Anesthesiology Research and Practice

Pain Management Techniques and Practice: New Approaches, Modifications of Techniques, and Future Directions

Guest Editors: Andrea Trescot, Hans Hansen, Standiford Helm, Giustino Varrassi, and Magdi Iskander

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Editorial

Pain Management Techniques and Practice: New Approaches, Modifications of Techniques, and Future Directions

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The practice of pain medicine has radically changed over the last twenty years, morphing from an almost exclusively anesthesia-based, recovery room, and procedure-oriented part-time practice into a multidisciplinary, multimodality, multispecialty field. These changes have been the consequence and the stimuli for the expansion of new medications and techniques, which have improved the diagnosis and treatment of painful conditions. This issue attempts to highlight some of the advances in anesthesiology and pain, including epidural analgesia, spinal cord stimulation, and trigger point diagnosis and treatment. There is also a case report of a technique utilizing transforaminal blood patches to treat intracranial hypotension, analogous to postdural puncture headaches. Particularly intriguing, given the current controversy regarding the role of opioids in the management of chronic pain, is the report of the lasting developmental delays seen in infant rats exposed to fentanyl. This observation could have a significant impact on the decision to initiate opioids in human infants and children and adds data to the current dilemma.

Pain medicine is a rapidly growing field, and the innovations described in this issue move the field further into the future. Hopefully, the reader will be encouraged to utilize and expand on these topics in their own practice.

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Review Article

Recent Advances in Epidural Analgesia

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Neuraxial anesthesia is a term that denotes all forms of central blocks, involving the spinal, epidural, and caudal spaces. Epidural anesthesia is a versatile technique widely used in anesthetic practice. Its potential to decrease postoperative morbidity and mortality has been demonstrated by numerous studies. To maximize its perioperative benefits while minimizing potential adverse outcomes, the knowledge of factors affecting successful block placement is essential. This paper will provide an overview of the pertinent anatomical, pharmacological, immunological, and technical aspects of epidural anesthesia in both adult and pediatric populations and will discuss the recent advances, the related rare but potentially devastating complications, and the current recommendations for the use of anticoagulants in the setting of neuraxial block placement.

1. Introduction

Neuraxial anesthesia is the term for central blocks involving the spinal, epidural, and caudal spaces. While it is now an invaluable adjunct and even occasionally an alternative to general anesthesia, its use is not a new phenomenon. Physicians such as Corning published studies documenting success with neuraxial blocks as early as 1885 [1]. Even more ambitious physician-scientists such as Bier became knowledgeable about spinal anesthesia, in particular, through self-investigation [2]. It unfortunately was also through this type of dedication that he became all too familiar with postdural puncture headaches. Despite its early use, though, much of the gains we have with neuraxial blocks did not occur until the early 1900's. Limitations in this particular area of anesthesia were limited to lack of drug diversity and a lack of adequate equipment. Prior to 1904, the only drug available for neuraxial use was cocaine, and development of epidural technology was still a ways off. With a larger drug base and equipment advancements came an expansion of the role of neuraxial anesthesia in anesthesia practice.

Excluding the obvious fact that surgical conditions primarily dictate the type of anesthesia performed, most operations below the neck can be performed under neuraxial anesthesia. Various studies have shown a decrease in postoperative morbidity and even mortality when used either with general anesthesia or alone. Neuraxial blocks have even been shown to reduce the incidence of venous thrombosis and pulmonary embolism while also minimizing transfusion requirements and respiratory compromise following thoracic and upper abdominal surgery. A decreased stress response has also been noted which may have positive cardiac benefits such as reduced perioperative and postoperative ischemia. Despite these proposed advantages of neuraxial blocks, adverse reactions and complications can occur. These can range from self-limited back soreness to permanent neurologic deficits and even death. Because an expansive review of neuraxial blocks is beyond the scope of this review, we have chosen to focus our discussion to epidural and caudal anesthesia. In doing so, we will review pertinent epidural knowledge, and present cutting edge advances specific to epidural and caudal anesthesia.

2. Anatomy for Epidural Placement

The anatomy for the placement of an epidural goes beyond the epidural space itself. It is for this reason that this section will not only cover anatomy of this space, but also important surrounding anatomy.

The epidural space extends from the base of the skull to the sacral hiatus. Its lateral boundaries are the vertebral pedicles, while the anterior and posterior boundaries are

the dura mater and ligamentum flavum, respectively. The contents of the space include fat, lymphatics, and veins with nerve roots that cross it. Determinants of epidural fat include age and body habitus with obese patients having the greatest amount of epidural fat [2]. The amount of epidural fat within the space is just one of the factors that determine volume necessary for adequate anesthesia or analgesia.

Veins within the epidural space form a plexus called Batson's venous plexus. These veins connect with the iliac and azygos veins and are significant because of a lack of valves commonly found in veins. It is the lack of these valves in conjunction with a compressed inferior vena cava from a gravid uterus, which results in the venous engorgement of epidural veins found in parturients.

Traditional thought on epidural anatomy was that it is one continuous space. A more recent thought is the concept of it being a potential space with septations or crevices formed by layering of epidural contents (fat). The anatomic layering and texture of epidural contents create inconsistent paths that ultimately make flow through it less uniform [3]. The idea of these septations or crevices forming variable paths for the flow of a solution is the rationale given for unilateral or partial epidural blockade [4].

Vertebral spinous processes help define the midline. In the cervical and lumbar areas they are horizontal, while in the thoracic vertebrae (specifically T4 through T9) they are caudally angulated. The space between these caudally angulated spinous processes are often difficult to access leading some to favor a paramedian approach to thoracic epidural placement as opposed to the traditional midline approach. While the surgical site dictates the level of the epidural placement, the safest location is one whereby inadvertent spinal cord damage can be avoided. In adults, the spinal cord typically ends at the lower border of the L1 vertebra while in children it is at the level of the lower border of L3. By the age of 8 years, one can safely target the same lumbar levels for safe epidural placement as in the adult, while under the age of 7 years, a caudal approach to the epidural space is safest. One generally accepted landmark for assessing lumbar level for epidural placement is the superior aspect of the iliac crest. A horizontal line drawn between the superior borders of either iliac crest corresponds to the L4 vertebral body or the L4-5 interspace. For thoracic epidural placement, the inferior border of the scapula is the usual site of the T7 vertebral body/spinous process, and is typically used to approximate thoracic level of epidural placement for thoracic or intraabdominal surgical procedures. The approximate distance from the skin to the epidural space in 80% of individuals is 4–6 cm with the caveat that thin and obese patients may vary outside of this range [5].

3. Choices for Epidural Infusions

Local anesthetics are the mainstay of therapy for obtaining analgesia or anesthesia with an epidural. Understanding the pharmacology of local anesthetics is therefore paramount. Specifically, factors such as surgical location and duration, desire to have a sensory and/or motor block, or the expected potency and duration of a specific local anesthetic agent should be considered prior to placing an epidural block. The choice of which local anesthetic agent to use can be categorized based on desired length of action. Regardless of the class of local anesthetic, these drugs can be divided into ones that are short, intermediate, or long acting. The shortest-acting local anesthetic agent is chloroprocaine. Its short length provides ample anesthesia for short surgical procedures, and its quick elimination obviates the need for prolonged recovery room discharges.

Lidocaine has traditionally been the agent of choice for slightly longer surgical procedures that require an intermediate-acting local anesthetic. In place of lidocaine, some centers have also adopted the use of mepivacaine for its longer length of action with a similar onset profile. The intermediate length of action of either agent can be prolonged by the addition of epinephrine. Of note is the potential for an increased incidence of hypotension due to venous pooling from the beta effects of epinephrine containing solutions. This phenomenon seems to be especially true of patients receiving lumbar epidural analgesia.

Longer-acting local anesthetics used for epidural blockade typically consist of either bupivacaine or ropivacaine in varying concentrations. Greater concentrations of either will produce a greater motor block in addition to the sensory block that is typically desired. Ropivacaine, an analog of mepivacaine, has a lesser intense and shorter duration of motor block in addition to a lower toxicity profile than an equipotent dose of bupivacaine [6]. The cardiac toxicity profile of bupivacaine is the highest among all the choices of local anesthetics. It is due to a high degree of protein binding and a greater blocking effect on cardiac sodium channels.

Multiple attempts have been made to find various additives to improve the onset and duration of an epidural block. Alkalinization with sodium bicarbonate has proven effective in a dose of 1 mEq/10 mL local anesthetic for chloroprocaine, lidocaine, or mepivacaine. A lower concentration of sodium bicarbonate (0.1 mEq/10 mL of local anesthetic) is necessary for bupivacaine and ropivacaine due to the potential of precipitation with higher concentrations. The addition of epinephrine to a local anesthetic increases the duration of action by decreasing the vascular absorption. While this phenomenon has been shown to be true with the short- and intermediate-acting local anesthetic agents, it appears to be less effective with longer-acting agents. With the low doses typically used in the epidural space, the overall cardiovascular response seems to be vasodilation (causing a decrease in mean arterial pressure), in addition to an increase in heart rate and contractility. These effects ultimately result in maintenance of cardiac output. Phenylephrine has also been used to prolong the effects of neuraxial local anesthetics. In contrast to the use of epinephrine in the epidural space, it causes an increase in peripheral vascular resistance without the added benefits of an increase in chronotropy or contractility. The resulting drop in cardiac output is the reason most anesthesiologists avoid phenylephrine in the epidural space.

Opioids remain the analgesic adjuvant of choice for augmenting the effects of local anesthetics in the epidural space. Epidural administration of fentanyl intraoperatively has been

shown to significantly reduce volatile agent requirements by more than twofold in some instances [7]. Despite the benefits of neuraxial opioids, side effects do occur. Some of the more common side effects are pruritus (specifically in the mid-facial area), nausea, and urinary retention. Hypotension can also occur which is attributed to the reduction of sympathetic outflow via opioid receptors in the sympathetic ganglia.

Another class of analgesic adjuvants includes alpha-adrenergic agonists. Clonidine is the main drug used in this class due to its production as a preservative-free preparation. The effects of epidurally administered clonidine are seen as early as 20 minutes after injection, with peak effects occurring in 1 hour. The analgesic potency has been described as being comparable to epidurally administered morphine [8]. Adding clonidine to opioids in the epidural space has an additive effect, which results in a lower dose of narcotic necessary for optimal pain control. This as a consequence diminishes the incidence of respiratory depression that potentially occurs with neuraxial opioids. Clonidine is lipophilic, and as a result is quickly redistributed systemically despite neuraxial injection. It therefore has both central and peripheral effects. At lower doses, the central effects cause sympatholysis leading to hypotension, while the peripheral effects at higher doses cause vasoconstriction. Clonidine administered in the low thoracic or lumbar region typically produces blood pressure effects similar to that seen with intravenous administration [9]. When given in the mid or upper thoracic regions, epidurally administered clonidine causes an even greater decrease in blood pressure [10]. This more substantial drop in blood pressure is attributed to blocking thoracic dermatomes that contribute to sympathetic fibers innervating the heart. In addition to the hypotensive potential of clonidine, bradycardia, and nausea with or without vomiting are also potential side effects. The cause of bradycardia is twofold. Clonidine has vagomimetic effects in addition to inhibiting norepinephrine release. Additional side effects such as sedation and dry mouth are possible, but seem to be dose related. Even more esoteric compounds such as neostigmine, ketamine, ketorolac, midazolam, and dexamethasone are being studied with hopes to develop additional tools to supplement or even replace the neuraxial analgesia and anesthesia of local anesthetics. While this discussion focuses on epidural use of these agents, their clinical use may have far greater application. Current studies are not only investigating these agents in the acute pain setting, but are also for use in various chronic pain disorders.

4. The Effect of Anesthetic Technique on Immune Function

Surgery is associated with a wide range of metabolic, endocrine, hematological, and inflammatory/immunological responses, known collectively as surgical stress response. Surgical stress response has been identified as a major factor accounting for perioperative immune suppression [11]. The extent to which this adaptive response can be modified appears to be dependent on the anesthetic and analgesic technique used, and with regards to postoperative outcomes, has been extensively studied [12, 13]. There is evidence that regional anesthesia, particularly epidural blockade, attenuates or inhibits surgical stress by blocking afferent neural stimuli from reaching the central nervous system, as well as by blocking the efferent activation of the sympathetic nervous system [14, 15]. The nervous system accounts for the main common pathway mediating the surgical stress response [16]. Immune response is subject to neuroendocrine regulation and elicits neuroendocrine changes [17], augmenting or blunting the neuroendocrine response. It therefore affects postoperative immune function, and ultimately long-term outcomes [18, 19].

5. Perioperative Immunosuppression and the Impact of Anesthetic Technique on Postoperative Outcomes

Impaired perioperative immunity is related to the neuroendocrine stress response. Evidence suggests that the factors that are associated with immunosuppression during surgery are surgical stress response, general anesthesia, and opioid analgesia.

Surgical trauma in itself induces the release of catecholamines, adrenocorticotropic hormone, and cortisol, depresses cell-mediated immune responses including natural killer cell and cytotoxic T-cell function [13, 19–21], and promotes tumor vascularization [22, 23]. Additionally, risk factors, such as pain [24], blood transfusion [25], hypothermia [26], and hyperglycemia [27], further impair immunity. Pain activates the HPA axis, and may induce accelerated lymphocyte apoptosis [28]. Hypothermia impairs neutrophil oxidative killing by causing thermoregulatory vasoconstriction and thus decreasing oxygen supply [29]. Perioperative hyperglycemia impairs phagocytic activity and oxidative burst, as there is less NADPH available due to the activation of the NADPH consuming polyol pathway [30–32]. Earlier studies suggested that cell-mediated immune function [33, 34] is reduced by allogenic blood transfusion. Transfusion has more recently been suggested to facilitate host T_h2 cells to produce immunosuppressive IL-4 and IL-10; however, the exact mechanism of causality is yet unclear [25].

