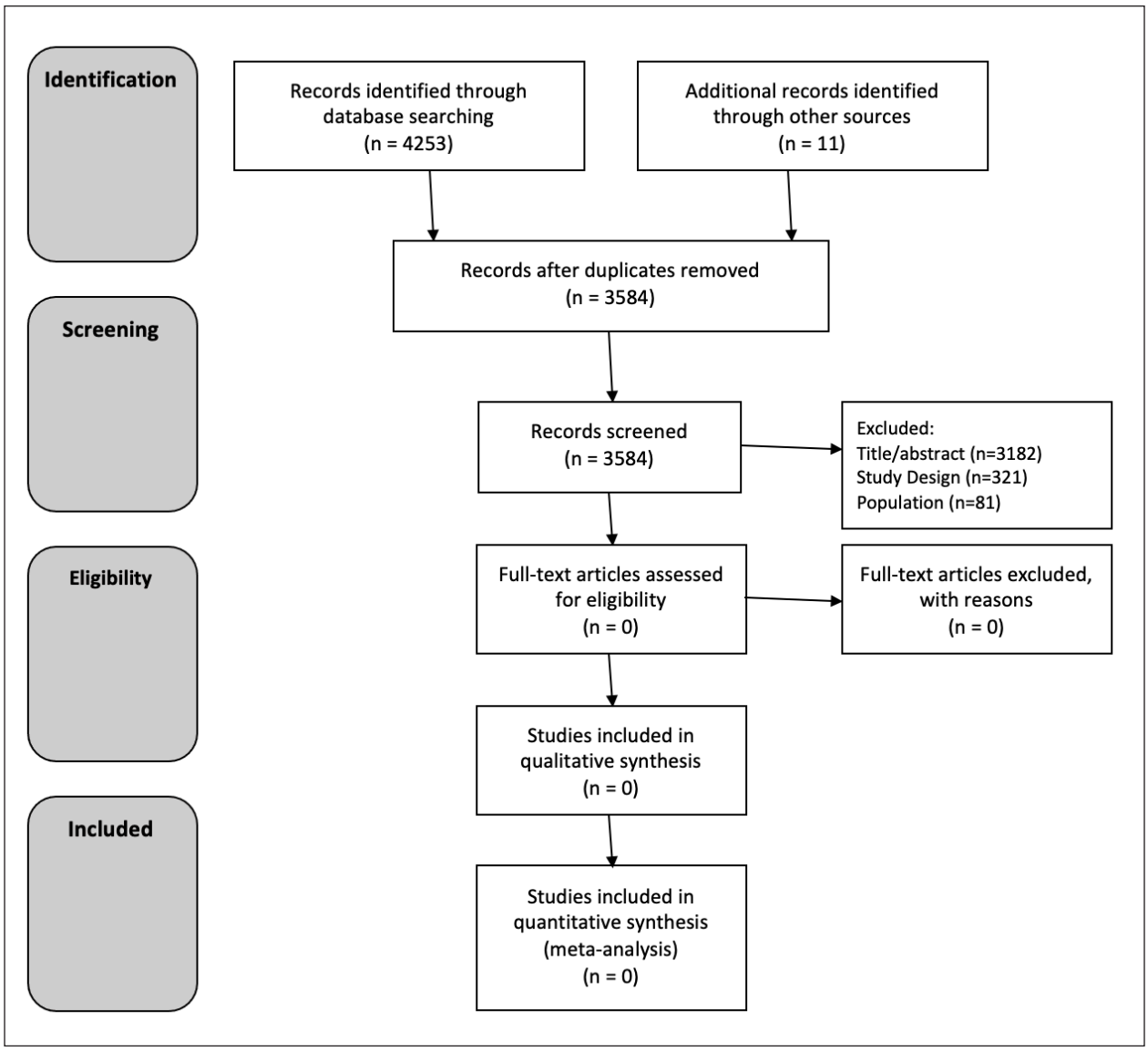

Figure 1. Flow diagram for selection of studies.

there is evidence that pain is a recognized factor in an adult's decision to opt out of recommended immunizations, no studies conducted to date have examined the prevalence of fear and anxiety of pain from immunization in frail adults13. This may be one reason why no studies were found to examine effective methods to mitigate pain and improve vaccine uptake in the older adult population.

Furthermore, frailty has been extensively studied and established to increase adverse outcomes in vaccine-preventable illnesses22. The 2015 updated evidence-based Canadian clinical practice guideline aimed at reducing pain during vaccine injections contains recommendations for healthy adults, including finding a comfortable seated position, distraction techniques or coughing during injection, and topical anesthetics; however, studies for translation of these into the frail older adult population have not been developed or tested23. Efforts should be made to examine and establish efficacy of these strategies in the frail older adult population. Furthermore, once effective pain-mitigating strategies are established, research should include development of programs that allow dissemination of strategies available to those being immunized and an examination of whether this improves overall satisfaction and improved immunization uptake.

Conclusion

Our systematic review found that there were no studies that examined the effectiveness of pain mitigating strategies during vaccine injections of frail adults. Based

on our review, recommendations for pain mitigation during vaccine injections of this population must currently be extrapolated from the clinical guidelines established for the non-frail adult population. Additional research is warranted in this area, particularly the investigation of whether there is an issue with avoidance of vaccination in frail adults due to fear and anxiety of pain from immunization and if so translation of efficacy of pain-mitigating strategies established for the non-frail adult population.

