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Scope of spinal anaesthesia extends beyond the administration of dose of hyperbaric bupivacaine

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Abstract
In the last few decades, there has been a resurgence of interest in using regional anaesthetic methods for a wide variety of routine surgical procedures. The hyperbaric solution of bupivacaine is used frequently for practically all types of surgery by the great majority of anesthesiologists across the world. But they fail to see the additional benefits of spinal anaesthesia. This method is best suited for specific types of patients. This article demonstrates the relationship between spinal anaesthesia and sensory and motor blocking using hyperbaric and isobaric solutions. The feasibility of administering spinal anaesthesia to just one side of the body is discussed. Using posterior spinal anaesthesia demonstrates that only sensitive spinal anaesthesia may be administered, without motor block.
The scope of surgery that can benefit from isobaric and hypobaric solutions has expanded greatly. Recent years have seen an increase in the usage of thoracic continuous spinal anaesthesia, as it was demonstrated to be effective and safe for a variety of surgical procedures. Spinal anaesthesia for laparoscopic surgery, including thoracic spinal anaesthesia, segmental spinal anaesthesia, and continuous procedures, are all demonstrated in this article.

Keywords: Anesthesia, spinal anesthesia, thoracic, laparoscopic, combined spinal-epidural anesthesia

Introduction

Spinal anaesthesia

The convenience and security of a spinal anaesthesia has remained enticing. When the spinal anaesthetic solution is injected, the anesthesiologist no longer has control of the situation; rather, the result is dictated by the response of the local anaesthetic administered to the cerebral spinal fluid. I contributed my skills, but the combined effort is not the result of my efforts alone. Is this statement true? Education is required for spinal anaesthesia innovation. However, judgements cannot be reached when information is inadequate.
Understanding how it performs for each individual receptive and type of surgery necessitates knowledge of both traditional and contemporary anatomy, local anaesthetics, the density of them, approaches, administration pace, medications, various kinds of penetration, puncture locations, and adjuvant association. As anesthesiologists, we work with patients, physicians, and healthcare organisations. Technical competency is critical in evaluating the way we perform and the patient outcomes for these clients. We require coworkers who can be counted on to provide great service. Their superior people skills enable them to serve a diverse range of consumers while keeping a pleasant workplace. For this reason, the entire range of spinal anaesthesia capabilities must be comprehended.
Since Covino initially presented spinal anaesthesia in 1989 [1] it has been hailed as the pinnacle of excellence in regional anaesthesia. When evaluating spinal and lumbar anaesthesia, spinal has greater advantages and fewer disadvantages [1]. For us, delivering spinal anaesthesia entails personalising treatment to each patient's particular needs whilst making the best possible use of the procedures at our disposal.
Most anesthesiologists have forgotten what spinal anaesthesia is and assume it consists of a spinal puncture and the injection of 15 mg of hyperbaric bupivacaine. The aim of this research is anaesthesia in the spinal for a variety of operations, not a generally applicable hyperbaric solution dose.

Mortuary anatomy

In the mediaeval era, Leonardo da Vinci was hailed as the "discoverer" of anatomy [2].

Leonardo da Vinci dissected over 30 bodies throughout the course of his career, and he wrote up his findings in the Anatomical Manuscript A, which consists of 18 pages. The spinal canal serves as a protective sheath for the spinal cord, a conductive neural cylinder that extends from the foramen magnum in the skull to the medullary cone [3]. The spinal cord, meninges, arachnoid trabeculae, cerebrospinal fluid, ligaments, arteries, and veins are all located within the vertebral canal. The vertebral canal is essential because it provides a safe passageway for the spinal cord as it runs along the spine, allowing the body to be properly innervated. The spinal cord is the largest organ underlying the vertebral canal. There are three membranes that shield the spinal cord and define the neuraxial spaces [3]. The meninges consist of the dura mater, the arachnoid, and the pia mater, listed in order from the outermost to the interior membranes [3]. Pia mater connects to the spinal cord directly.

Spinal fluid and the brain

The most common kind of regional anaesthesia is spinal anaesthesia, in which a local anaesthetic is administered directly into the cerebrospinal fluid (CSF) surrounding the spinal cord and spinal nerves. In all vertebrates, the tissue that encases the brain and spinal cord contains a clear, colourless fluid called cerebrospinal fluid (CSF). The ventricles of the brain are constantly pumping out CSF, which is then absorbed by the circulatory system [4]. Between 125 to 150 millilitres (mL) of CSF are thought to be present in the body of an individual at any given moment. Multiple critical roles for CSF have been postulated [4]. The provision of a buoyant force for the support of the brain is one such function.