General anesthesia is also considered to be immunosuppressive, either by directly affecting immune mechanisms, or by activating the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system [12, 29]. Volatile anesthetics, by mechanisms that are only partially elucidated, impair NK cell, T cell, dendritic cell, neutrophil, and macrophage functions. Furthermore, opioid analgesics were found to inhibit both cellular and humoral immune function in humans [35, 36]. Melamed and colleagues showed that ketamine, thiopental, and halothane, but not propofol, had inhibitory effects on NK cell activity and increased metastatic burden in rats [37].

Opioids suppress the innate and adaptive immune responses [38, 39]. While neural and neuroendocrine responses are also involved [40], the presence of opioid-related receptors on the surface of immune cells increases the likelihood of a direct immune-modulating effect [41]. De

Waal and colleagues found different opioids to have differing immunosuppressive effects [42]. Synthetic opioids, however, do not appear to attenuate immune response [43, 44].

These immunosuppressive factors occur simultaneously during surgery and in the immediate postoperative period. The perioperative period is therefore a decisive period during which interventions that promote host defense may especially benefit the patient [11]. This may be of particular interest in patients undergoing tumor resection. While surgery is essential to reduce tumor burden, and among various treatment options, it is considered to be the most effective treatment for solid tumors; a rapid spread and growth of malignant tissue is often observed after tumor resection [45]. Cancer surgery, even with the best technique, is usually associated with dissemination of malignant cells through the lymphatics and the systemic circulation, and, at the time of surgery, many patients have already established micrometastases [46]. The clinical manifestation of this minimal residual disease is a function of both the host immune competence (particularly NK cell function) and the tumor's proliferative and angiogenic abilities [22, 23, 45, 47]. Regional anesthesia reduces the amount of intraoperative general anesthetics required, has opioid sparing effects, and markedly attenuates the neuroendocrine stress response to surgery as well as preserving NK cell function and T_h1 cell activity better than general anesthesia [48]. It is hypothesized that regional anesthesia and analgesia help preserve control of tumor progression. Modification to anesthetic management might thus reduce the risk of recurrence [18].

6. Imaging Techniques during Epidural Catheterization

Identifying the epidural space and correct needle positioning is often challenging for the novice anesthesiologist. Epidural catheter placement is thought to be among the most difficult techniques to acquire [49], with a success rate of as low as 60% at the first attempt [50], and an overall success rate of nearly 90% [51]. Factors contributing to the success or failure of catheter placement can be surgery related, as the type of surgery determines the specific region of the vertebral column for block placement [52]; patient dependent, such as body habitus, presence or absence of identifiable anatomical landmarks, or spinal anatomy; or operator dependent, such as the degree of personal experience, patient positioning, needle size, or the use of conventional "blind" versus imaging-guided techniques [53]. Previous reports suggest that the conventional "loss of resistance" technique used in the thoracic and lumbar region may have a false-positive success rate of as high as 30%, and, although generally considered reliable for epidural anesthesia, when used as a sole tool, this clinical sign may not offer the same potential to accurately identify the epidural space, as when complemented with an imaging tool [54, 55]. Visualization of the interlaminar space, accurate estimation of the depth to the epidural space, and optimal needle insertion angle are known to facilitate epidural block placement [50, 56, 57]. With the rapidly evolving imaging technology, there has been an increasing interest in the use of various imaging tools, to improve success rates of neuraxial blocks. Several studies have shown the usefulness of both ultrasound guided and fluoroscopically guided catheter insertion techniques [49, 58, 59].

6.1. Ultrasound Guided Epidural Catheter Placement. Ultrasound is a radiation-free imaging tool that is now widely used in clinical practice. The first successful sonographic measurement of the epidural space dates back to the 1980s, when Cork and colleagues [60], and Currie [61] were able to localize and estimate the distance from the skin to the epidural space. More recently, Bonazzi and de Gracia identified the ligamentum flavum in the lumbar vertebral region [62]. Technical improvement in sonographic visualization, such as the ability to digitally depict anatomical structures at high resolution, has much increased the clinical feasibility of ultrasound in epidural catheter insertion and visualization [57, 58]. The increasing popularity of this technique over the past three decades has been attributed to a more accurate estimation of epidural space depth, a more optimal determination of the needle insertion point, and insertion angle particularly in cases of difficult anatomy (such as obesity, especially during obstetric anesthesia, or scoliosis), or the presence of implanted hardware [63], and reduced failure rate [56]. While the use of ultrasound offers a greater likelihood of successful catheter placement in the obese patient, morbid obesity may pose technical difficulties to the visualization of the vertebral anatomy and the epidural space.

Besides the obvious benefits of this radiation-free technique compared to the conventional "blind" method, there are disadvantages of ultrasound use in the setting of epidural block placement. Technically, it can be difficult to simultaneously stabilize and advance the Tuohy needle, and maintain the acoustic window, holding the ultrasound probe in the optimal position. Also, it can be difficult to maintain continuous visualization of the Tuohy needle tip during advancement. The use of ultrasound in adults is helpful for anatomical identification, but there is limited published evidence available for the same degree of usefulness of real time needle insertion, compared to the pediatric population. A recent study by Belavy and colleagues, evaluating the feasibility of real-time 4D ultrasound for epidural catheter placement in cadavers, found that 4D ultrasound potentially improves operator orientation of the vertebral column at the cost of needle visibility and resolution [64–67]. Slight discrepancy between the sonographically and clinically measured epidural space depth should be anticipated, likely due to factors such as tissue deformation during needle passage, deviation from the midline, and deviation from the 90 degree insertion angle that has been found to most precisely correlate with the sonographically measured skin-epidural space distance. When compared to the fluoroscopic visualization, ultrasound guidance does not offer the advantage of placing the epidural catheter exactly at the desired vertebral level; also, the depth of the inserted needle may not always be adequately assessed.

6.2. Fluoroscopically Guided Epidural Catheter Placement. The usefulness of fluoroscopic guidance in epidural block placement in various regions of the vertebral column has been established [49, 55, 61]. Previous studies have shown that more than 50% of lumbar epidurals, in the absence of appropriate imaging tools, were actually performed at a level other than the one predicted [68]. A study by Renfrew and colleagues found that caudal blocks without the use of fluoroscopy resulted in a 52% incidence of erroneous needle placement [69], likely due to the subfascial compartment that provides low resistance to injection. Fluoroscopic guidance offers the advantages of precise needle angulation and localization of the catheter at the targeted vertebral level even in the presence of difficult or unreliable surface anatomy, as well as accurate identification of the epidural space, or the assessment of injectate dispersal, with the use of contrast dye to confirm the epidural placement. These factors may also obviate complications [59]. Fluoroscopy therefore improves the success rate of epidural block and provides a reliable delivery of therapeutic substances into the epidural space; however, both the patient and the operator are exposed to radiation. Furthermore, this method may only be safe in patients without contraindication to the use of contrast dye or radiation itself.

While the use of imaging tools for epidural catheter placement is gaining increasing popularity for their potential to increase success rate and reduce complications, the potential risks and benefits of these methods should be thoroughly assessed, and the choice of imaging technique should be determined on an individual basis. It should be remembered that the use of ultrasound guidance does not eliminate the need for using the conventional "loss of resistance" technique, and it is as important as when using the blind insertion technique.

7. Considerations in the Pediatric Population

With the development of advanced skills with ultrasound, guided techniques has attracted an increased interest in its use for neuraxial blocks. The benefits of identifying anatomy and directly visualizing needles and catheters, as found with peripheral blocks, can be of great value for improved success and confirmation of neuraxial blocks. Because of the large variation of each patient's body habitus due to age, it can be difficult to predict the puncture depth to reach either the epidural or intrathecal spaces [70].

In pediatric population, checking the anatomy with the ultrasound before and during performing the procedure gains and assures a lot of success. Visualization is clearer than in the adult population due to less ossification of the vertebral column and easiness to predict the epidural and/or the intrathecal spaces. Loss-of-resistance technique to identify the epidural space can be very challenging in neonates due to presence of less fibrous tissue limiting the tactile feedback [71].

Visibility of the spread of fluid is a promising technique during injection through the needle and catheter, which could confirm the position. Using an epidural electrical stimulation test is another method but the clinical value of electrical stimulation in caudal needle placement has not been extensively studied [72].

7.1. Caudal Needle and Catheter Placement under Ultrasound. Caudal anesthesia is one of the most popular regional blocks in the pediatric population to provide perioperative analgesia. Placement of a single shot caudal block or a lumbar/thoracic epidural catheter achieved through the caudal epidural space is an advanced skill. This technique becomes even more complex when considering variation in patient age, weight, and varying levels of bone ossification. Ultrasound guidance for this procedure is helpful in identifying the underlying anatomic structures. The ones most commonly of interest include the sacral hiatus, sacral cornua, coccyx, and sacrococcygeal ligament. While probe orientation can be done using either a transverse or longitudinal view of the midline, it is typically best to orient and assess landmarks prior to performing the procedure (Figures 1, 2, 3, 4, and 5).

When introducing a catheter into the caudal space to reach the lumbar or thoracic spine, a technique similar to the above is used for cannula placement. The catheter can then be directly visualized during advancement with the ultrasound at each level of the spine above the sacrum (Figures 2(a), 2(b), and 3).

As is the case during the assessment, either the longitudinal or transverse axes can be used to visualize the underlying structures and catheter position.

Confirmation of catheter placement can be performed through visualization of local anesthetic spread as well as through direct visualization of the catheter within the epidural space. Catheter tip visibility may be improved with the injection of a bubble-based fluid or local anesthetic spread and a swoosh test (using a stethoscope to listen to fluid movement).

7.2. Tunneling of Caudal Epidural Catheter. Bacterial colonization is regarded as a causative factor for infectious complications of caudal catheters in children [73]. In addition to the routine measures of wearing personal protective equipment (hats, masks, and gloves), prepping the area with an alcohol-based solution, and maintaining a sterile field, another option is to tunnel the catheter after placement. A small subcutaneous placement of the proximal portion of the catheter not only decreases the length of tubing potentially exposed to contamination, but it also helps in gaining a more secure catheter placement. Both of these features become especially advantageous in prolonged epidural catheter use.

8. Complications of Epidural Anesthesia

Epidural anesthesia and analgesia are generally considered to be safe with regards to adverse post procedural events, as their complications, resulting in permanent deficits, are rare. Besides their indications and obvious benefits, knowledge of adverse outcomes should also comprise an essential part of clinical decision making.

Complications of central neuraxial blockade, much depending on the experience in patient management, as well

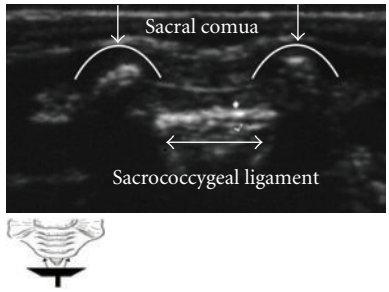
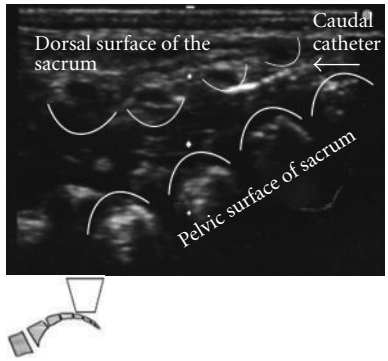
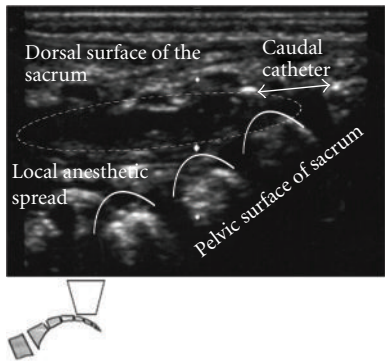


Figure 1: Placing the probe transverse plane at the coccyx, the sacral cornua (represented in white arrows heading down) are viewed laterally as humps. Sacral hiatus is located between an upper hyperechoic line, representing the sacrococcygeal membrane or ligament and an inferior hyperechoic line representing the dorsum of the pelvic surface of the sacrum (bidirectional sided arrow).



(a)



(b)

Figure 2: (a) Placing the probe longitudinally between the sacral cornua will capture the dorsal surface of the sacrum, the dorsal aspect of the pelvic surface of the sacrum, and the sacrococcygeal ligament. Angiocatheter penetrated the sacrococcygeal ligament and lies in the epidural space. (b) Local Anesthetic spread through Caudal Angiocatheter in caudal epidural space.

as materials, equipment, and the presence of risk factors, have been reported to occur at various frequencies [74, 75]. An epidemiologic study conducted in Sweden over a period of 10 years revealed an increasing trend (1 in 10,000 neuraxial anesthetics) of severe complications after central neuraxial blockade [74]. Relatively recent literature suggests that most

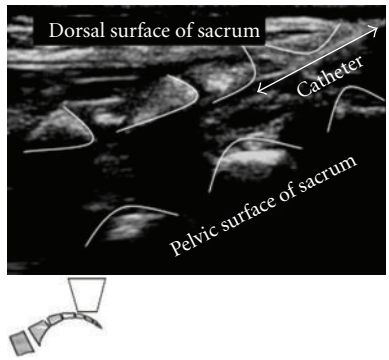


Figure 3: Caudal epidural catheter passing through Angiocatheter in the epidural space.