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Review Article

Uptake in the practice of medical assistance in dying (MAiD) and involvement by physician speciality over time in Nova Scotia, Canada

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Abstract

Legislation on medical assistance in dying (MAiD) was enacted in Canada in 2016. There is limited research on the topic available from Atlantic Canada. This study provides early data on the uptake of MAiD in Nova Scotia based on analysis of administrative billing data. It presents the number of MAiD cases by year from 2017 through early 2020. It also provides data on physician involvement in the MAiD process by specialty, broken down by assessors and providers of MAiD. Our data agrees with provincial- and national-level data that family physicians are highly involved in the MAiD process. Our study also documents physician involvement in conducting MAiD assessments by specialty, a metric which is not widely available in the literature. This study emphasizes the need for robust, provincial-level data on the demographics of providers involved in MAiD.

Introduction

Canada's federal legislation on medical assistance in dying (MAiD) was enacted in June 2016[1]. In doing so, Canada joined several countries, American states, and other jurisdictions where MAiD is now legal in some form[2]. Prior to the introduction of this federal legislation, the province of Quebec alone had put forth similar legislation which permitted medical aid in dying for patients who were terminally ill[3,4]. In Canada, MAiD refers to the prescription of medications to cause a person's death, to be administered by a provider or by the patient themselves[1]. In Nova Scotia, the MAiD procedure is administered intravenously by the provider[5]. The process requires assessments by two independent clinicians, typically physicians or nurse practitioners[6,7]. In Nova Scotia, referrals are sent to a centralized MAiD Coordination Centre to be triaged and referred for assessment[3]. The first assessor determines a patient's eligibility against a set of criteria, the second assessor confirms the patient's eligibility, and one of these assessors may then provide the procedure. The 2016 criteria limits eligibility to adults with a "grievous and irremediable medical condition", which is considered serious and incurable; causing an advanced state of decline and intolerable suffering; and whose natural death is reasonably foreseeable[1]. These adults must have capacity to make medical decisions, and make the request for MAiD voluntarily[8]. On March 17th of 2021, the criterion of reasonably foreseeable natural death was removed, and mental health was excluded as a medical condition until March 17th, 2023[8].

According to Health Canada Reports, nearly 22,000 Canadians have received MAiD since the enactment of federal legislation[9]. Health Canada recently released the Second Annual Report on MAiD, providing information on cases for the 2020 year. This report follows up on the First Annual Report on MAiD and is based on robust data collection and reporting requirements, and expands on interim reports published from 2016 through 2018[10–13]. Together, these reports suggest that MAiD demographics have been similar across provinces and between years. The average age of MAiD recipients is in their 70's, with an almost equal distribution between women and men. Malignancy has been the most common primary diagnosis, representing approximately 60% of cases, depending on the province or year. Neurodegenerative and cardiorespiratory diseases comprise smaller proportions of MAiD services. In 2020, private residences accounted for 47.6% of MAiD administration settings, and 28% took place in hospitals[9]. This was a marked change from 2019, during which private residences accounted for 35.1% of MAiD administration settings and hospitals accounted for 36.4%[9].

Various centres across Canada have begun to outline their specific experiences providing MAiD. Most of this literature comes from the province of Ontario[2,14–18], with fewer reports available from British Co-

lumbia[19] and Alberta[20,21]. The Atlantic provinces are under-represented in this literature. It is only in the 2019 Health Canada report that data from Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland and Labrador was not included as an aggregate.

The legalization of MAiD represents a significant change in practice for healthcare providers in Canada, in particular for family physicians. In countries like the Netherlands, up to 88% of MAiD provision is done by family physicians[22]. In the 2019 Health Canada report, which provided data on the specialties of MAiD providers for the first time, 65% of all providers were family physicians[1]. In the 2020 Health Canada report, 68.1% of MAiD procedures were provided by family physicians[9]. It is less clear how involved family physicians are as MAiD assessors and referring physicians, as this report does not differentiate provider specialty for each role (assessor versus provider)[1,9]. Family physicians are well-placed to be involved in all of aspects of the MAiD process as a specialty that emphasizes patient values and context and is privy to the specific details of patient illnesses and disease trajectories[6]. They are also a primary point of contact with the healthcare system, and thus may play an important role in MAiD access and uptake[6].

This study presents all data to date on MAiD in Nova Scotia based on an analysis of administrative billing codes. It describes the uptake of MAiD and physician involvement as a first assessor, second assessor, and provider by specialty from 2017 to early 2020.

Methods

The Nova Scotia Department of Health and Wellness provided the study team with anonymized, aggregate billing code data tables of MAiD provision from January 1st, 2017 to the end of February 2020, as requested by the authors. This administrative billing data are collected by the Nova Scotia Department of Health and Wellness for service billing fees submitted by physicians for services rendered. Reporting is based on the calendar year (January to December). Billing data for MAiD services provided by nurse practitioners are not available as they are paid via contract and do not submit billing claims for this service. Data for 2020 were only available for January and February, and so no comment can be made through these data about the impact of the COVID-19 pandemic on MAiD provision in Nova Scotia. Ethics approval was not required due to the aggregate nature of this reportable data offered by the Nova Scotia Department of Health and Wellness.

Results

Summaries of billing codes showed the number of times physicians billed for a visit associated with MAiD, and whether this visit was for a first assessment, second assessment, or the provision of medications (a proxy for the provision of MAiD). The number of MAiD cases was extrapolated from these data, equal to the number of medication provision billings. In accordance with Canadian legislation, the prescribing physician had to be either the first or second physician assessor; however, the data do not specify which of the two was the provider.