Image-based anatomy

Spinal anaesthesia is popular among anesthesiologists, however new imaging studies [5-7] demonstrate that its ancestors had anaesthesia all throughout their spine for no good reason before the invention of intubation. The cauda equina nerves within the sac known as the dural sac have previously been the subject of substantial technologically-assisted research. The radicles extend laxly, filling the back of the lumbar spine [8, 9]. Using digitalized investigations with 2D MRI, the volume of CSF has been measured by anteroposteriorly measuring the space between the subarachnoid artery and the spinal cord dimension [10].

Movement of the spinal cord and cauda equina occurs over its entire length when the patient adopts the lateral decubitus posture, with the highest degree between the L2-L3 gaps (measured at 3.4 1.0 mm) [11]. The discrepancy was 1.0 mm or less in the lower thoracic area [11]. The spinal cord and cauda equina are displaced dorsally in the subarachnoid space when the spine is flexed forcefully. The medullary nerve tissue moves from the lowest thoracic area to the sacrum region as a result of forced bending of the lower parts of the body [11].

Baricity

We published an essay in 2017 titled "Exploring the Many Facets of Spinal Anaesthesia" [12], in which we attempted to do just that. Most anesthesiologists favour hyperbaric solution over isobaric or hypobaric, as well as unilateral or posterior anaesthesia, thoracic spinal, combined spinal-epidural, or continuous spinal anaesthesia, for any and all procedures. CSF densities in normal individuals of both sexes range from 1.00103 to 1.00013, as measured by cutting-edge instruments [13]. All local anaesthetic and adjuvant solutions were measured for density with a densimeter (DMA 450) [14]. If the density of a local anaesthetic solution is more than 1.00103, we call it hyperbaric; if it's lower than 1.00013, we call it hypobaric; and if it's in the middle, we call it isobaric. The CSF reacts differently to each solution. The baricity of a solution is altered when several hypobaric adjuvants are used in the same injection [14]. Different local anaesthetics have different onset times, distribution patterns, and motor block durations when injected into the spinal canal at different pressures. Accordingly, these solutions will spread in a manner that is relative to the location of the puncture. Although spinal anaesthesia has been around for more than 120 years, it wasn't until 2006 that the distinctions between solutions and puncture location for motor block were described [15].

Placement of the Needle

Anesthesiology education is offered by two different institutions. Both a supine and a lateral decubitus approach to teaching the puncture are proposed. Neither programme typically includes supine puncture as a method of administering posterior (sensitive) spinal anaesthesia in its curriculum. The patient can be in any of three postures during a spinal puncture: seated, lateral decubitus, or prone jackknife.

Position: Seated

A well-trained assistance is necessary for positioning the patient and keeping them there safely. When under a heavy dose of sedation, it's hard to stay in a chair. When a patient has a deformity in their spine (such as scoliosis) or is overweight, this posture might help them find their midline. The patient should sit comfortably with their feet up on a stool and their legs draped over the side of the operation table. A typical autonomic reaction including the cardiovascular system causes vasovagal syncope in individuals. Parasympathetic activation and sympathetic inhibition are probable mediators of the observed cardioinhibitory response and/or vasodepressor response [16]. Patients in this situation should be seated with their legs propped up on the side of the operation table. When a person is seated, the cephalic distribution of isobaric anaesthetics (somewhat hypobaric) and adjuvants (completely hypobaric) is often more pronounced [17, 18]. Caudal dispersion is more pronounced with hyperbaric anaesthetics when the patient is seated, which might cause a condition known as cauda equina sickness [19, 20].

Deflection laterally

A well-trained aid can be of great assistance in getting the patient into the safe posture with their knees flexed on their belly and their chin flexed on their chest. With the right dose of sedation, the patient can be put in this posture while still being cooperative. A well-trained assistance is necessary for positioning the patient and keeping them there safely. When under a heavy dose of sedation, it's hard to stay in a chair. Hyperbaric anaesthetics produce a longer-lasting sensory block than a motor block in the position of lateral decubitus, with the block being more pronounced on the down side [12, 15]. Conversely, the motor block from an

isobaric (Slightly hypobaric) anaesthetic lasts longer than the sensitive block from an anaesthetic administered to the ipsilateral side [12, 15].