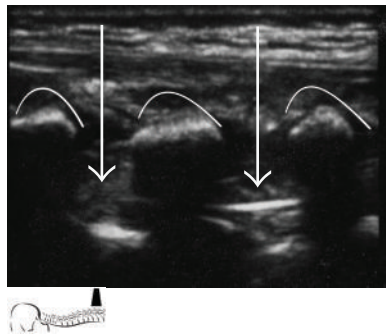


Figure 4: Longitudinal view at the thoracic spine level, viewing the advancement of the caudal epidural catheter. Curved lines show spinous processes. Arrows show epidural catheter in between spinous processes.

of these occur with the perioperative use of epidural block [74, 76]. The incidence of major complications (permanent harm including death) of epidural and combined spinal-epidural anesthesia were at least twice as high as those of spinal and caudal blocks, as reported by Cook and colleagues. This study also found that the incidence of epidural catheter-related serious morbidity and mortality was higher when blocks were placed in the perioperative setting, as opposed to catheter placement in obstetric and pediatric populations, when inserted for chronic pain management, or when placed by non-anesthetists [77]. While prognosis is infrequently reported, retrospective reviews report full recovery in 61–75% of patients, epidural hematoma accounting for two-thirds of residual neurological deficits [77, 78]. Serious complications, if not recognized and treated at an early stage, may thus result in permanent loss of function [74, 79]. With regards to the timing of catheter placement, there is still substantial controversy: while many anesthesia providers believe that epidural catheters should be placed in awake or mildly sedated patients capable of providing feedback [80], Horlocker's retrospective review found no evidence of an increased risk for neural injury in anesthetized patients receiving epidural anesthetic [81]. Thoracic epidural placement, however, should never be attempted on an anesthetized patient. Having increasingly become

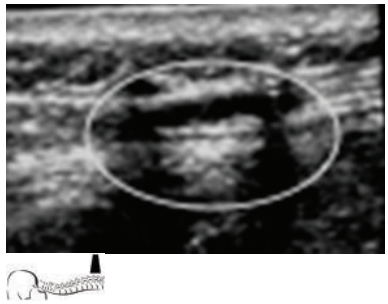


Figure 5: Longitudinal view at the lumbar spine. Visualization of the local anesthetic spread confirmed the position.

the focus of attention, and as a result of both meticulous adherence to sterile, atraumatic catheter insertion technique and management, as well as careful risk-benefit assessment, major complications of epidural anesthesia are now rare, particularly those not involving infection or bleeding, and many resolving within 6 months [74]. The estimation of the incidence of all adverse outcomes, however, is often inaccurate.

Complications may occur early if related to traumatic catheter insertion, or later in the operative-postoperative course if caused by catheter-related spinal space-occupying lesions such as epidural hematoma or abscess formation, and are infrequent among the general population. Although its incidence is lower than when associated with spinal anesthesia [80], transient neurological injury has been found to account for the majority of short-term epidural catheter related complications (1 in 6,700) in a meta-analysis by Ruppen and colleagues, followed by deep epidural infections (1 in 145,000), epidural hematoma (1 in 150,000–168,000), and persistent neurological injury (1 in 257,000) in women receiving epidural catheter for childbirth [82, 83]. Spinal epidural hematoma, however, has been recently suggested to occur in a rate as high as 1 in 3,600 in female patients undergoing knee arthroplasty [74, 84, 85]. These findings were consistent with those previously reported in the ASA Closed Claims Project database analysis by Lee et al; however, limitations of that study design and database do not allow risk quantification specific to regional anesthetic techniques or populations [86].

Adverse events may result from direct mechanical injury or adverse physiological responses. Neurological complications resulting from accidental penetration of the dura are similar to those that occur with spinal anesthesia. Inadvertent dural puncture and postdural puncture headache, direct neural injury, total spinal anesthesia, and subdural block have been commonly reported. The incidence of inadvertent dural puncture ranges between 0.19–0.5% of epidural catheter placements. Postdural puncture headache (PDPH), described as a positional, bilateral frontal-occipital, nonthrobbing pain, may develop in as much as 75% of patients [87–89]. PDPH is thought to develop as a result of persistent transdural leakage of cerebrospinal fluid (CSF) at a rate that is faster than that of CSF production. The subsequently decreasing CSF volume and pressure causes traction on the meninges and intracranial vessels, which refer pain to the frontal-occipital region, often extending to the neck and shoulders, more pronounced in the upright position. Available measures of prevention besides conservative measures are immediate intrathecal catheter placement, prophylactic epidural blood patch, epidural or intrathecal administration of saline, and epidural administration of morphine [90]. Direct neural injury has a reported incidence of 0.006% [82], and has been associated with paresthesias during needle placement and pain on injection [80]. Total spinal anesthesia may occur if the solution used for epidural anesthesia is inadvertently administered into the intrathecal space in large volumes. Symptoms are of a rapidly arising subarachnoid block, potentially resulting in cardiovascular collapse and apnea requiring prompt resuscitation. Provided that immediate, skilled resuscitative efforts are made, complete recovery should be expected [91]. While clinically not always distinguishable from epidural blocks, the incidence of clinically recognized subdural block was found to be 0.024% in a prospective study [92]. A subdural block may present as high sensory block, often with sparing of motor and sympathetic fibers, is slow in onset, and the blockade is disproportionately extensive for the volume of anesthetic injected. Clinical signs and symptoms may be mistaken for accidental intrathecal injection, migration of epidural catheter, or an asymmetrical, patchy or inadequate epidural block. Subdural placement is thought to occur independently of the operator's expertise. Although there are no established risk factors, recent lumbar puncture and rotation of the needle may predispose to subdural injection [93].

Hemorrhagic complications are serious adverse outcomes that may arise from neuraxial anesthesia. Epidural hematoma is a rare, but potentially devastating, complication that requires emergency decompression in case of clinical deterioration. It is rarely attributed to an arterial source, and can develop spontaneously [94, 95]. While paralysis may occur even after hematoma evacuation, it is still not precisely understood why several of the spinal epidural hematomas associated with concurrent anticoagulant use involving less blood than the volume injected when performing a therapeutic blood patch [85]. Clinically significant bleeding is more likely with congenital or acquired coagulation abnormalities, thrombocytopenia, vascular anomalies or anatomical abnormalities, advanced age and female gender, repetitive attempts at catheter insertion, and traumatic block placement [74, 96–98]. The risk is reported to increase 15-fold when there is a concomitant use of anticoagulants, and appropriate precautions are not taken [85]. Appropriate timing of anticoagulant administration is important in decreasing the risk of bleeding [99]. The commonest presenting symptoms of spinal epidural hematoma are new back pain, radicular pain, and progressive lower extremity weakness. Symptoms rarely present immediately after surgery, but may develop while the catheter is still in place. These symptoms can occur 15 hours to 3 days after catheter insertion [78, 98]. The diagnostic investigation of choice is MRI. A delay in diagnostic imaging may lead to devastating outcomes, and is a common error, as manifesting neurological symptoms and back pain may be attributed to the use of epidural

infusion and a prolonged effect of local anesthetic, and to musculoskeletal origin [78, 100]. Cauda equina syndrome due to hematoma formation, a rare complication with a reported incidence of 2.7/100,000 epidural blocks, was found to result in permanent deficit in more than two-third of the cases [74]. Classic manifestation is low back pain, altered proprioception and decreased sensation to pinprick and temperature in the lumbar and sacral nerve distribution, voiding and defecation disturbances, and progressive loss of muscle strength. Outcomes are primarily function of interval to hematoma evacuation and the severity of the neurological deficit, and are favorable if decompression is performed within 8 hours of the development of symptoms [98].

Epidural catheter related infections are rare complications both in adult and in pediatric patients. A retrospective database analysis by Sethna et al. found an expected incidence ranging between 3–13/10,000 catheters in children [101]. Epidural abscess and meningitis has been reported to occur in 1 : 1000 and 1 : 50,000 catheter placements, respectively [74]. Although epidural catheters are placed under aseptic conditions, needle or catheter contamination does occur even during aseptic puncture and sterile handling of devices [102]. Of patient risk factors, skin colonization at the puncture site and bacterial migration along the catheter is proposed to be the most likely route of infection; however, immunosuppression [74, 103], diabetes mellitus [104], chronic renal failure, steroid administration, cancer, herpes zoster, rheumatoid arthritis [105], systemic or local sepsis, and prolonged infusion duration are also identifiable risk factors. The rate of skin colonization at puncture sites is reported to be higher in children than in adults, with an overall incidence as high as 35% [101]. The incidence of infection increases after three days [106]. The classic presentation signs and symptoms are severe midline back pain, fever, and leukocytosis, with or without neurological symptoms (worsening lower limb weakness and paraplegia, incontinence, irradiating pain, nuchal rigidity, and headache). Symptoms commonly appear after removal of the epidural catheter [78]. Neurological deficits have been found to be persistent in more than 50% of patients developing epidural abscess [105]. Barrier precautions, skin disinfection [107], as well as the use of closed epidural system, and patient-controlled epidural analgesia [101] have been suggested as ways to decrease the incidence of epidural catheter-associated infections. Frequent syringe changes, on the other hand, may be associated with a higher rate of epidural infections [108]. Frequently implicated infecting organisms are Methicillin-resistant Staphylococcus aureus (MRSA), Staphylococcus aureus, and Coagulase-negative Staphylococcus [101, 109]. Outcomes are favorable when diagnosed and treated promptly. Adhesive arachnoiditis, presenting in various forms, is a sterile inflammatory response to accidental subarachnoid injection of local anesthetics, preservatives, detergents, or antiseptics [110–112], and has also resulted from traumatic puncture or epidural abscess. Medical literature suggests an extremely low incidence [113, 114].

Complications of epidural anesthesia are rare events that may result in detrimental sequelae. Strict adherence to prophylactic measures and treatment without delay is essential to further lower the incidence of adverse outcomes.

9. Epidural Anesthesia and Thromboprophylaxis

Some controversy exists with regards to reduced coagulation and neuraxial anesthesia and challenges are emerging as new agents are introduced into clinical practice. Spinal epidural hematoma, although still considered to be a rare complication occurring at a previously reported rate of less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics in patients with normal coagulation status, is now suggested to occur in a rate as high as 1 in 3,000 in some patient populations [84, 85]. Patients receiving antithrombotic or antiplatelet therapies are more at risk for this potentially dramatic adverse event, in particular after invasive procedures [98]. In the United States, the estimated incidence of spinal epidural hematoma with concurrent administration of antithrombotic drugs (low molecular weight heparins) is 1 : 40,800 for spinal anesthesia, 1 : 6,600 for single-shot epidural anesthesia, and 1 : 3,100 for continuous epidural anesthesia [85]. Risk factors for epidural bleeding were established as coagulation disorders, antithrombotic or fibrinolytic therapy, or the use of any agents interfering with coagulation, female gender, age, difficult vertebral or spinal cord anatomy, difficult or traumatic catheter insertion, and lack of guidelines [96, 98, 115, 116]. Catheter removal carries nearly the same risk as insertion [98]. Appropriate time intervals between the administration of anticoagulants, neuraxial block placement, and catheter removal are crucial in the prevention of hematoma formation [117, 118].

The American Society of Regional Anesthesia and Pain Medicine (ASRA), and more recently, the European Society of Anaesthesiology (ESA) published their consensus statements on neuraxial anesthesia and the use of antithrombotic and thrombolytic agents [99, 119]. While providing guidelines in clinical decision making, and having the aim of minimizing hemorrhagic complications, these recommendations do not guarantee a specific outcome, and allow of variations based on the judgment of the anesthesiologist. The guidelines of the American Society of Regional Anesthesia and Pain Medicine and the European Society of Anaesthesiology are based on previously published national recommendations, hematology, pharmacology, and risk factors for surgical bleeding, and incorporate updated information since the time of their publication.

With regards to epidural catheter placement, the ASRA recommends that patients receiving thrombolytic therapy be queried and their medical records reviewed for a recent history of lumbar puncture or neuraxial analgesia. Neuraxial anesthesia should be avoided, or, if received concurrently with the fibrinolytic/thrombolytic therapy, close neurological monitoring should be continued along with the administration of neuraxial solutions that minimize sensory and motor block. There is no definitive recommendation for epidural catheter removal in patients receiving fibrinolytic and thrombolytic therapy. Thrombolytics, if scheduled,

should be avoided for 10 days after puncture of noncompressible vessels [99].

Patients receiving unfractionated heparin (UFH) thrice a day, if recommended by recent thromboprophylaxis guidelines, may be at an increased risk of surgical-related bleeding. The ASRA recommends that the patient's—potentially simultaneous—anticoagulant and antiplatelet medication be daily reviewed. There is no contraindication to epidural blockade in patients receiving subcutaneous UFH prophylaxis at daily doses of 2×5000 U. The risk of bleeding may be increased in debilitated patients receiving prolonged therapy, and may be decreased by delaying the heparin injection until after neuraxial block placement. The safety of central neural block in patients receiving subcutaneous UFH in a dosing regimen of more than 10,000 U daily has not been established, and an increased risk of a spinal epidural hematoma has also not been elucidated. Patients receiving heparin for greater than 4 days should be assessed for heparin-induced thrombocytopenia (HIT). In patients with known coagulopathies, combining neuraxial techniques with intraoperative heparinization should be avoided however, this technique is acceptable in patients with no other coagulation disorders, if

(1) heparin administration is delayed for 1 hour after puncture,

(2) epidural catheters are removed 2 to 4 hours after the last heparin dose and the patient's coagulation status is assessed. the next heparin dose may be administered 1 hour after catheter removal,

(3) patient is closely monitored for early signs of neurologic dysfunction while receiving neuraxial solutions that minimize sensory and motor block postoperatively.