Table 1. Total MAiD cases in Nova Scotia by year.

Year	Months	Cases	Cases per month (average)
2017	12	6	0.5
2018	12	63	5.2
2019	12	236	19.7
2020	2	108	54
Cumulative	38	413	10.9

** Data from 2020 includes January and February only.*

Four hundred and thirteen people received MAiD in Nova Scotia between January 2017 and February 2020 (see Table 1). MAiD cases are reported per year and as an average per month, to better reflect the uptake over time as the billing data for 2020 only included January and February (2 months total). At least five medical specialties have been involved in MAiD in Nova Scotia as providers and assessors. The involvement of each specialty is reported as a proportion of total MAiD cases for each role by year (see Table 2) and overall (see Table 3). Totals may not add to 100% due to rounding. Two specialties were combined into "other" due to small numbers and to preserve physician privacy.

Discussion

Our study reports on the uptake of MAiD in Nova Scotia using data from provincial administrative billing codes. It provides information on the number of MAiD-related deaths and physician involvement in the MAiD process from 2017 through 2020.

Our data are in agreement with the 2020 data from Health Canada that family physicians are the specialty most often providing MAiD (68.1% of providers)[1]. Our study adds additional information to this by documenting which specialties are frequently involved in

Table 2. Involvement in MAiD by physician specialty and role over time.

	First assessor (%)				Second assessor (%)				Provider (%)			
Physician Specialty	2017	2018	2019	2020	2017	2018	2019	2020	2017	2018	2019	2020
Anaesthesia	15	32	25	4	33	49	65	9	0	44	55	17
Family medicine	81	51	44	76	67	45	25	64	83	46	26	60
Internal medicine	4	14	9	14	0	0	5	18	0	0	2	19
Psychiatry	0	0	16	0	0	0	0	0	0	6	14	0
Other	0	3	6	6	0	6	4	8	17	3	3	5

**Data reported as proportion of total MAiD cases for each year.*
** Data from 2020 includes January and February only.*
** Percentages shown without frequencies as some cell counts are less than 5.*

first and second MAiD assessments. This metric is not readily available in the Canadian literature, and was not reported in the 2019 or 2020 annual report[1,9]. The federal report on MAiD identifies the primary specialty of providers involved in MAiD provision being family medicine, followed by palliative medicine, nurse practitioners, anesthesiology, internal medicine, critical or emergency care, oncology, and psychiatry[9].

Based on our data, family physicians are also heavily involved in first and second MAiD assessments in Nova Scotia (56% and 39% of all first and second assessors, respectively). Anesthesiologists are also heavily involved in MAiD as first assessor, second assessor, and provider. This is likely due to their familiarity with the processes and medications involved in the provision of MAiD[23] as well as their experience providing care for patients with complex and chronic health concerns. Our data also suggest there are specialties who are less commonly MAiD providers but are still involved in conducting first and second assessments such as internal medicine. The federal reporting system does not currently collect data on the specialties involved in first and second MAiD assessments. Another area for future inquiry is the specialties of providers referring patients for MAiD. Nationally, almost 30% of written requests are received from a practitioner outside of the care coordination service (such as a social worker, family physician, or nurse) but their specialty is unknown[1]. This may also represent an area of significant involvement by family physicians. A study of MAiD requests from London, Ontario between 2016 to 2018 reported that 19% of referrals came from family physicians[15]. Collecting data on the specialty of MAiD assessors and referring providers – which is not currently included in the national reporting requirements – would provide a more fulsome picture of family physician involvement in MAiD.

It is also important to consider how the physician workforce may impact MAiD access and uptake. In 2019, 14.5% of Canadians reported not having access to a regular healthcare provider – whether that be a family physician, specialist or nurse practitioner[24]. There are few studies which comment on barriers that Canadian patients face when accessing MAiD. A study of all MAiD-related deaths in Ontario between 2016 and 2018 reported access barriers in 6.6% of cases[14]; an earlier study of the first 100 cases in Ontario suggested access barriers were more common, at 16%[17]. A recent study in Nova Scotia found that there was no significant difference in completion of MAiD services for those with or without a family provider among patients who have requested MAiD[3]. However, this inter-

Table 3. TInvolvement in MAiD by physician specialty and role (as a percentage of all cases from 2017 to 2020).

Specialty	First assessor n (%)	Second assessor n (%)	Provider n (%)
Anaesthesia	98 (20)	150 (48)	176 (43)
Family medicine	280 (56)	121 (39)	160 (39)
Internal medicine	52 (10)	23 (7)	25 (6)
Psychiatry	41 (8)	0 (0)	36 (9)
Other	26 (5)	17 (5)	16 (4)
Total	497 (100)	311 (100)	413 (100)

**Data reported as proportion of total billings (i.e. MAiD cases) for each role from 2017 to 2020.*

pretation does not include patients who wish to request MAiD services but were unable to because they did not have a provider or for other reasons. A small Canadian study found that patients experienced barriers such as a lack of information about MAiD, issues around final consent, stigma associated with MAiD, and others[25]. The barriers in Nova Scotia associated with MAiD access and uptake is an important area for future research.