In a dorsal (Jackknife) posture

The prone jackknife posture can save valuable time during spinal puncture procedures. The intervertebral discs can be opened by placing a cushion under the lower back. This method requires less of an aid than the seated and horizontal decubitus positions. Orthopaedic, anorectal, and plastic surgery are only few examples of longer procedures that may need the patient to be in the prone position [21].

Distinction between positions

No significant differences were found between isobaric and hyperbaric 0.5% bupivacaine in terms of sensory block, motor block, hemodynamic parameters, or patient satisfaction in a study of elderly patients undergoing orthopaedic surgery [22]. Patients over the age of 65 may find more comfort lying on their side, rather on their back [22, 23]. According to the results of a research that compared giving anaesthesia to pregnant women when they were sitting or lying down (lateral decubitus), the latter may provide better outcomes for both the mother and her newborn child [24]. Despite the increased risk of hypotension and complications, the lateral position may have more positive outcomes in terms of time to anaesthesia onset and appropriate analgesia. The lateral decubitus posture for lumbar puncture, which he shown in a recent meta-analysis [25], appears to be an effective option for reducing the risk of post-dural puncture headache (PDPH). Infants from 1 to 90 days of age showed no statistically significant difference in outcomes between the transverse and sitting positions [26].

Lumbar puncture ultrasound guidance system

A recent literature review found that randomised studies using ultrasonography (US) to guide lumbar puncture improved success rates, decreased the number of tries, and decreased the frequency of traumatic tapping [27]. Twelve trials with a total of 957 patients were found in the meta-analysis, and 90.0% of patients had success with landmark-based lumbar puncture [28]. Higher success rates, lower numbers of traumatic punctures, shorter times to success, lower needle passes, and reduced patient pain ratings were all shown to be related with US-assisted lumbar puncture. All lumbar punctures, but notably those in patients with challenging anatomy, should be considered only after US has been performed. For spinal anaesthesia, a lumbar puncture is rarely performed in the United States in Brazil. Pregnant obese people are more likely to experience it, and the outcomes are quite positive [29]. Patients with anatomical challenges benefit greatly from spinal blocks performed with ultrasonography because it reduces the likelihood of injury and CSF not being obtained [30].

Point of entry

The objective is to arrange the patient so that the midline is easily seen. The anesthesiologist positions the patient correctly and then makes use of the palpating hand to locate the intervertebral gap.

Lumbosacral puncture

To get accessibility to the subarachnoid area in the lower spinal canal, a lumbar puncture is performed. The CSF solution fills the subarachnoid space that exists between the arachnoid and pia mater. The risk of PDPH can be reduced by using an atraumatic needle, as shown by recent studies. The anesthesiologist will use their expertise and discretion to choose the appropriate needle size. After penetrating the skin and subcutaneous fat, the needle travels through the supraspinous ligament, interspinous ligament, ligamentum flavum, dura mater, subdural space, and arachnoid mater to reach the subarachnoid space.

Diagnosis and treatment of thoracic puncture

When attempting to block the neuro-axis in the thorax area, it is crucial to have a firm grasp of the relevant anatomy. Needle incision is easily felt when doing a combination spinal-epidural block and getting close to the subarachnoid area. The paramedian technique is typically used when the needle or catheter needs to be inserted into the thoracic cavity. Paramedian access also provides useful information for pinpointing the epidural needle's entry point by revealing the distance from the skin to the epidural space. Anesthesiologists have the option of doing a thoracic puncture with the patient seated or in the position known as lateral decubitus. Recent research into the anatomy of the thoracic vertebrae [7] suggests that putting a patient in a supine or seated position causes the spine to curve excessively, moving the spinal cord further anteriorly and reducing the needle's impact on the nervous tissue. Multiple accounts of conus damage caused by the use of pencil-point needles imply that this is the case because of the depth of penetration required (More than 2 mm down into the cerebrospinal space). This is yet another argument in favour of using a Quincke needle with a cutting bevel for thoracic spinal anaesthesia [31].