Per the ASRA guidelines, in contrast with the ESA recommendations that suggest considering postponement of the procedure, difficult or traumatic block placement should not necessarily prompt postponing surgery; however, the potential benefits should be carefully weighed against all potentially detrimental outcomes in each individual. With regards to the full anticoagulation of patients undergoing cardiac surgery, the ASRA finds insufficient evidence available to determine an increased risk of neuraxial hematoma. Close postoperative monitoring of neurologic function, as well as administration of neuraxial solutions that minimize sensory and motor block to facilitate detection of signs and symptoms of cord compression, is however suggested [99, 119].

Patients on low molecular weight heparin (LMWH) anticoagulation have not been found to be at an increased risk of bleeding in high-risk groups, contrasting with patients receiving UFH-thromboprophylaxis. Also, compared to UFH, LMWH-therapy has been associated with a significant decrease in the risk of HIT, as demonstrated by Warkentin and colleagues [120]; nonetheless, LMWHs are contraindicated in such condition due to the high level of cross-reactivity. To avoid an elevated risk of bleeding complications, an interval of 10 to 12 hours between preoperative LMWH administration at prophylactic doses and needle placement or catheter removal is recommended. Administration of LMWH the night before surgery does not thus interfere with epidural block placement on the day of surgery. In patients on therapeutic doses of LMWH, catheter placement should be delayed for a minimum of 24 hours after the last dose. Patients undergoing general surgery and receiving LMWH 2 hours prior to surgery are not ideal candidates for a neuraxial blockade, and are thus recommended against neuraxial techniques. Patients receiving postoperative LMWH thromboprophylaxis may safely be administered both single-dose and continuous catheter techniques. With regards to management, timing of the first postoperative dose, dosing schedule, and total daily dose are authoritative. Concerning the management of patients receiving LMWH, the ASRA recommends against the routine monitoring of anti-Xa level and concurrent administration of medication affecting hemostasis, regardless of LMWH dosing regimen [99, 119].

The management of patients receiving perioperative oral anticoagulants is still controversial. In the United States, much like in Europe, therapeutic oral anticoagulation is considered as a contraindication to central neuraxial blockade. As opposed to Europe, however, perioperative thromboprophylaxis is still possible in the United States. According to the recommendation of the American Society of Regional Anesthesia and Pain Medicine, warfarin therapy must be stopped ideally 4-5 days before the scheduled procedure, and the INR checked before neuraxial block placement. In patients receiving an initial preoperative dose of warfarin, INR should be measured before needle puncture if the administration of the first dose exceeded 24 hours, or if a second dose of such anticoagulant has been administered. In patients at risk for an enhanced response to oral anticoagulants, a reduced dose of drug should be administered. In patients receiving low-dose warfarin during epidural analgesia, INR should be monitored daily. Epidural catheters should be removed when the INR is less than 1.5. If the INR is greater than 1.5 but less than 3, indwelling epidural catheters should be done with caution. The ASRA recommends against concurrent use of agents, such as UFH, LMWH, or platelet aggregation inhibitors, that influence other components of the clotting system, as these, without affecting the INR, may increase the risk of bleeding. Medical records should be reviewed for such agents. Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on oral anticoagulants, and should be continued for at least 24 hours after catheter removal, until the INR returns to the desired prophylactic range. In patients with INR greater than 3, the American Society of Regional Anesthesia and Pain Medicine recommends that the warfarin be held or reduced, without making a definitive recommendation regarding the management to facilitate catheter removal in these patients [99, 119].

Platelet aggregation inhibitors, such as acetylsalicylic acid, thienopyridines (clopidogrel, ticlopidine, and prasugrel), glycoprotein (GP) IIb/IIIa antagonists (eptifibatide, tirofiban, and abciximab), the novel ADP P2Y12 receptor

antagonist ticagrelor, and the selective phosphodiesterase IIIA inhibitor cilostazol, have diverse effects on platelet function. No wholly accepted test exists to guide antiplatelet therapy. It is therefore critical to perform a careful preoperative risk assessment to identify factors that might potentially contribute to bleeding. Although administration of nonsteroidal anti-inflammatory drugs (including aspirin) does not appear to significantly increase the incidence of hematoma formation, concurrent administration of LMWH, UFH, or oral anticoagulants resulted in a higher rate of complications in both surgical and medical patients, their use along with NSAIDs, including aspirin, is therefore not recommended. Cyclooxygenase-2 inhibitors have minimal inhibitory effect on platelet aggregation, and should be considered in patients requiring anti-inflammatory therapy in the presence of anticoagulation. The actual incidence of spinal epidural hematoma related to thienopyridines and GP IIb/IIIa inhibitors is not known. Management should be based on labeling precautions and the experience of professionals involved in the clinical care of the patient. However, as it has been suggested by recent guidelines, ticlopidine and clopidogrel therapy should be discontinued 14 and 7days prior to neuraxial block, respectively. If needle puncture is indicated between 5 and 7 days of discontinuation of clopidogrel, normalization of platelet function should be documented. GP IIb/IIIa antagonists exert a dose-dependent effect on platelet aggregation. After the last administered dose, the time to normal aggregation is 4 to 8 hours for eptifibatide and tirofiban, and 24 to 48 hours for abciximab. Neuraxial blockade should be avoided until normal platelet function is achieved. Should a patient, despite the contraindication, be administered GP IIb/IIIa inhibitors within 4 weeks of surgery, careful neurological monitoring should be performed [99, 119].

Both the ASRA and the ESA guidelines recommend against the mandatory discontinuation of herbal agents (most commonly: garlic, Echinacea, Gingko biloba, ginseng, aloe vera, and ephedra of dwarf palm), neither should neuraxial techniques be avoided, as there is insufficient evidence that these, by themselves, significantly increase the risk for spinal hematoma formation. There is insufficient evidence to conclude that thrombin inhibitors, such as lepirudin, desirudin, bivalirudin, or argatroban, are safer to use in patients receiving spinal or epidural anesthesia; performance of these techniques in the presence of these agents is thus not recommended. Until sufficient evidence is available, neuraxial techniques in patients receiving fondaparinux should only be performed if single needle pass, atraumatic block placement, and avoidance of indwelling catheters are feasible, or a different method of prophylaxis should be considered [99, 119].

10. Summary

Epidural and caudal anesthesia is a versatile neuraxial anesthetic technique with an expanding area of indication. It can be used in the perioperative setting as the sole anesthetic, or in combination with general or spinal anesthesia. Its potential to decrease postoperative complication rate by its beneficial physiological effects has been clearly demonstrated in several studies. The absolute contraindications to its use have traditionally been well defined. Despite its rare, but potentially devastating complications, neuraxial anesthesia is considered to be safe. Performing such procedures in the presence of anticoagulants is however controversial. With patients presenting with medical conditions that predispose to clinically significant bleeding and an increased number of patients taking various anticoagulants, there is greater concern for an increased incidence of epidural hematomas. The key to maximizing the advantages while minimizing the disadvantages of epidural and caudal anesthesia is to become familiar with the anatomical, physiological, pharmacological, and technical aspects of block placement. The review and advances discussed here allow both adult and pediatric populations a form of care that is often considered indispensable.

Conflict of Interests

The authors declare no conflict of interest.

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Research Article

Lasting Developmental Effects of Neonatal Fentanyl Exposure in Preweanling Rats

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The present study aimed to determine whether neonatal treatment with fentanyl has lasting effects on stressed developing brain. Six-day-old rats were assigned to one of three groups (10 males/group): (1) fentanyl (incision+fentanyl), (2) saline (incision+0.9% saline), and (3) unoperated (unoperated sham). Pups with a plantar paw incision received repetitive subcutaneous injections of fentanyl or vehicle through postnatal days (PNDs) 6 to 8. A nonoperated sham group served as nonstressed control. Studies included assessment of development from PND 6 to PND 21 (growth indices and behavioral testing). Fentanyl administered twice daily for three days after surgical incision had no impact on early growth and development, as measured on PND 9, but showed a lasting impact on later growth, enhanced behavioral development, and lower anxiety, as measured through PNDs 10–21. While this does not completely support a benefit from such treatment, our findings may contribute to support the neonatal use of fentanyl, when indicated, even in premature newborns.

1. Introduction

Fentanyl, a potent μ-opioid agonist, is a synthetic drug that has been widely used for pain management [1, 2] and as a general anesthetic for surgical procedures in pediatrics [3–5], namely in surgical neonatal intensive care units. In a previous study, fentanyl was identified as being within the 5 medications with the highest exposure rates in a pediatric intensive care unit [2].

Fentanyl is an appropriate medication that has rarely been linked to significant adverse effects on the central nervous system (CNS) or other systems, with proper monitoring [6]. However, concerning fentanyl use in pediatric critical care population, this is one of the many medications which are not properly tested for pediatric use [2].

It is well documented in clinics [7] and in experimental work [8, 9] that gradual increases of standard doses of fentanyl [7], illicit fentanyl abuse [10], drug interactions [11], or individual susceptibility may lead to severe neurotoxicity and death [10]. Animal studies have also reported adverse effects. Kofke et al. [8] evaluated the neuropathological effects of fentanyl in the brain and showed that it produces limbic system brain damage in rats and that the damage occurs over a broad range of doses. In another study, regarding fentanyl effects in rat brain ischemia, Kofke et al. [9] showed that fentanyl, in both high and low doses, can exacerbate incomplete forebrain ischemia in rats. Additionally, it is well known from the literature that large-dose opioids in rats produce hippocampal hypermetabolism, epileptiform activity, and neuropathologic lesions [12]. These doses in rats are comparable in potency to a large-dose regimen that might be used in humans [12].

The neonatal period is a time of rapid growth and development of the brain, and perturbations to the normal series of developmental events during this time can lead to adverse functional consequences that manifest later in life. Lack of data on the impact of fentanyl's repeated use during this vulnerable period of brain development raises special concern, as is well known that the developing CNS of the neonate is recognized as very sensitive to most anesthetics, in animal research studies.

Our study's primary goal was to further investigate the possibility that repeated administration of this opiate,

in a window of developmental susceptibility, could have lasting impact on neurodevelopment. It was hypothesized that neonate rat pups, exposed to both postoperative and repetitive parenteral fentanyl, would show growth restriction and abnormal neurobehavioral functions. As postnatal growth and development are sensitive measures of central neurotoxicity and brain maturation, we assessed growth and development in the infant male rat after exposing a neonate rat model of postoperative pain to repeated administration of subcutaneous fentanyl during early postnatal life.

2. Materials and Methods

2.1. Ethics Statement. Animal protocols for this study were written in strict accordance with the recommendations in the European legislation and meet the standards of the National Institutes of Health, as set forth in the Guide for the Care and Use of Laboratory Animals [13]. These protocols were approved in advance by the Ethics Committee of the Faculty of Medicine of the University of Coimbra.

2.2. Subjects. For this experiment, the progeny (~12 per litter) of 9 multiparous Wistar rats (Charles River Laboratories, L'Arbresle Cedex, France) was used. Litters (3 per group) were assigned to the following groups: (1) fentanyl (incision + fentanyl, $n = 10$ males), (2) saline (incision + 0.9% saline control, $n = 10$ males), and (3) unoperated (unoperated sham control, $n = 10$ males). Lactating dams were maintained with their litters for 21 days, housed in polypropylene cages in a temperature-controlled environment (20–22°C) with a 12-hour light dark cycle and *ad libitum* access to water and pelleted rat chow.

2.3. Procedures. Figure 1 summarizes study tests and procedures timeframe.

Each litter was transferred together with the dam to a clean cage with fresh bedding on postnatal day 6 (PND 6). After baseline testing and weighing, rat pups received subcutaneously in the neck either the first dose of fentanyl (B|Braun Medical Lda. Barcarena, Portugal), 25 μg per kg body weight (0.1 mL per g weight of solution of fentanyl diluted to 0.25 μg/mL in 0.9% saline solution), or 0.9% saline solution, 0.1 mL per g body weight; this was immediately followed by creation of a deep plantar paw incision, as previously described [14]. Briefly, the plantar aspect of the right hindpaw was prepared in a sterile manner with a 10% povidone-iodine solution. Using a no. 11 surgical blade we performed a midline incision from the heel to the base of the toes under local anesthetic (ethyl chloride spray). The underlying flexor muscle was elevated and incised longitudinally. The skin incision was closed with nylon sutures (6/0). Equivalent subcutaneous doses of fentanyl, or 0.9% saline, were repeatedly given 8–12 hours apart from the first dose for three consecutive days, with a total of 6 doses (average total dose per animal: 135 μg/kg weight).

Any incidence of adverse effects (namely, respiratory depression) was recorded. Control sham animals underwent local anesthesia with skin preparation, but no incision.

On PND 9, at least eight hours after the last injection, assessment of growth and development was performed. Growth and physical development, such as teething, number of eyes open, was monitored daily through PND 6–21. The number of eyes open was scored; the observations for each item were coded as 0 (both eyes closed), 1 (1 eye open), and 2 (both eyes open).

Rats were assessed for motor and cognitive performance between postnatal days 18 and 21 through behavioral studies in the open-field, elevated plus maze, wire hanging maneuver, novel object recognition test of short-term memory and accelerating rotarod. Between test phases and animals, apparatus, and objects were thoroughly cleansed with 70% ethanol. Behavior experiments were recorded using a camera mounted above the testing apparatus and data were reviewed without knowledge of each rats' group.

Although every litter contained pups of both sexes, growth and behavioral results reported here include data collected only from males (10 per group).

Anesthetized rats were killed on PND 21.

2.4. Early Outcome Assessment (Acute Effects of Fentanyl Exposure)

2.4.1. Righting Reflex. This test took place on PND 6 (baseline information) and PND 9. It consists in the time in seconds required for a pup placed on its back to right itself (all 4 paws flat on the surface). The amount of time required for the pup to right itself on all 4 limbs was measured using a stopwatch, with a maximum of 30 seconds. This test, performed as previously described, assesses subcortical maturation [15].