There was an increase in MAiD cases each year in Nova Scotia from 2017 to 2019 observed in our data. Although the data from 2020 are incomplete, they suggest an increase for 2020. This is in keeping with provincial trends reported by Health Canada[9]. On a national level, rates of MAiD have also increased year after year, from 0.6% of all deaths in 2016 to 2.5% of deaths in 2020[1,9,11]. According to the second annual report on MAiD in Canada, there was a growth in MAiD cases of 34.2% between 2019 and 2020[9]. Other jurisdictions have seen similar trends – in the Netherlands and Oregon, rates of MAiD increased on a yearly basis following legalization and have since stabilized in more recent years[22,26–29]. In 2019, MAiD represented 4.2% of all deaths in the Netherlands[22] and 0.5% of all deaths in Oregon[30]. Proposed reasons for this initial rise and subsequent plateau include changes in reporting requirements, physician comfort, patient interest, public awareness, and/or population changes[26]. Further research is needed to explore how the new MAiD legislation and changes to eligibility criteria for MAiD impacts provision. There may be a growing demand for MAiD services as access increases with the new changes to the eligibility criteria for MAiD. The COVID-19 pandemic also enabled innovations in primary care access which may also play a role in increasing demand and availability of MAiD. Over the last decade, Nova Scotia has also incrementally invested in collaborative family practice teams staffed by family physicians, nurse practitioners, registered nurses, and other allied health professionals with the goal of improving access to primary care for Nova Scotians[31]. As these teams continue to grow, access to family physicians and nurse practitioners who provide MAiD may also increase.

Limitations

There are some discrepancies between our administrative billing data and the data reported by Health Canada on the number of MAiD cases by year. This is likely attributable to differences in reporting cycles; how dates were accounted for (e.g., by date of visit versus billing submission); lack of inclusion of MAiD cases provided by nurse practitioners in our data (who are documented to provide MAiD in the province)[1]; billing errors (underreporting, poor introduction of billing codes)[32–34]; or differences in billing between fee-for-service and salaried physicians[32]. The administrative billing data is also missing much of the work that is done by family physicians which may not have been billed such as MAiD referrals and other work completed for patients who do not end up receiving MAiD for a variety of reasons (natural death before MAiD, loss of capacity, etc)[35]. Our dataset reports provider specialty based on the Royal College or College of Canadian Family Physicians designation. This has implications for specialties such as Palliative Care, whose designation is created by way of Fellowship or certification. This is also relevant to ICU and emergency medicine. These specialties would be included under family medicine, internal medicine, and/or other in our dataset. This limits our interpretation of physician involvement by specialty, but which data source is more accurate is not evident.

Compared with other provinces, the raw numbers for MAiD in Nova Scotia are small. This leaves the data on physician involvement more open to being skewed by random variations in physician activity (e.g., retirement or leaves of absence). Finally, there are many aspects of MAiD which were not captured by the administrative billing data available to our study team. These include primary diagnosis; location of the MAiD procedure; and referral sources. This information was not previously available at a provincial level in Health Canada's interim reports, but is captured in their most recent release[1]. These represent important aspects of MAiD to document.

Conclusion

Our study adds to the limited literature on MAiD from the Atlantic provinces, and more specifically from Nova Scotia. It presents data on the number of cases of MAiD from 2017 to early 2020 and physician involvement in the assessment and provision by specialty and role, previously unknown. Our findings support data reported by Health Canada that shows year after year increases in rates of MAiD since federal legislation was enacted in 2016. Existing literature suggests family physicians are highly involved as MAiD providers, and this study documents that they are similarly involved in MAiD assessments. The specialty of MAiD assessors is not currently reported by Health Canada and not otherwise available in the literature. Whether the specifics of the family physician workforce in Nova Scotia, or nationally, affects MAiD uptake and access remains to be seen. This is an important area of study given the proportion of patients with no family physician or limited access to their provider[32,36,37]. Future research on MAiD in Nova Scotia could be directed at gaining a better understanding of the demographics of physicians involved in MAiD, including such aspects as payment models, gender, and years in practice. A qual-

itative inquiry could provide important insights on patient barriers to accessing MAiD and physician barriers to providing MAiD.

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Case Report

Pneumorrhachis complicating acute pain management using a thoracic epidural catheter

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Abstract

The use of thoracic epidural catheters to infuse local anaesthetics and opioids is a common practice in acute pain management to attenuate the pain associated with thoracic and abdominal surgical procedures. The placement and maintenance of epidural analgesia is known to be associated with a variety of potential complications. A rare complication is the development of air of within the spinal canal (pneumorrhachis). Although pneumorrhachis is typically asymptomatic and resolves spontaneously, it rarely can be associated with neurological dysfunction. Here we describe a case of pneumorrhachis that led to symptomatic acute spinal cord compression in a 27 year old man who had a thoracic epidural placed to help with pain management following laparotomy for the management of Crohn's disease. Postoperatively, the patient developed unilateral weakness in his upper and lower extremities and sensory dysfunction in the upper extremity. Urgent neuroimaging demonstrated epidural air causing mass effect on the cervical spinal cord. His symptoms resolved completely following conservative management. This rare presentation of pneumorrhachis highlights the need for close vigilance regarding neurological function in patients with epidural catheters for acute pain management. This presentation also promotes mitigation of factors that may be associated with the administration of air into the epidural space, such as changing epidural infusion solution bags and malfunction of epidural infusion pumps.