Blocks of sensitivity and motor control

There is no correlation between the amount of anaesthetic used and the success of installing sensory and motor blocks. Analgesia is distributed differently depending on whether the patient is seated or lying down after receiving an isobaric solution injection. If this solution is injected when the patient is seated (slightly hypobaric) and then the patient is put in the supine posture, the front (motor) roots will be stimulated more than the rear (sensitive) roots. Therefore, the duration of the motor block will be greater than that of the sensitive block [15, 32]. When administered in lateral decubitus (either left or right), the downed limb will have a shorter-lasting full block (sensory and motor) than the uplimb [15, 32]. One must consider the impact of gravity on the flow of the hyperbaric solution inside the subarachnoid space while utilising the hyperbaric solution. Since the maximal specific weight of CSF is 1.0090 and all hyperbaric solutions include glucose at a concentration of between 5% and 8%, with a specific weight of between 1.0260 and 1.0360, absolute baricity is utilized. When the patient is seated, the block is more likely to remain at a low, caudal position. Because of posture biases such extreme lordosis or kyphosis, the distribution will fall in line with your spine's natural curves. The concentration gradient in the spinal canal is not affected by scoliosis alone. Higher thoracic levels are associated with more cranial migration in the Trendelenburg position [33].

There is currently no hypobaric product on the market. At the moment of usage, the anesthesiologist is responsible for preparing them. Preparing the hypobaric 0.15% bupivacaine

and 50% to 0.15% enantiomeric excess levobupivacaine solution from the 0.5% commercial solution is necessary. It is from the commercial 2% solution that the 0.6% solution is made. This solution is likely to remain suspended above the LCS, where it will mostly soak up by the top-most roots. Because of the decreased sympathetic activity and the increased venous return from lying on one's back, a unilateral selective block can be achieved with little effects on hemodynamics. These benefits must be weighed against the drawback of allowing the lower leg to move freely. It is especially helpful for pocketknife proctological procedures involving orifices. Puncturing the subarachnoid space can be done with the patient in the operating prone position. A saddle block, with a diluted solution and no sympathetic compromise, is promoted after a hypobaric anaesthetic injection because the block seeks for the highest point, which is the sacral area. There is no possibility of low blood pressure, slow heart rate, or slowed breathing. Motor block is localised to the anal region, which leaves the lower limbs unaffected by floating the solution [34, 35].

Anaesthesia of the spine, one side only

Patients pierced and kept in the lateral decubitus posture for a certain amount of time should have unilateral spinal anaesthesia after receiving an infusion of a non-isobaric local sedative. Unilateral spinal anaesthesia requires careful attention to needle type and gauge, local anaesthetic density in relation to cerebrospinal fluid (CSF), patient position, administration speed, and solution dose/concentration/ volume [34]. 80 percent of patients receiving hypobaric (0.15%), 76 percent receiving hyperbaric (0.5%), and 28 percent receiving isobaric (0.5%) 5 mg bupivacaine reported sidedness [35]. Providing evidence that unilateral spinal anaesthesia is not necessary when using an isobaric solution. Rapid onset of sensory and motor block, duration, and patient satisfaction were all dose-dependent when 0.4% enantiomeric excess levobupivacaine (S75: R25) was combined with 5% glucose for unilateral orthopaedic surgery [36]. Thus, the respective periods for recovery at 4, 6, and 8 mg were 75, 117, and 174 minutes.

Anaesthesia of the Spine from the Back

We recently published an essay [37] advocating for increased use of posterior spinal anaesthesia by penetration in the lying down position (Jackknife position). The prone position is used for a variety of procedures in the fields of orthopaedics, anorectology, and plastic surgery that last anywhere from a few minutes to a few hours. Therefore, the puncture in the location on which it will be performed simplifies matters for the patient and the entire operating room staff. To achieve sensitive spinal anaesthesia without motor block, hypobaric solutions of local anaesthetics should be advised for posterior spinal anaesthesia [37]. To get sensory and motor blocks, however, during orthopaedic procedures where a pneumatic tourniquet is required, spinal anaesthesia with an isobaric solution of local anaesthetics is used. Poorly localised, dull, tight, agonising pain at the location of tourniquet application is typical of tourniquet discomfort [38]. A dull, ill-defined aching 45 to 60 minutes after a tourniquet is inflated is typical for conscious patients undergoing extremities surgery under regional anaesthesia blocking. Most cases occur during procedures on the lower extremities, and it is more prevalent under general anaesthesia (53-67 percent). Although the precise cause is unknown, researchers believe a cutaneous neuronal mechanism is at blame [39]. The start and duration of 0.1% hypobaric bupivacaine in the prone position were found to be comparable to those of 0.5% hyperbaric bupivacaine in the seated position [40], although the hyperbaric solution had a longer duration and the hypobaric solution had a greater incidence of proprioception. All patients were able to make their own way from the surgical table onto the stretcher when surgery was complete. The 0.1% bupivacaine solution was selected because it provides a safer level of hypobaricity than the 0.15% bupivacaine solution [41].