2.4.2. Negative Geotaxis. This test took place on PND 6 (baseline information) and PND 9. It consists on the time in seconds required for a pup placed head down on a 25° incline to turn 180° and begin crawling up the slope. The cutoff time was 60 sec. The time spent for a turn of 180° upward was recorded using a stopwatch. If unsuccessful, each pup was given up to 3 trials. Each failed trial was recorded as value 61. Negative geotaxis, performed as previously described, is believed to test reflex development, motor skills and vestibular labyrinth, and cerebellar integration [15].

2.4.3. Locomotor Activity. This test took place on PND 6 (baseline information) and on PND 9, at least eight hours after the last fentanyl injection. Rat pups were individually placed in a circular hole (6 cm diameter/2 cm height), and locomotor activity was scored during 3 min as follows: 1: immobility and head down; 2: raises head up; 3: forepaws over borders; 4: climbs the borders.

2.5. Later Outcomes Assessment

2.5.1. Behavior in the Open-Field Arena. This test took place on PND 18 and was used with the aim of assessing locomotor activity. The test was performed as previously described [16], with slight modifications. Briefly, rats were placed

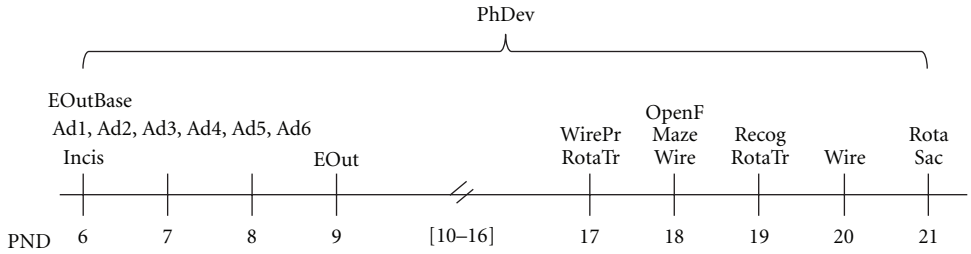

Figure 1: Study tests and procedures timeframe. PhDev: growth and physical development assessment (PND 6–21); EoutBase: baseline testing (righting reflex, negative geotaxis, and locomotor activity) (PND 6); EOut: early outcome assessment (PND 9); Adm: administration procedure, according to group (administration of fentanyl, administration of 0.9% saline solution, or manipulation) (PND 6–8); Incis: incision or manipulation, according to group (PND 6); WirePr: wire hanging maneuver pretest (PND 17); Wire: wire hanging maneuver test (PND 18 + 20); RotaTr: accelerating rotarod training (pretest) (PND 17 + 19); Rota: accelerating rotarod test (PND 21); OpenF: behavior in open-field arena (PND 18); Maze: elevated plus maze test (PND 18); Recog: novel object recognition test of short-term memory (PND 19); Sac: sacrifice (PND 21).

Table 1: Early outcomes.

Measures	Groups			P
	Fentanyl	Saline	Unoperated	
Weight, mean (±SD), g:				
PND 6	12 (±1)	11 (±2)	11 (±2)	>.05
PND 9	18 (±2)	16 (±3)	16 (±2)	>.05
Righting latency, median (IQR), sec:				
PND 6	2 (1-2)	2 (2-2)	2 (2-2)	>.05
PND 9	1 (1–1.3)	1 (1-2)	1 (1–1.3)	>.05
Geotactic latency, median (IQR), sec:				
PND 6	183 (152–183)	29 (20–145)	34 (12–48)	<.05*
PND 9	19 (13–27)	23 (11–44)	22 (12–48)	>.05
Locomotor activity score, median (IQR):				
PND 6	1 (1-2)	2 (1–2.3)	1 (1-2)	>.05
PND 9	2 (1.8–3)	3 (2-3)	3 (2.8–3)	>.05

PND: postnatal day; IQR: interquartile range; P: significance for independent samples.
Locomotor activity scores: 1: immobility and head down; 2: raises head up; 3: forepaws over borders; 4: climbs the borders.
Fentanyl versus saline ($P = 0.005$) and fentanil versus unoperated ($P = 0.007$), both $^*P < .05$.

Table 2: Later Outcomes.

Measures	Groups			P
	Fentanyl	Saline	Unoperated	
Weight PND 21, mean (±SD), g	43 (±3)*§	36 (±6)*	36 (±4)§	*F versus S =.001; §F versus Un <.001;
Eye opening score, PND 14, median (IQR)	2 (1-2)	1 (0–2)	0 (0–2)	NS
Open field, line crossing, mean (±SD)	68 (±23)	62 (±24)	48 (±27)	NS
Latency time wire, median (IQR), sec:				
PND 18	127 (20–183)*	183 (183-183)*	183 (162–183)	*F versus S =0.035
PND 20	25 (15–98)	75 (12–183)	76 (9–183)	NS
Recognition index, mean (±SD)	0.8 (±0.3)*	0.6 ± (0.3)*§	0.8 (±0.2)§	*F versus S =0.045; §Un versus S =0.025
Time (%) spent open arms, median (IQR)	18 (17–32)*§	7 (3–17)*	10 (7–16)§	*F versus S =0.034; §F versus Un =0.045
Best latency time fall rod, mean (±SD), sec	173 (±24)*§	123 (±73)*	128 (±24)§	*F versus S =0.022; §F versus Un =0.04

PND: postnatal day; IQR: interquartile range; P: significance for independent samples: NS: nonsignificant; F: Fentanyl; S: Saline; Un: Unoperated.

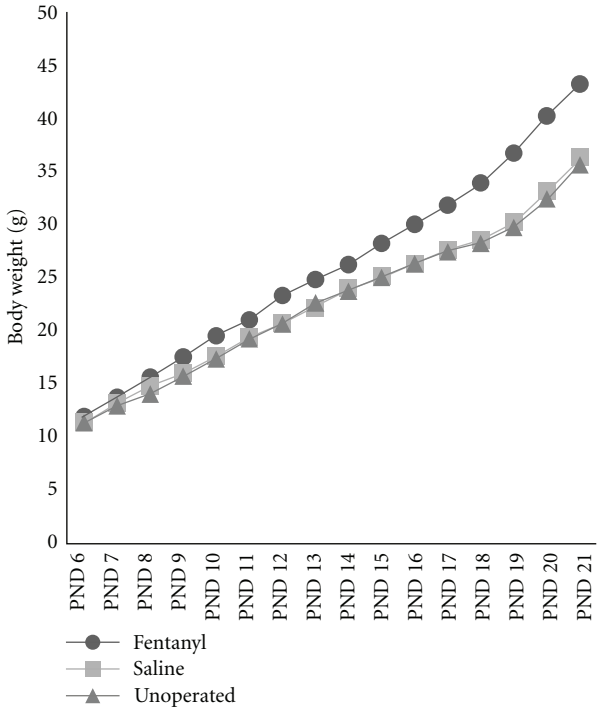

Figure 2: Growth curves representing mean body weight (g) through postnatal days (PNDs) 6–21. Fentanyl group showed enhanced weight gain compared to controls, after PND 12.

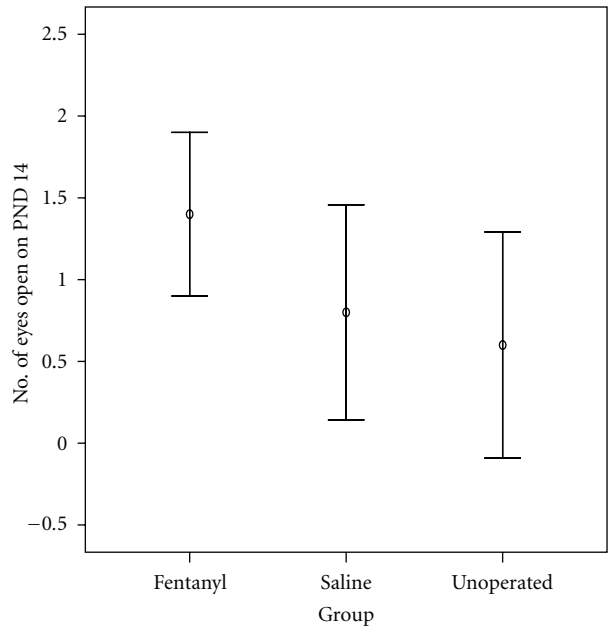

Figure 3: Number of eyes open on postnatal day (PND) 14. The number of eyes open was higher in the fentanyl group than in both the saline and unoperated groups ($P > 0.05$). Values represent mean and 95% confidence interval for mean.

individually in a transparent box (60 × 40 × 25 cm) with the floor divided into twelve identical areas in a dim room. Line crossings (with all four paws placed into an adjacent area) were recorded in a 5 min period.

In addition, the presence/absence of exploratory behaviors such as rearing (standing on hind legs), grooming (using paws or tongue to clean/scratch body), and corner-facing (standing or sitting with the face directed toward the corner of the box) was recorded.

2.5.2. Anxiety-Like Behavior. This test was performed on PND 18 to assess anxiety-like behavior as previously described [17], with slight modifications. Rats were placed in an elevated plus maze which consisted of a cross-shaped platform (height: 49.5 cm) with four arms (width: 10 cm; length: 110.5 cm), two of which were enclosed by walls 30.5 cm high. Each rat was placed into the central area facing an open arm and allowed to explore for 5 min. The percentage of time spent on the open arms and number of entries into the open arms were used as measures of anxiety-like behavior.

2.5.3. Wire Hanging Maneuver. Wire hanging maneuver assesses neuromuscular and locomotor development [16]. This test was conducted over 3 days (maneuvers performed on PNDs 18 and 20). Rats were allowed 1 pretest on PND 17. Normal pups suspended by the forelimbs from a horizontal wire supported between two platforms (15 cm above the table top) tend to support themselves with their hind limbs, preventing falling and aiding in progression along the wire to reach the platform [16]. A sponge at the base of the apparatus served as protection for the falling rats. Latency to reach one of the platforms from the wire was measured and recorded in seconds, with a cutoff time of 60 sec. Each unsuccessful trial was recorded as value 61, with a maximum of 3 trials allowed each day. Therefore, latency values may vary from 1 to 183 per test.

2.5.4. Novel Object Recognition Test of Short-Term Memory. This test, based on the natural tendency of rodents to investigate a novel object instead of a familiar one, was carried out as previously described [18]. On PND 19 each rat was allowed to move freely in an open-field box for 3 min, as habituation, followed by an exposition trial in which the rat was placed in the center of the box containing two identical objects (transparent white blocks) located in two adjacent corners. The cumulative time spent exploring each object was recorded during a 5 min period. Exploration was defined as actively touching or directly facing the object. One hour later the rats were tested for memory using the same procedure, except that one of the familiar objects was replaced with a novel different looking object. The time of exploration of each object (t_n and t_f for novel and familiar objects, resp.) was recorded for determination of the recognition index (RI): $\text{RI} = t_n/(t_n + t_f)$.

2.5.5. Rotarod. This test was performed as previously described [15], with slight modifications, to examine potential effects of fentanyl exposure on motor balance and coordination, using the accelerating rotarod (Rota Rod LI 8200; Letica

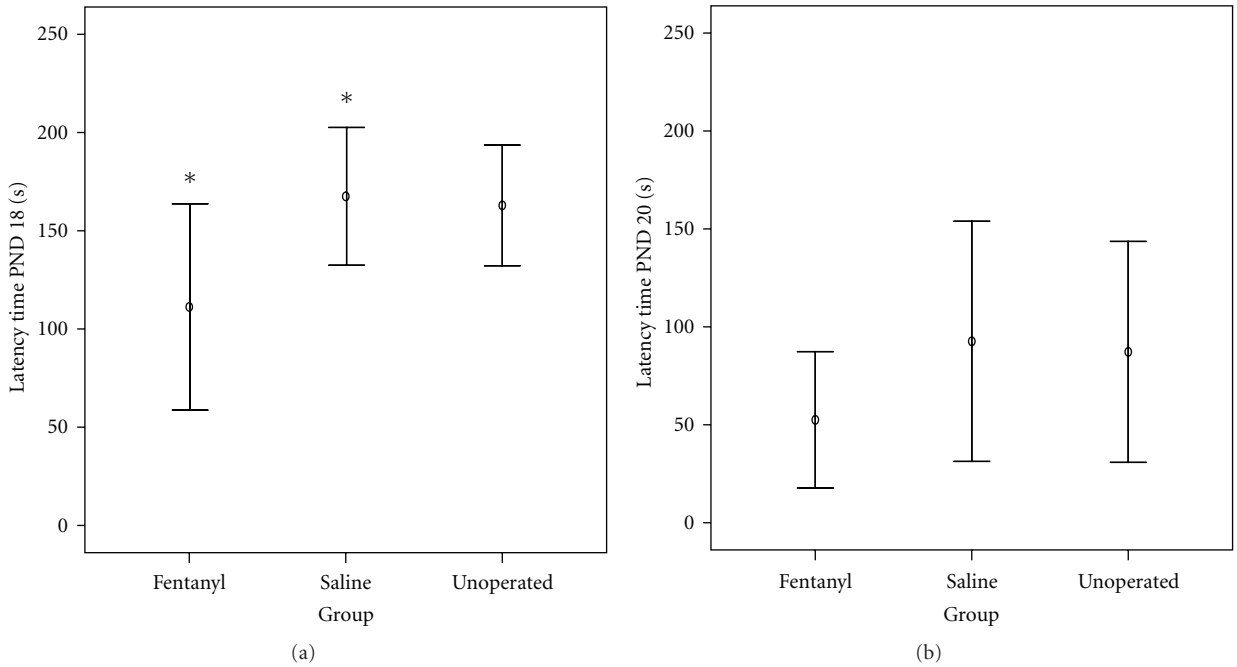

Figure 4: Latency times to complete the task of reaching the platform in the wire hanging maneuver on (a) postnatal day 18 and (b) postnatal day 20. Both on PND 18 and 20, rats in the fentanyl group were faster than controls, with statistical difference to the saline group ($^*P = 0.035$) on PND 18. Values represent mean and 95% confidence interval for mean.