Introduction

Although the infusion of opioids and local anaesthestics via thoracic epidural catheters is known to help with pain management following abdominal and thoracic operations, catheter placement and use can be associated with a variety of complications. First described in 1977 by Gordon and Hardman in the context of head trauma with pneumocephalus and concomitant air in the cervical subarachnoid space, the development of pneumorrhachis, or air within the spinal canal, is one such rarely reported complication[1]. It is thought that pneumorrhachis is usually asymptomatic and found incidentally on imaging[2]. It has been reported to occur in the context of spinal trauma, conditions associated with increased intrathoracic pressure, infections of the spine or from contiguous areas, spinal surgery, and even spontaneously[2]. Iatrogenic anaesthesia-related pneumorrhachis cases are rare, especially those associated with neurological deficits, and these cases have occurred in the context of the administration of medications in the lumbar epidural space for the management of acute, chronic or labour pain[3-7]. We report a unique case in which pneumorrhachis developed following epidural placement at the thoracic level and for acute pain management and presented with signs and symptoms of acute spinal cord compression. Air within the spinal canal acted as a space-occupying lesion compressing neural structures. This case emphasizes the need to maintain vigilance for neurological dysfunction following thoracic epidural placement and discusses management options for symptomatic patients.

Report

A 27 year old man with Crohn's disease, obesity (BMI 44), and obstructive sleep apnea (OSA) who was undergoing a small bowel resection with end ileostomy via laparotomy received a thoracic epidural catheter preoperatively. The catheter was inserted on a second attempt at the T8 / T9 level using a 17 g Tuohy needle and midline approach with loss of resistance to air (LORA) obtained at 10 cm needle depth. The catheter was secured at 13 cm to the patient's back. Pre-incision, 3mL of 0.25% bupivacaine (Marcaine) was administered via the catheter. Intraoperatively, the patient received fentanyl 50 mcg and 3 mL of 0.25% bupivacaine

(Marcaine) about 1.5 hours after surgery started and then another 4 mL of 0.25% bupivacaine (Marcaine) 2.5 hours later. The patient's operation proceeded with general anesthesia using sevoflurane. No intra-operative surgical complications were noted. Upon arrival to the Post-Anesthesia Care Unit 4.5 hours after surgery started, the patient complained of midline incisional and umbilical area pain. Neurological examination by the Acute Pain Service (APS) team was normal in terms of motor and sensory function in the upper and lower extremities. An infusion of hydromorphone (Dilaudid) 0.03 mg/mL with bupivacaine (Marcaine) 0.125% was started at 5 mL / hour after a 4 mL bolus, and the pain subsided. After about three hours in PACU, the infusion was changed to 0.125% bupivacaine (Marcaine) alone because of the OSA.

Approximately 5 hours post-operatively, the APS physician was informed by the ward nurse that the patient was experiencing new numbness and weakness in the left hand and arm and new weakness in the left leg in addition to increased incisional pain. Assessment revealed 60% decreased sensation to light touch in most of the left hand and arm and decreased sensation to ice from the left hand to elbow. There was normal sensation to the left abdomen and thoracic regions and legs. Motor examination showed normal strength on the right side but on the left side grade 4- finger flexion, extension, and abduction, grade 4+ elbow flexion and extension, and grade 4 hip flexion (Medical Research Council Scale). More distal left leg strength was normal. Constitutionally, the patient had hemodynamics within normal limits and was otherwise well with no evidence of sepsis.

The epidural infusion was stopped to determine if neurological function would improve and subcutaneous hydromorphone (Dilaudid) was ordered for pain management. When function had not improved after 2 hours, urgent neuroimaging was arranged since a space-occupying lesion (epidural hematoma) was at the top of the differential diagnosis of the clinical findings. Computed tomography (CT) showed epidural air extending from C5 to T12 and pushing the spinal cord anteriorly, extending around multiple nerve roots and also surrounding the right brachial plexus (Figure 1). Air was visualized along the paravertebral muscles and soft tissues from T11 to L2. There were no abnormal imaging findings in the cranium.

Conservative management was pursued after consultation with the Spine Service. The epidural catheter was removed with no complications and the catheter was not noted to have any new structural abnormalities. No steroid administration or surgical interventions were suggested by the Spine Service and the patient was treated with supplemental oxygen by face mask.

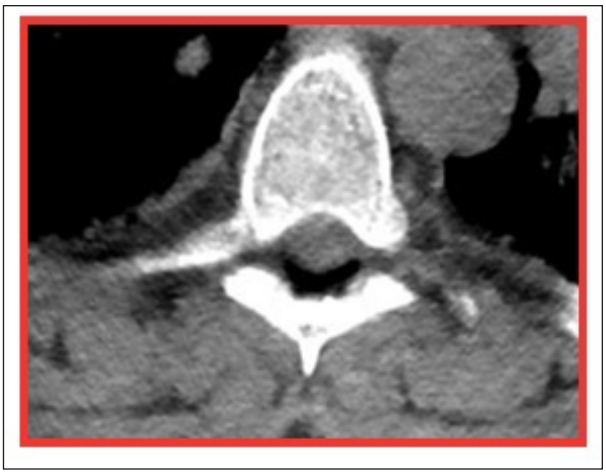

Figure 1. Representative coronal CT image through the upper thoracic spine demonstrating pneumorrhachis pushing the spinal cord anteriorly.

His symptoms improved by the first post-operative day and completely resolved by post-operative day 2.