Cholecystectomy under spinal consciousness induction

General anaesthesia with complete paralysis of the patient's muscles, tracheal intubation, and intermittent positive pressure breathing is often the only anaesthetic options available for upper abdomen laparoscopic surgery, according to most anesthesiology services. Recent research has compared spinal anaesthesia for laparoscopic procedures to general anaesthesia, finding some benefits for regional method [42, 43]. Recently, magnetic resonance imaging was used to study the thoracic spinal canal architecture in 50 individuals [7]. The combined spinal-epidural technique, which involves a puncture at T_{10}, has also been shown to be safe [44, 45]. Over the last 11 years, 4,645 individuals have had spinal anaesthesia [46]. Another research with 3,492 patients found that spinal anaesthesia was the preferred method for laparoscopic cholecystectomy [47]. This was corroborated by a comparison between high and low dosages of general anaesthesia [43, 48]. Spinal anaesthesia as the only anaesthesia approach is practical, safe for planned laparoscopic cholecystectomy [50], as shown in a recent study outlining the process and benefits of spinal anaesthesia for laparoscopic cholecystectomy [49].

Anaesthesia of the thoracic spine

Two recent reviews of thoracic spinal anaesthesia have been published. An MRI study published in 2016 [51] and numerous more papers with over a thousand patients and no neurological issues [45, 48, 52, 53] support the idea that thoracic spinal anaesthesia is a safe and effective operation. Another 2018 study pondered the question of whether or not to do thoracic spinal anaesthesia, and its authors concluded that while the procedure has numerous advantages, it is not risk-free [54]. Three MRI images measured distances of 5.19 mm in T_2, 7.75 mm in T_5, and 5.88 mm in T_{10}, all well inside the safe zone for administering thoracic spinal anaesthetic with due care and without hitting the medulla [7]. Puncture success was seen in every patient with 20 (6.6%) paresthesia with little difference between the needles in a recent study contrasting two types of instruments (Quincke vs. Whitacre) for thoracic spinal anaesthesia on 300 patients [52]. There were no long-term neurological effects from the paresthesia. Because the hole in a pencil tip needle is lateral and measures 0.8 mm to 1.7 mm at its widest point, two millimetres of penetration into the subarachnoid space are required for the CSF to be seen [31]. When a cut-point needle is inserted into the subarachnoid space, cerebrospinal fluid (CSF) instantly emerges from a terminal orifice. Therefore, it appears that a needle with a hole closer to its tip, rather than its end, is safer to insert.

Anaesthetic spinal segmentation

Depending on the area being punctured, epidural segmental

anaesthesia may be administered at the cervical (C7-T1), thoracic (T_4-T_{10}), lumbar (L2-L4), or sacral level. Common applications of this method include cervical-brachial surgery, orthopaedic surgery of the upper limbs, thoracoabdominal surgery, cosmetic surgery of varying sorts, surgery of the lower limbs (both thoracic and orthopaedic), and labour analgesia. In spite of its potential, segmental spinal anaesthesia is rarely employed [55].

While doing procedures on the neck, head, upper limbs, and thorax, a puncture is made between the T_2 and T_{12} vertebrae, whereas a puncture is made between the T_{12} and L1 vertebrae while performing procedures on the lower abdomen and lower limbs [56]. The puncture between T_7 and T_8 is notoriously challenging and unnecessary. Spinal anaesthesia, like segmental epidural anaesthesia, can be targeted to just the surgical site to reduce or eliminate unwanted side effects. As a result, segmental spinal anaesthesia can be achieved with a single thoracic puncture [48, 52, 53] or with combined spinal-epidural anaesthesia [44, 45]. Rapid start of action, a low rate of arterial hypotension, and the absence of neurological sequelae were found in a study of 636 patients undergoing various types of surgery (Gynaecological, laparoscopic, orthopaedic, and urological) using a single thoracic puncture with a low dosage of local anaesthetic [53]. Lower thoracic puncture is safe, as shown by a study of 300 patients who underwent two different needle types (Whitacre and Quincke) and compared the incidence of paresthesia to lumbar puncture; all paresthesia was temporary, and no neurological problems were found.