SA Scientific Instruments). The rotarod test was conducted over 3 days and consisted of 2 pretests which took place on PND 17 and 19 and a test performed on PND 21. In the 2 pretests, the rats underwent habituation and training, by placement on the still rod to acclimate, followed by training on the moving rotarod, beginning at a constant speed of 5–10–20 revolutions per minute (rpm) on a schedule of three 5-minute trials. This training was repeated under the same protocol on PND 19.

On PND 21 the rats were tested using the accelerating rotarod: the apparatus was set to accelerate linearly from 4 to 40 rpm over 300 seconds. The sessions consisted of three 5-minute trials. The latency to fall from the rotarod during a 300 sec trial was recorded. Each animal was given 3 trials, and the best latency of three trials was calculated for each animal.

2.6. Statistics. Statistical analysis was performed using SPSS statistical software package (version 17, SPSS, Inc., Chicago, Il). Normality of distribution was determined using Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons were made using multigroup, one-way ANOVA to test for the significance of changes among the different groups, followed by the Least Significant Difference test to compare differences between groups. If the data were not normally distributed, the Kruskal-Wallis test (nonparametric ANOVA) was used, and, where differences were identified, pairwise comparisons were performed using Mann-Whitney U test with appropriate correction by Holm-Bonferroni method. All differences were considered significant at $P < 0.05$. Values are expressed as means ± standard deviation (±SD) or as median and interquartile range (IQR): 25th and 75th percentiles, mean and 95% confidence interval for the mean (95% Cl), or number (percentage), as appropriate.

3. Results

3.1. Early Outcomes. There were no deaths. All animals reached PND 9. Table 1 summarizes the most relevant outcomes.

Baseline characteristics of the groups were equivalent. No significant ($P > 0.05$) intergroup differences were found in the baseline (PND 6) body weight, locomotor activity score, and righting reflex latency. However, rats in the fentanyl group showed significantly longer baseline geotactic responses than saline ($P = 0.005$) and unoperated rats ($P = 0.007$).

During the early period of the experiment, from PND 6 to PND 9, all rats increased body weight in a steady manner, showing no delay in physical development.

When compared to baseline results, outcomes of the fentanyl, saline and unoperated groups, recorded on PND 9, showed an improvement in all parameters, such as weight gain, enhancement of locomotor activity score, and reduced postural reflex latencies.

Comparison of the PND 9 results between fentanyl group and the controls did not show significant differences ($P > 0.05$) on righting reflex latency, negative geotactic latency, or locomotor activity score (Table 1).

3.2. Later Outcomes. Table 2 summarizes the most relevant outcomes.

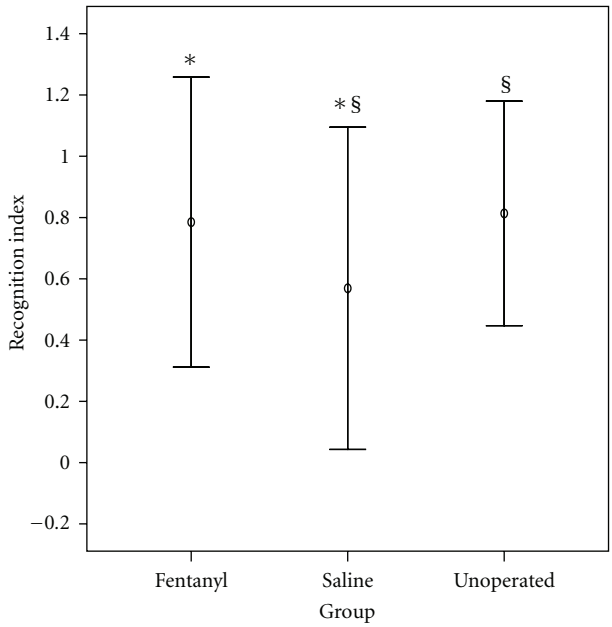

Figure 5: Object recognition test of short-term memory. Recognition index of novel object exploration is exploration time on new object/total exploration time (RI $= t_n/(t_n + t_f)$). The recognition index (RI) of a novel object in fentanyl group was not significantly different from that for the unoperated sham controls. However, a significant difference ($^*P = 0.045$) was evidenced between the fentanyl group compared to the saline group, showing better cognitive function for the first group. A difference was also seen between the controls: unoperated sham rats displayed significantly ($^{\S}P = 0.025$) better short-term memory compared to saline-treated rats. Values are mean ± SD.

3.2.1. Developmental and Growth Indices. As expected, all animals reached the defined endpoint (PND 21).

All rats maintained weight gain throughout the study; however, fentanyl-treated rats weighed significantly more than saline-treated and unoperated controls, from PND 12 to PND 21 (Figure 2). The mean weights (±SD) for fentanyl, saline, and unoperated rats on PND 21 were 43 (±3) g, 36 (±6) g, and 36 (±4) g, respectively. Significant differences between fentanyl versus saline ($P = 0.001$) and fentanyl versus unoperated rats ($P < 0.001$) were seen. There was no significant difference between the control groups ($P > 0.05$).

Eyes started to open from PND 14. The median number of eyes open (scored as 0 or 1 or 2 eyes open) on this day was higher in fentanyl (2) than in saline (1) and unoperated groups (0), although without statistical significance ($P > 0.05$) (Table 2 and Figure 3).

3.3. Behavior in the Open Field. There were no observable intergroup differences on locomotor activity and exploratory profile. Although there was a trend for an increased mean number of line crossings in the fentanyl group (mean number: 68), compared to the saline (mean number: 62) or the unoperated ones (mean number: 48), the differences between groups were not statistically significant ($P > 0.05$), as seen in Table 2. Additionally, all rats showed a similar exploratory behavior profile, characterized by immediate beginning of locomotor activity (latency up to 20 sec) following the placement of the animal in the central area of the open field apparatus; they also showed similar profiles in the type of exploratory activity periods (with rearing and grooming behaviors) and preference for the corners exploration over that of the central area.

3.3.1. Behavior during the Wire Hanging Maneuver. On PND 17 (habituation trial) all rats failed the task of platform reaching.

The success in reaching the platform differed among groups both in PND 18 and PND 20. On PND 18, 60% of the rats in the fentanyl group, 10% in the saline group, and 20% in the unoperated sham group successfully completed the task of reaching the platform; these differences were statistically significant (data not shown). Moreover, rats in the fentanyl group were faster than controls. The median latency time to complete the task in fentanyl group (127 sec) was not significantly different from that in the unoperated sham group (183 sec); however we found a significantly ($P = 0.035$) shorter median latency time in the fentanyl group (127 sec) when compared to the saline group (183 sec), as seen in Table 2 and Figure 4.

On PND 20, while 100% of the rats in the fentanyl group completed the task successfully, only 60% in the saline and 70% in the unoperated sham groups were successful (data not shown). Again, median latency time to reach the platform was shorter ($P > 0.05$) in the fentanyl rats (25 sec) compared to saline (75 sec) or unoperated ones (76 sec), as seen in Table 2 and Figure 4.

3.4. Effects of Neonatal Fentanyl Exposure on Novel Object Recognition Task of Short-Term Memory. Cognitive performance in an object recognition task of short-term memory, performed on PND 19, evidenced no adverse lasting impact in preweanling rats after neonatal exposure to six doses of fentanyl (average total dose per animal: 135 μg/kg weight).

The mean recognition index (RI) of a novel object in fentanyl group (0.79) was not significantly different ($P > 0.05$) from that for the unoperated sham controls (0.8). However, a significant difference ($P = 0.045$) was found between the fentanyl group (0.8) compared to the saline group (0.6), showing better cognitive function for the first group. A significant difference was also seen between the controls; unoperated sham rats displayed significant ($P = 0.025$) better short-term memory (0.8) compared to saline-treated rats (0.6), as seen in Table 2 and Figure 5.

3.5. Effects of Neonatal Fentanyl Exposure on Anxiety-Like Behavior. Fentanyl-treated rats were significantly less anxious than the saline-treated rats ($P = 0.035$) or the unoperated ones ($P = 0.043$) in the elevated plus maze, as indicated by the increase in the median percent time spent in the open arms by the fentanyl-treated rats (18%, IQR 17–32), compared to the saline (7%, IQR 3–17) or to the

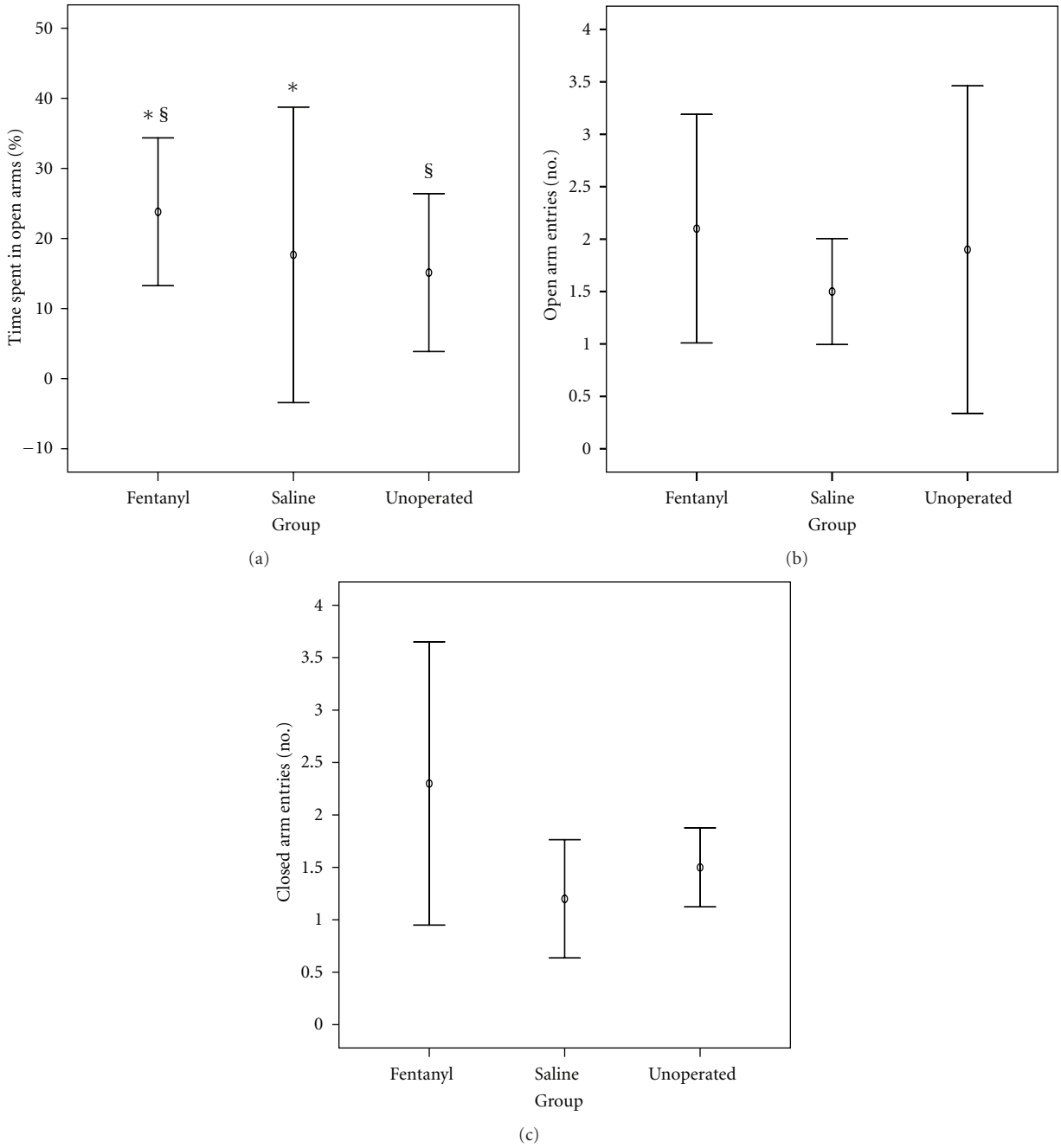

Figure 6: Performance in the elevated plus maze: (a) percent time in the open arms was significantly increased in fentanyl rats compared to saline rats ($^{*}P = 0.034$) or unoperated controls ($^{\S}P = 0.045$), suggesting that neonatal fentanyl exposure reduces some measures of anxiety-like behavior on the elevated plus maze; (b) and (c) represent the number of open arm and the number of closed arm entries, respectively, showing no significant differences between groups. Values represent mean and 95% confidence interval for mean.

unoperated sham controls (10%, IQR 7–16). However, there were no significant intergroup differences between open or closed arm entries (Table 2 and Figure 6).

3.6. Effects on the Accelerating Rotarod. The effects of fentanyl exposure on locomotor coordination and balance, as measured by the accelerating rotarod, are shown in Figure 7.

The best (largest) of the three fall latency values (mean ± SD) achieved per rat on PND 21 was used for data analysis. Mean latency to fall from the rod for fentanyl group was 173 sec, for saline group was 123 sec, and for unoperated sham rats was 128 sec. Rats treated with fentanyl spent significantly more time on rod, compared to rats treated with saline ($P = 0.022$) or unoperated sham rats ($P = 0.04$), as seen in Table 2 and Figure 7.