Discussion

Acute spinal cord compression causing neurological dysfunction secondary to pneumorrhachis associated with thoracic epidural catheter placement has hitherto not been reported. Other cases have presented with radicular pain, radicular sensory and motor deficits, cauda equina syndrome and even cardiac arrest[4,5,7-10]. Most other reported cases have involved epidural-related procedures at the lumbar level with only one other case involving placement of an epidural in the thoracic spine[3-10]. In that case, the epidural catheter was placed at T4 in order to administer opioids for metastatic cancer-related pain in the cervicothoracic and interscapular areas[9]. Only one other report involving the use of an epidural catheter describes spinal cord compression occurring in the context of medication infusion[3]. In that case, a lumbar epidural catheter was placed to manage recurrent unilateral lumbar radicular pain via the administration of local anesthetic and steroid[3]. The catheter was replaced twice when it became occluded and ultimately removed after the patient developed headaches and upper extremity weakness and numbness[3]. Imaging demonstrated pneumorrhachis in the cervical, thoracic, and lumbar spine[3]. Other than cancer-related pain, which was the reason for epidural catheter placement in only one other case report, other cases involving pneumorrhachis were seen in the context of the administration of medications epidurally for chronic back or radicular pain, labour pain or as the intended method of anaesthesia for a lower extremity vascular operation[3-8,10]. Other rare, concerning complications of epidural anesthesia causing neurological

deficits include formation of epidural abscess or hematoma. However, with such complications their presentation is often delayed and the deficits are expected to be at or near the level of the epidural placement.

The introduction of air into the epidural space could have occurred in a variety of ways. Although the LORA technique is well-recognized manner of identifying the epidural space, some have argued that epidural air could lead to patchy or incomplete analgesia[2]. It is not known what volume of air can be safely injected without causing harm[6]. Presumably the greater the number of attempts using LORA, the increased amount of air that could be administered and so it would seem prudent to limit the amount of air used during LORA techniques[4]. In our case, although two attempts were required in order to identify the epidural space, it is unlikely that any pneumorrhachis thus created caused any neurological deficits since the patient was neurologically intact for several hours post-operatively. Clinically significant pneumorrhachis may have developed when the infusion solutions were changed and then run through an infusion pump. This was the suspected etiology in a case in which air was inadvertently introduced by the patient into the epidural catheter medication bags[10]. In our case, once a critical volume of air was present within the cervicothoracic epidural space, the air likely acted as a space-occupying lesion manifesting with signs and symptoms of cord compression[2,6]. That the patient did not have any symptoms attributable to air around the right brachial plexus suggests that no mass effect was exerted by that collection of air on those nerves, perhaps because the soft tissues surrounding the plexus were better able to accommodate pressure from the air collection than the rigid confines of the cervicothoracic spinal canal. The injection of autologous blood into the epidural space is an established therapy for the treatment of post-dural puncture headache, with volumes of blood of 16 to 20 millilitres being common[11]. Endpoints to injection can include back pain or pressure[12]. It is unusual, however, for patients to develop signs and symptoms of acute spinal cord compression despite this, although such cases have been reported[12,13]. It has been suggested that factors such as spinal stenosis, obesity, and decreased compliance of the epidural compartment may be risk factors for the development of spinal compression symptoms with epidural blood patch procedures[13,14]. In our case, obesity may have been the risk factor associated with the spinal compression symptoms. We cannot be certain as to why there was air found in the paravertebral space and muscles in addition to within the spinal column. We hypothesize that this may have been introduced during the process to place the catheter. The patient was obese and this can increase the technical challenges associated with catheter placement. However not enough details were provided in the anesthetic record to let us know exactly how much air was used during catheter placement attempts.

Reports indicate that CT is the modality of choice to diagnose pneumorrhachis[2,6]. It has been acknowledged, however, that the resolution of CT is such that it will not necessarily allow discrimination between intradural and extradural air and magnetic resonance imaging would be more sensitive to provide that information[2] .

The management of pneumorrhachis in our case is consistent with that provided in other iatrogenic anaesthesia-related cases. Over time, air within the epidural space is reabsorbed and associated with improvement of symptoms[3,4,7-10]. Because pneumorrhachis with neurological dysfunction is such a rare entity, there are no established management guidelines[2]. Most other cases have used conservative management including the provision of supplemental oxygen to hasten the reabsorption of air[3-5,7-9]. Other treatments that have been used include the administration of steroids[2]. Rarely have more aggressive interventions, such as hyperbaric oxygen therapy or percutaneous aspiration of epidural air been necessary[2,5,10] .

This case highlights the need for vigilance to neurological dysfunction when managing patients' acute pain with thoracic epidural catheters. Lack of resolution of neurological symptoms with cessation of administration of epidural medications should prompt investigation of potential causes of neural compression to rule out the need for urgent surgical intervention. If pneumorrhachis is found, conservative management is usually sufficient.

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Review Article

Risk factors for prolonged opioid use and adverse events following orthopedic surgery

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Abstract

Over the past few years, the field of opioid research has been aimed at targeting the opioid crisis affecting communities across Canada. One way that health care workers have been contributing to this field is by identifying risk factors that predispose patients to prolonged opioid use. Given opioids have long been used for post operative pain control in orthopaedics, this article aims to address some of the more common and severe risk factors seen in orthopedic surgery patients. Included with each of the risk factors are potential mitigation strategies to reduce the risk of opioid dependence or adverse effects, including medication interactions.