Continuous spinal anaesthesia of the lumbar spine

Using a catheter beyond the cutting-tip needle indicates minimal insertion difficulty, demonstrated a low prevalence of hypotension, paresthesia, and headache in a recent prospective article in constant spinal anaesthesia (CSA) with 455 orthopaedic patients done between 1998 and 2015 [57]. There were no neurological side effects, such as cauda equina syndrome or temporary neurological symptoms, reported. Excellent pain relief was achieved throughout labour with this catheter and no PDPH was seen [58]. Microcatheters with tiny gauge needles are cumbersome to work with, sluggish to administer local anaesthetic, and can even break. They can produce cauda equina syndrome because to insufficient blocks provided by inefficient anaesthetic dispersion hyperbaric in the subarachnoid area [59, 60]. After hearing about these cases of cauda equina syndrome caused by a mistake in methodology, the American FDA recommended cutting out the microcatheters. The fundamental benefit of CSA is that the local anaesthetic may be injected gradually, with CSF dispersion controlled to meet the specific requirements of each patient. The manufacturer's decision to stop making this catheter means that we anesthesiologists no longer have access to a valuable treatment tool [57].

Spinal anaesthesia for the thorax in a constant flow

Recently, thoracic CSA has been done for radical cystectomy in patients over the age of 80 by puncturing the T_{10}-T_{11} intervertebral space with a novel catheter (Spinolong polymedic kit) [61]. Both a 21G Tuohy-shaped spine needles and a 24G intrathecal catheter were included in the package. The kit includes both a needle with a sharp tip and a transitional catheter. This pilot study demonstrates that CSA and analgesia are a viable alternative for reducing morbidity and mortality in fragile octogenarians after radical cystectomy. Thoracic CSA may be a safe and effective alternative to general anaesthesia for elderly patients at high risk of complications during major abdominal surgery, according to an investigation examining one year of experience with 90 patients conducted in an Italian geriatric hospital [62]. The authors of the Editorial argue that pleural CSA is a viable alternative to GA [63].

Epidural and spinal block anaesthesia

When both spinal anaesthesia and catheter epidural are administered to the same patient at the same time, the result is a combined spinal-epidural (CSE) block. There are benefits and drawbacks to using either method in the neuroaxis. In 1937 [64], doctors pioneered a method called combined spinal epidural anaesthesia to simultaneously numb both the spinal column and the epidural space. The CSE is now the norm for pain relief during labour and delivery. The rapid onset of action, efficacy, and safety of CSE anaesthesia make it a popular choice for major orthopaedic surgeries [65-67]. This type of anaesthesia can also be used to improve an inadequate blockade, extend the duration of anaesthesia during the surgical procedure, and provide sufficient management of postoperative analgesia with an epidural catheter. A 0.5% isobaric bupivacaine dosage based on height was employed in a recent retrospective research including 230 participants. Catheter augmentation was used in 7.3% of patients, demonstrating that the CSE anaesthetic technique is efficient, secure, and generates a stable cardiovascular with the capability of extending surgical analgesia for any length of time based on the amount of time of surgery [68]. Researchers found that CSE analgesia and low-dose epidural anaesthesia both produce similar results in terms of pain reduction and mother and foetal outcomes in labour [69]. Women who are already far along in the labour process may benefit from CSE because of how quickly it starts working.

Conclusion

I didn't enter the world already knowing how to use a needle, but by the time I graduated medical school, I was already proficient enough to utilize spinal anaesthesia in my practice as an anesthesiologist. Because of my identification with spinal anaesthesia, I was able to break a bone and suck out the considerable marrow with such clarity that the metaphor became literal. Spinal anaesthesia is a tried and true method that requires little skill or preparation. The study of anatomy, physiology, and pharmacology is crucial to grasping its complexity.

Conflict of Interest

Not available

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Not available

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