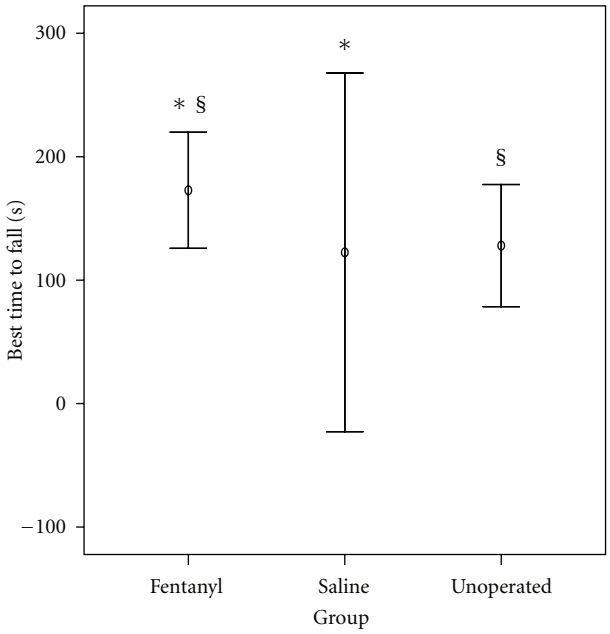

Figure 7: Best latency time to fall from the accelerating rotarod (speed 5–40 rpm). Rats administered fentanyl spent significantly more time on rod, compared to rats administered saline ($^*P = 0.022$) or unoperated sham rats ($^§P = 0.040$). Values are mean ± SD.

4. Discussion

The present study was designed to assess whether exposure to repetitive injections of fentanyl during brain development influences later physical and neurological outcomes. Using a neonatal postoperative pain model, this study demonstrates, for the first time, lasting effects on growth and behavior of rat pups that underwent repeated fentanyl exposure during early postnatal life, when tested as later pre-weanling rats. The results showed that repeated fentanyl exposure of an immature stressed animal significantly interferes with growth, cognitive function, behavioral reactivity to stress, neuromuscular and locomotor development, and balance and coordination. All these outcomes (Table 2) suggest a neurological impact with possible consequences, either positive or negative, later in life.

To examine the role of fentanyl administration in the development of behaviors that occur following repeated exposure to this medication, both in immature CNS and pain settings, we combined two strategies: the model for the study of neonatal neurodevelopment (6-day-old rat pup) was combined with the postincisional pain of Brennan paw incision [14], as a model for neonatal neurodevelopmental and postoperative pain. Translation of developmental ages from rodents to humans continues to be debated. A review paper by Vidair [19], which discusses the adequacy of the postnatal rat to serve as a model for neurodevelopment in the postnatal human, concludes that the rat in the third postnatal week is the neurodevelopmental equivalent of the newborn human and that the two species share numerous pathways of postnatal neurodevelopment. Therefore, our neonatal rat model roughly corresponds to a human premature. Brennan's model of incisional pain [14] was chosen since it simulates the usual clinical setting involving critically ill prematures in neonatal intensive care units.

Premature newborns typically present a broad range of comorbidities which make them a complex group to study, given the many variables, painful/stressful procedures, and pharmacologic exposures involved. Therefore, experimental studies using animals allow us to exclude potential confounding variables. In our study we used a model without comorbidities in a postoperative pain and stress setting. Such a preclinical model, which leads to pain-related events that mirror the symptoms observed in patients undergoing surgery [20], gives us the opportunity to explore whether repetitive fentanyl exposure, early in neonates subject to painful stimuli, leads to later neurodevelopmental anomalies. The postoperative pain model we used was previously described by Brennan and coworkers [14]. This rat model consists of an incision of the plantar paw skin, with damage of the underlying muscle, which results in localized mechanical hypersensitivity that lasts 3–5 days. Further research by Brennan's group showed release of excitatory amino acids, such as glutamate and aspartate, activation of dorsal horn cells, and central sensitization [21].

Concerning protocol design, the dose of fentanyl used in this study, although at first sight much higher than the neonatal human recommended dose, was chosen according to the species known metabolism to relate to that typically encountered in clinical settings reflecting antinociceptive ED50 values for PND6 rats [22]. We assessed behavioral problems in our neonatal stressed model using a validated set of tests usually chosen for drug toxicity screening.

Among major findings in the present study, we highlight the significant enhancement of weight gain in fentanyl group compared to controls, as summarized in Table 2. Neither fentanyl nor control conditions had significant effects on normal early pup weight gain. In contrast, there were significant group differences in rat weights on PND 21. Rats in the fentanyl group weighed more than those in the saline and unoperated sham groups, with the difference becoming significant around PND 12 and expanding as the pups aged until weaning. These outcomes suggest that the effects of the early postnatal exposure were subtle but, nonetheless, predisposed the pups to abnormal weight gain. Many hypotheses are possible to explain this finding, namely, metabolic derangements, behavior anomalies related to eating disorders, or decreased physical activity. An important issue that can be raised is whether the weight change is transitory or if it can continue into adulthood.

Other major findings in the present study were behavioral changes induced by administration of fentanyl in our model. Somewhat surprisingly, the results point towards an overall apparently "positive" effect on neurodevelopment, instead of the expected negative one. This "positive" impact was evidenced by an apparent lack of significant acute toxic effects on early development. Moreover, later, in infant rats who were treated with fentanyl, we found enhancement

of the recognition index of a novel object, lesser anxiety-like behavior, and better performances on the wire hanging maneuver and on the accelerating rotarod. Furthermore, there was a trend for sooner eye opening in this group, suggesting that the eye command center of CNS of rats in the fentanyl group ages earlier.

Interestingly, aversive stressful procedures performed in the current study, which should be associated with increased anxiety, seemed blunted by fentanyl treatment. In fact, fentanyl-treated rats were significantly less anxious than the saline and the unoperated rats in the elevated plus maze. This outcome is not clearly explained, but calmer subjects can probably better explain other outcomes found in this study, such as enhanced cognitive function, motor, and balance and coordination. It is possible that all these results are at least partially explained by a fentanyl impact on the development of central neuronal circuits, given the great plasticity of the CNS characteristic of the immature mammalian brain [23].

The effects of the impact of fentanyl on SNC are probably complex and multivariate with different possible mechanisms found in the literature, both potentially protective or detrimental, such as faster CNS myelination and enhanced neurogenesis by NeuroD activity level increase (a transcription factor essential for the development of the CNS) [24] eventually translating into enhanced performance or, on the other hand, cytotoxic lesion/blockade of the ventral hippocampus by N-methyl-D-aspartate (NMDA) receptor interference, manifesting as reduced anxiety [25]. It is well known from the literature that fentanyl modulates important cellular and molecular neuronal mechanisms, interfering not only in anatomically distributed neural network involved in generating states of anesthesia but also in mechanisms involved in hippocampus neurogenesis. In this setting, fentanyl may regulate the functions of the developing hippocampus, a region highly related to learning, memory, stress responses, and emotionality [25].

There is a growing body of evidence showing that drugs interfering in the SNC functions may cause pharmacologic neuroprotection or, on the opposite, detrimental effects, depending on the pathological conditions [19, 26–28]. Negative impact alerts are particularly alarming in the context of very ill preterm infants who usually present a multitude of physiological derangements and pathological pain conditions coupled with a very immature brain, therefore it is important to define safe indications and doses for the use of these drugs, such as fentanyl, in this stage.

In conclusion, the current study is the first to demonstrate that rat pups exposed to parenteral fentanyl in a painful context have lasting growth and behavioral changes. The study highlights behavioral changes that could potentially affect brain function either in a positive or negative manner. These results should serve as a basis for further research and should lead investigators to focus on specific pathways relevant to the changes in behavior we have shown. Our findings may contribute to support the neonatal use of fentanyl, when indicated, namely in postsurgical settings, even in premature newborns. However, extrapolating our data to a clinical setting must be done with caution, as with every animal study.

Authors' Contribution

Dora Catré is responsible for design, intellectual and scientific content, and writing of the paper. Maria Francelina Lopes supervised all phases of the experimental study and writing of the paper. António Silvério Cabrita is responsible for collecting and processing of study information.

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Review Article

Spinal Cord Stimulation: The Clinical Application of New Technology

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The use of neuromodulation for pain relief is among the fastest-growing areas of medicine, involving many diverse specialties and impacting on hundreds of thousands of patients with numerous disorders worldwide. As the evidence of efficacy improves, the interest in spinal cord stimulation (SCS) will increase because it is minimally invasive, safe, and a reversible treatment modality with limited side effect profile. While the mechanism of action evades complete understanding, the technological improvements have been considerable and current neuromodulation developments have been coupled with the rapid growth of the neuromodulation device industry resulting in the development of the next-generation neuromodulation systems. The development, the newest technicaliti and the future for the clinical application of spinal cord stimulation (SCS) are reviewed here.

1. Introduction

Neuromodulation is among the fastest-growing areas of medicine, involving many diverse specialties and impacting on hundreds of thousands of patients with numerous disorders worldwide [1]. Historically, electricity, either in the form of the torpedo fish or man-made electrotherapy, has been used to try and cure various ailments [2]. For example, in the middle of the 18th century "electroanalgesia" became advocated for the treatment of angina pectoris, gout, headaches, pleuritic pain, and sciatica. However, by the 20th century the enthusiasm for the medical use of electricity became associated with "quackery" [3] and was banned from clinical practice. In 1965 Melzack and Wall presented the "Gate Theory" [4], which postulated that stimulation of nonpainful stimuli can inhibit painful afference, thereby offering the opportunity to align basic research with the clinical application of electricity which has resulted in the development of neuromodulation techniques as we know them today [5–7]. While the mechanism of action evades complete understanding, the technological improvements have been considerable and current neuromodulation developments have been coupled with the rapid growth of the neuromodulation device industry resulting in the development of the next-generation neuromodulation systems. The development, the newest technicalities, and the future for the clinical application of spinal cord stimulation (SCS) are reviewed here.

2. Principles of Neuromodulation

Essentially there are two components of a fully implanted SCS system: the electrodes (or lead) and an implantable pulse generator (IPG). In SCS the placement of epidural electrodes is generally targeted at the dorsal column of the spinal cord; however, in patients with segmental pain (single dermatome), stimulation is focused at the corresponding dorsal root. This is where the ascending tracts pass without decussation to the gracile and cuneate nuclei of the medulla oblongata. These tracts are composed of a wide range of fiber diameters which are the central processes of the primary afferent neurons located in the spinal ganglia. As the tracts ascend, they receive accession from the dorsal roots, resulting in a somatotopic organization [6]. The recruitment of fibers is correlated directly with the diameter of the fiber and inversely with the distance between the electrode contacts

and the fibers [6]. Hence the thickness of the cerebrospinal fluid layers [8], the individual anatomy, and the electrodes each influence the recruitment of the dorsal column [8–11] and dorsal root fibers [12].

In addition the large diameter fibers of the dorsal root and dorsal column have different orientation with respect to the spinal anatomy and hence in a different position in the electrical field evoked by the stimulation pulses. Furthermore, the distance between the electrode and the thickness of the dorsal cerebral spinal fluid (dCSF) layer influences the sensitivity of the fibers to the stimulation. Computer modeling predicted that a "bipolar" or a narrow guarded cathode programming sequence selectively stimulates dorsal cord fibers when the dCSF is small. In contrast, dorsal root stimulation is favored the most in "monopolar" stimulation when dCSF is wide [8–10]. In pain patients with segmental pain, stimulation can be focused on dorsal root fibers of the corresponding dermatome, whereas in patients with complex pain a multitude of dorsal column fibers related to multiple dermatomes should be stimulated. The results of these computer-based model studies led to the development of electrode arrays with similar geometric properties [13].

Once an electrode/lead is suitability positioned, the most common way to increase the intensity of the stimulation is to increase the amplitude (i.e., the current, the voltage provided); increasing the pulse rate beyond physiological limits (approximately 300 pulse per second) is not traditionally seen as providing therapeutic benefit as neural transmission may become blocked. Similarly the pulse width was traditionally set at 200 μs in order to provide adequate amplitude while conserving the energy of the battery. With modern technological advancements, these concepts are now facing an interesting challenge and may influence the future of some aspects of SCS.

3. New Electrode Contact and Lead Design

Remarkable technological advances have been achieved in terms of electrode contact/lead design. Firstly, the new multicontact arrays available in traditional and five-column paddle leads (St. Jude Medical, Inc, USA) have resulted in the ability to provide improved programmable capability and possible treatment outcome. Mathematical modeling has highlighted the potential benefits of tight-electrode spacing in electrode contact design whereby gaps in stimulation are avoided (Boston Scientific Neuromodulation, Valencia, Calif, USA). Indeed, to obtain large paraesthesia coverage, all active contacts (anodes and cathodes at one or more arrays) should be closely spaced.

In the beginning SCS stimulation involved only a single channel, which meant that the stimulator had only one cathodal voltage output and one anodal voltage output, each one being connected to one or more lead contacts. Only recently multichannel systems have been produced (Boston Scientific Neuromodulation, Valencia, Calif, USA). In these systems any active lead contact is driven independently with a preprogrammed current pulse. The only condition is that the sum of all cathodal and anodal currents is zero and that all pulses are synchronized. The number of settings increases exponentially from 50 combinations with four electrode contacts to tens of millions when 16 electrode contacts are available [14]. Intuitively one would be forgiven for assuming that with the newer multicontact or the multichannel systems [15] significant clinical improvements would follow, but these technical advantages have not necessarily improved treatment in all indications [16]. In fact, despite the large number of contacts available, the actual number of active contacts will generally be small (bipole, tripole, or quadruple).