Backrgound

Opioids have been used for thousands of years, both for medication as well as other cultural purposes. Over the years, the opium poppy has been referred to by a number of names, including the "Joy Plant" by the ancient Sumerians, and has been widely praised for its analgesic effects. Over the past 150 years, however, an extensive number of opioids have been synthesized in labs, facilitated by the advent of the hypodermic needle in the 1850s[1].

The first documented cases of opioid addiction can be traced back to the 16th century in western, Arabian, and Chinese cultures. In the United States, opioid addiction was previously known as "the soldier's disease" due to the use of morphine in Civil War soldiers who subsequently became addicted. For years, drug manufacturers have been trying to develop non-addictive opioids. In fact, some of the most popular opioids used today including hydromorphone (Dilaudid) and oxycodone (OxyContin) were originally marketed as non-addictive alternatives for morphine[2].

The use of opioids is associated with a number of very common side effects including sedation, dizziness, anorexia, and nausea/vomiting. It is also associated with more severe, and potentially life-threatening side effects such as respiratory depression and hypotension[3]. Naloxone is a competitive opioid antagonist used to treat opioid overdose, including the associated respiratory depression, the incidence of which appears to be highest within the first 24-hours after surgery[4,5].

In Nova Scotia, opioid-related death rates are among the lowest in the country, lying approximately 75% below the national average[6]. In 2020, approximately 45 Nova Scotians died from opioid overdoses, down from 57 the year before[7]. Since 2011, benzodiazepines have contributed to ~56% of the opioid-related deaths in the province, and anti-depressants to another 21%[8]. Importantly, despite the fact that Nova Scotia has relatively low rates of opioid deaths, it is estimated that in over 90% of these deaths, victims received their opioids from pharmaceutical sources (e.g. prescriptions)[6]. This emphasizes the need for health care professionals to closely examine their prescribing habits and tailor them to the individual patient.

Orthopedic surgery has been previously identified as a significant contributor to the overall number of opioid prescriptions in the United States, with orthopedic surgeons contributing upwards of 10% of opioid prescriptions in 2009[9]. For the most part, these prescriptions are written by residents, and there has been growing concern over the lack of education new physicians are receiving in this regard[10–13]. In addition to this, it appears as though a large proportion of patients are not disposing of their leftover medication properly, further contributing to the number of opioids in the community[14–17].

There are several risk factors that have been associated with prolonged opioid use and adverse events following orthopedic surgery including, but not limited to anxiety and depression, pre-/perioperative opioid use, alcohol misuse, and larger discharge prescriptions. Others that should be noted, but will not be further discussed here include increased BMI, age under 65,

lower socio-economic status, and a history of chronic pain18–20. The aim of this article is to provide an overview of these risk factors and discuss ways to minimize the potential for harm and/or abuse.

Anxiety and Depression

Of all of the risk factors predicting prolonged opioid use after orthopedic surgery, anxiety and depression are by far the two most common[20–23]. While the pathophysiology of these illnesses is not well understood, it is generally accepted that they are the result of neurotransmitter imbalances, leading to changes in emotion and subsequent physiological changes including fatigue, difficulty concentrating, and insomnia[24]. The link between opioids and anxiety has been studied since the 1970s and a considerable body of research demonstrates that opioids have potent anxiolytic effects in people with anxiety, thus it is not surprising that this population would be more prone to consuming opioids after their prescription has run out due to the symptomatic relief caused by opioids[25]. Furthermore, the presence of opioid receptors in the amygdala supports this idea and introduces a potential mechanism as this region of the brain is linked to fear and anxiety[26]. Patients going through opioid withdrawals tend to be more prone to panic attacks, a phenomenon that can be mimicked through the use of naloxone in healthy patients[27,28]. Taken together, this suggests a close-knit relationship between opioid signalling and anxiety.

Opioids have been studied as treatments for depressive episodes since around the late 19th century due to the euphoria that is associated with their use[29]. The general consensus surrounding this is that patients/animals with depression show diminished endogenous opioid signalling compared to healthy individuals[30]. This means that these patients may be more prone to long-term opiate use in an attempt to replace signalling that has been lost due to their illness. On top of this, opiate use at the time of a traumatic response is known to impair memory consolidation, and prolong the emergence of depressive symptoms after a traumatic experience, such as surgery[30].

Two common medication classes used to treat anxiety and depression include benzodiazepines (BZDs) and Selective Serotonin Reuptake Inhibitors (SSRIs)[24]. BZDs may enhance the depressant effects of opioids, including respiratory depression, and increase the risk of death four-fold, so patients should be given the lowest possible opiate dose to achieve therapeutic benefit[31]. In this case, immediate release opioid formulations are preferred. These patients should also be counselled on the use of naloxone. Opioids are currently contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or who have ceased MAOI use within the past 14 days due to the increased potential for serotonin syndrome, as certain opioids are known to inhibit serotonin transporters[3].

Pre-/Perioperative Opioid Use

Another major risk factor for prolonged opioid use following orthopedic surgery is pre-operative opioid use[21,22,32]. This is likely because reward pathways associated with opioid use have already been activated for extended periods of time, thus increasing the likelihood that these patients will continue using opioids long-term. Research has also shown that patients with more frequent pre-operative opioid dosing were between 2-12 times more likely to exhibit prolonged opioid use, depending on their pre-operative dose[33]. In terms of mitigation strategies, chronic pre-operative opioid users should have a discussion with their surgeon to determine the lowest dose needed to provide analgesia, keeping in mind they may require a higher dose than opioid-naïve patients. Extra care should also be given to re-iterate the importance of educating on naloxone use for anyone using chronic opioid prescriptions.

When it comes to peri-operative opioid dosing and prolonged opioid use, the mechanism is much less understood. Currently, opioids are used during surgery to both reduce the dose of anesthesia required for sedation as well as for prophylactic pain control[34]. In terms of peri-operative risk management, other analgesics, such as high-dose acetaminophen have proven to be effective in reducing post-operative opioid consumption and nausea/vomiting with a potentially significant reduction in pain[35,36]. The reason that high dose acetaminophen reduces post-operative opioid consumption may, in fact, be the same reason why peri-operative opioid use is a risk factor for prolonged post-operative opioid use in the first place. A recently published narrative review examining medication adherence determined that in 6 out of the 10 studies included in the review, having prior exposure to a medication made patients more likely to use that medication in the future when given the choice[37].

Alcohol Misuse

The third risk factor of importance is alcohol misuse[20,38,39]. In Canada, it is estimated that upwards of 1 in 5 adults would fit the definition for "problematic drinking", so understanding this interaction is important in treating pain in patients with alcohol use disorders[40].

The interactions between alcohol and opioids are two-fold. Firstly, both of these drugs are central nervous system (CNS) depressants, therefore use of alcohol and opioids increases the risk of respiratory depression and other serious side effects[41]. Second, alcohol and opioids

are known to activate similar pathways within the body, conferring analgesic and euphoric effects in the short term, and therefore activating similar reward pathways in the brain. Furthermore, acute alcohol withdrawal is known to cause hyperalgesia, resulting in a cycle of pain and pain relief, so by consuming opioids, patients would be able to circumvent some of the unwanted symptoms of alcohol withdrawal[42]. While the exact proportion of patients who use opioids and alcohol concurrently is currently unknown, the most recent estimate as of 2020 is approximately 20% of opioid users[43]. People who regularly consume alcohol are more likely to then consume opioids, a phenomenon that would be facilitated by the administration of post-operative opioids following surgery[44].

Given the increased risk for respiratory depression and other serious side effects, alcohol and opioid co-administration should be considered carefully. Patients should be encouraged to avoid alcohol while taking opioids, however, they should also be made aware of overdose symptoms, such as excessive sedation and respiratory depression. Again, special consideration should be made regarding naloxone training. Patients being treated for alcohol use disorder can safely take opioids as they do not interact with disulfiram, acamprosate, or ondansetron[3].

Discharge Prescription/Opioid Reducing Protocols

An additional consideration when it comes to prolonged opioid use is the amount of opioids a patient receives at discharge. There has been a considerable amount of recent research into this topic. The general consensus is that surgeons/physicians are prescribing more medication than is necessary for patients, with upwards of 50-80% of the pills going unused[45–47]. Currently, the American Academy of Orthopedic Surgeons recommend no more than 400 morphine milligram equivalents (MMEs) following orthopedic surgery which is equivalent to 50 tablets of hydromorphone (Dilaudid) 2mg[48]. This is in stark contrast to what has been happening in the US, where the average discharge prescription is up to double the recommended amount. However, in more recent years, there has been a steady decline in opioid prescribing[48,49]. Originally, it was thought that larger discharge prescriptions would result in fewer refills, thus saving time, however this appears to not be the case and as previously mentioned, many patients do not know how to properly dispose of leftover medication[50–52]. Because of this, patients can use these pills for other purposes, including non-surgical pain, where opioids may not be indicated, leading to an increased risk of prolonged use, and inappropriate use by other members of the household.

Given the ongoing opioid epidemic, there has been growing interest in developing opioid reducing protocols around the world. Some states in the US, such as Florida, have introduced laws restricting the amount of opioids a patient is allowed to be prescribed[49]. While the methodologies and protocols tend to vary greatly, most opioid sparing protocols were able to reduce the number of opioids prescribed at discharge by 50-75%. This, in turn, has been associated with fewer refills and fewer leftover pills, with no decrease in patient satisfaction or increased pain levels[49,50,53,54]. In Canada, most provinces have a prescription monitoring program (PMP) or drug information system (DIS) which allows healthcare workers to monitor patients' prescriptions province-wide.

Risk Factors for Adverse Events

Opioid prescribers should also be aware of which patients are at an increased risk for severe adverse events, namely respiratory depression. Medications that might increase a patient's risk of opioid induced adverse events can be classified into to major categories: sedatives and other CNS depressant drugs, as well as those that can cause constipation due to additive effects. There are also various medical conditions that may predispose a patient to higher rates of respiratory depression and those include pre-existing cardiac disease, respiratory diseases (including asthma and chronic obstructive pulmonary disease), smoking, renal disease, and obstructive sleep apnea[3]. Patients are also typically prescribed a laxative when taking opioids, however, depending on what other medications they are currently taking, they may require a dosage adjustment.

Conclusions

There are a number of risk factors associated with prolonged opioid use following orthopedic surgery and while not be an exhaustive list, this article presents the most common and critical risk factors. Also presented are mitigation strategies to reduce the risk of developing an opioid use disorder as well as adverse effects. With the ongoing opioid epidemic, it is important for health care workers, especially those working with post-operative patients, to stay up to date with current opioid prescribing guidelines. Given the complex interaction involving opioids, it is also important to keep in mind the concept of patient-oriented care, and tailor prescriptions to the individual patient rather than the surgical procedure.

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