Secondly, the improved "steerability" of the leads combined with a variety of stylets to guide the positioning of the electrodes has resulted in a preference for the less invasive percutaneous insertion of the leads into the epidural space via a Touhy needle. The design of the Epiducer lead delivery system (St. Jude Medical, Inc, USA) is proposed to allow the advancement of a paddle lead without the use of a laminectomy.

Importantly, the improved flexibility of the leads has not compromised the lead fracture rate; this has fallen from 6% in earlier studies [17] to 3% [18]. Lead migration usually occurs in the first 12 months of implantation and varies between 8% [19] and 27% [20]. Migration may be related to the anchoring technique and not the actual lead design. The industry is striving to identify a solution to migration through the development of consistent and verifiable anchoring technology. Another development based on computer modeling is transverse tripolar stimulation, allowing the mediolateral steering of the electric field to correct for an inaccurate lead position [21]. Transverse tripolar steering principle led to even more complex configurations like the development of a 5-column paddle lead (Penta, St. Jude Medical).

A third technical challenge that remains is the lack of compatibility of the leads with magnetic resonance imaging (MRI) and radiofrequency diathermy which can be a significant limitation for some patients. Metallic implants (including nonferrous) are prone to heating when exposed to MRI or diathermy. In vitro comparisons showed that temperature changes near SCS electrodes were higher than those found with other metallic implants, reaching up to $4.88^{\circ}C/s^{-1}$ [22]. While the safe use of MRI in patients with SCS leads in place has been reported [23], so too has nonreversible damage and death [20, 24]. Most manufacturers are addressing the issue, and safer leads are expected.

4. IPG Advancements

Originally regarded as just a battery, the IPG has now evolved to become an engineer's paradise. Long gone are the nickel-cadmium systems which are replaced by lithium-based batteries thereby prolonging the lifespan of the device. With the advent of complex stimulation settings involving the activation of an increasing number of contacts the premature exhaustion of the battery is avoided by using automatic nocturnal, time-cycled, or manual interruption of stimulation. The industry has developed a variety of new

generation of compact rechargeable IPGs to meet the new requirements of SCS; thereby, energy consumption becomes less of a problem.

As previously mentioned the recruitment of dorsal horn fibers is correlated inversely with the distance between the electrode contact and the fiber [6]. Hence the thickness of the cerebrospinal fluid layers [8] the recruitment of the dorsal column [8–11] and dorsal root fibers [12]. Therefore as electrode/leads placement varies and stimulation intensity can vary depending on the position of the patient (e.g., supine or standing) to such an extent that patients cannot use the IPG without manually changing the program in order to avoid painful overstimulation.

The RestoreSensor (Medtronic Inc, USA) is the first implantable neurostimulator for spinal cord stimulation (SCS) that automatically adapts stimulation settings in response to position changes and provides objective patient activity data. The adaptive SCS is based on acceleration sensor that enables chronic motion sensing in battery-powered applications. It is robust to shock and represents the first practical, packaged, three-axis accelerometer suitable for chronic physiological measurements. The sensor's performance is also desirable for more general micropower applications like package tracking, vibration, and tilt detection.

Initial results from the Testing RestoreSensor Usability and Satisfaction (TRUST) survey [25] in 30 patients, mainly suffering from predominant leg pain due to failed back surgery syndrome or complex regional pain syndrome type I, followed up over a 10-week period are very promising. 80% of patients reported more effective pain relief. Use of the patient programmer became less difficult, and less necessary, with adaptive stimulation. Adaptive stimulation had a positive effect on sleep quality in all patients, which may have led to a perception of greater sleep quantity. In total, 58% of patients reported the ability to perform more activities with the therapy (e.g., standing, walking, sleeping, and staying in a particular position longer). Overall patient satisfaction was 97% at the end of the 10-week follow-up period [25].

5. Modification of the Pulse Width

In SCS, the pulse amplitude is usually the focus of stimulation control as it is intuitively understood by clinician and patient alike [26–29]. With advances in SCS technology, particularly rechargeable IPG implantable devices, pulse width (PW) programming ranges of now match that of older radiofrequency systems (with programmability up to 1000 μs). Traditionally PW was only changed when other parameter adjustments fail to achieve therapeutic goals. In neurostimulation the pulse amplitude and width relate directly to the depolarization of the cell membrane and are therefore critical parameters for determining the locus of excited tissue [30]. The value of PW programming was investigated in 19 subjects who had a fully implanted SCS in place for over 3 months to treat chronic intractable low back and/or leg pain. It was shown that the baseline median PW parameter was 295 μs (range 242–326 μs) with a median amplitude of 2.5 mA (1.3–3.3 mA). Following independent modification of the PW, the median PW of all patients' programs increased to 400 μs, approximately 48% higher (P = 0.01) and showed a significant increase in the paraesthesia-pain overlap (56%, P = 0.04). It was estimated that 10/19 patients appeared to have greater paraesthesia coverage, 7/19 patients selected the new PW programs, and 8/19 patients appeared to display a "caudal shift" of paraesthesia coverage with increased PW [31].

Mathematical modelling suggests that the mechanism behind such paraesthesia steering is due to the different selectivity of PW for larger and smaller fibers. The model considered incorporated realistic fiber size, density, and distributions in the dorsal columns, based upon human anatomic data. With a greater relative density of smaller fibers located more medial in the dorsal columns, an increase in PW will recruit smaller fibers more readily and thus result in greater midline axon recruitment. Clinically, this appeared to manifest as a caudal shift in paraesthesia. In summary variable PW programming in SCS appears to have clinical value, demonstrated by some patients improving their paraesthesia-pain overlap, as well as the ability to increase and even "steer" paraesthesia coverage [31].

6. High-Frequency Stimulation

Although SCS is a recommended treatment for patients with failed back surgery syndrome (FBSS) [32], if paraesthesia over the lumbar dermatomes cannot be obtained, then axial low back pain is very difficult to treat and clinical results are poor [33]. Ongoing multicentred European prospective trials [34] using dual octapolar, percutaneous leads placed sequentially near anatomic midline and connected to a rechargeable IPG capable of delivering waveforms with frequencies up to 10 kHz. (Nevro, Menlo Park, Calif) have shown that of 34 cases with full implantation the average back pain VAS decreased by 77% (8.9 cm baseline to 2.0 cm at 6 months, $P < .001$) and leg pain VAS decreased by 82% at 6-month follow-up. (5.5 cm baseline to 0.7 cm at 6 months, $P < .001$). In addition the average Oswestry Disability Index score decreased by 36% (from 58 to 37, $P < .001$). This approach is novel for several reasons: (a) the use of high-frequency stimulation provides sustained analgesia in a previously difficult patient cohort without paraesthesia—thus adequate axial low back pain relief is achieved without the overwhelming leg sensation one would have expected by increasing the frequency using a traditional IPG; (b) anatomical placement of the leads is possible and intraoperative paraesthesia mapping is avoided; (c) it has decreased programming requirements; (d) continued use of the system independent of position including night-time use is possible. To date, no adverse effect of such high-frequency stimulation has been reported however, the clinical outcome in the longer term is awaited. Pre-clinical studies in goats who received 10 days of continuous stimulation at amplitudes up to the sensory/motor threshold showed no difference in the behaviour or spinal cord neural histology between the therapy and control groups. Why such stimulation has

this remarkable effect still remains to be understood and may influence our approach to this co-cohort heretofore unsatisfactorily managed with conventional SCS technology.

7. New Clinical Applications

There are several established indications for SCS such as neuropathic back and leg pain, complex regional pain syndrome, spinal cord injury, and ischemic pain (vascular and angina pectoris). While it is beyond the remit of this paper to discuss each clinical indication, there is a growing database of clinical-based evidence to support the use of SCS. The economic evaluation in these areas is limited but the initial costs of SCS is generally both more effective and less costly then conventional management over a period of 3–5 years [33]. Unfortunately SCS is regarded as a last-resort option by many healthcare providers, and the real economic benefits may lie in the earlier introduction of the technique.

The recognition of new treatment modalities and the new application of SCS techniques will redefine our understanding of the pathophysiological concepts involved in different medical conditions. For example, painful bladder syndrome/interstitial cystitis and diffuse chronic abdominal/pelvic pain may be considered as neuropathic pain thereby offering the potential for exciting development. The evidence that cervical SCS increases cerebral blood flow (CBF) may lead to a role in cerebral ischemia. The modification of the autonomic system, particularly its sympathetic component by SCS, suggests that body functions under significant autonomic control could be subjected to modulation. It is suggested that in the future bronchospasm, gastrointestinal motility, and possibily metabolic disorders could become the focus of neuromodulation [35].

8. Conclusion

Modern medicine requires that any treatment modality is based on rational knowledge and well-documented theories; however, some conditions, particularly those involving chronic pain, often remain imprecise. SCS may be one of the few examples of a treatment that has significantly contributed to a change in attitudes and providing satisfactory relief to patients who in the past would have been left untreated.

Spinal cord stimulation has significant implications for the healthcare system offering a safe reversible treatment modality with a limited side effect profile. To ensure the deliverance of a high-standard quality of care spinal cord stimulation should be provided in small well-resourced centres able to address the aftercare needs of this patient cohort. Cost-effectiveness and efficacy are fundamental if SCS is to be accepted as the therapy of choice by the public, physicians, and the healthcare decision makers. Earlier introduction of the technique may prove to be critical. Research into the mechanism of pain, the diseases, and the action of SCS requires randomized control trials (RCTs). The inability (a) to blind patients (owning to the paraesthesia), (b) to select a comparative therapy (medical, surgical, rehabilitation), and/or (c) to address the ethical implications to participate in a trial are specific issues in the design of such a RCT.

As the evidence of efficacy improves and the number of indications increases, the interest in the neuromodulation and SCS will undoubtedly increase. SCS is minimally invasive, safe, and reversible treatment modality with limited side effect profile. It is only through the combined efforts of the biomedical industry, basic science researchers, and frontline healthcare providers will the technological advancements already made in this area continue to make significant clinical impact on the patients of tomorrow.

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Review Article

A New Look at Trigger Point Injections

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Trigger point injections are commonly practised pain interventional techniques. However, there is still lack of objective diagnostic criteria for trigger points. The mechanisms of action of trigger point injection remain obscure and its efficacy remains heterogeneous. The advent of ultrasound technology in the noninvasive real-time imaging of soft tissues sheds new light on visualization of trigger points, explaining the effect of trigger point injection by blockade of peripheral nerves, and minimizing the complications of blind injection.

1. Introduction

Myofascial pain syndrome is a common, painful musculoskeletal disorder characterized by the presence of trigger points. They have been implicated in patients with headache, neck pain, low back pain, and various other musculoskeletal and systemic disorders [1–4]. The prevalence of myofascial trigger points among patients complaining of pain anywhere in the body ranged from 30% to 93% [5]. Although the most important strategy in treatment of myofascial pain syndrome is to identify the etiological lesion that causes the activation of trigger points and to treat the underlying pathology [6], trigger point injections are still commonly practised pain interventional technique for symptomatic relief.

Despite the popularity of trigger point injections, the pathophysiology of myofascial trigger points remains unclear. Localization of a trigger point is often based on the physician's examination. However, such physical examination is often unreliable. Lack of objective clinical measurements has also been a barrier for critically evaluating the efficacy of the therapeutic methods.

Ultrasound is used extensively for noninvasive real-time imaging of soft tissues including muscle, nerve, tendon, fascia, and blood vessels. With the advent of portable ultrasound technology, ultrasound is now commonly employed in the field of regional analgesia. In this paper, we will look at the potential application of ultrasound in trigger point injections.

2. Diagnosis of Trigger Points

Physician's sense of feel and patient expressions of pain upon palpation are the most commonly used method to localize a trigger point. The most common physical finding is palpation of a hypersensitive bundle or nodule of muscle fibre of harder than normal consistency. The palpation will elicit pain over the palpated muscle and/or cause radiation of pain towards the zone of reference in addition to a twitch response [7].

In myofascial pain syndrome, trigger points have been classified into active or latent. In an active trigger point, there is an area of tenderness at rest or on palpation, a taut band of muscle, a local twitch response, and referred pain elicited by firm compression similar to the patient's complaint. Latent trigger points are more commonly seen. They may display hypersensitivity and exhibit all the characteristics of an active trigger point except that it is not associated with spontaneous pain [7].

Trigger points have also been further classified into key or satellite. An active key trigger point in one muscle can induce an active satellite trigger point in another muscle. Inactivation of the key trigger point often also inactivates its satellite trigger point without treatment of the satellite trigger point itself [7].

The diagnosis of trigger points depends very much on the subjective experience of the physician. Pressure algometry has been used to quantify the sensitivity of trigger points.

A hand-held pressure meter with a 1 cm^2 rubber disc attached to a force gauge calibrated up to 10 kg is applied over a trigger point to measure its pain threshold [8]. However, this method is not commonly employed clinically, and there have not been any imaging criteria for the diagnosis of trigger points.

3. Pathophysiology of Trigger Points

Trigger points are defined as palpable, tense bands of skeletal muscle fibres. They can produce both local and referred pain when compressed.

The local pain could be explained by the tissue ischemia resulting from prolonged muscle contraction with accumulation of acids and chemicals such as serotonin, histamine, kinins, and prostaglandins [9]. These changes are fed into a cycle of increasing motor or sympathetic activity and can lead to increased pain. A painful event can sustain itself once a cycle is established even after the initial stimulus has been removed [10].

The pathogenesis of trigger points is probably related to sensitized sensory nerve fibres (nociceptors) associated with dysfunctional endplates [11]. In fact, endplate noise was found to be significantly more prevalent in myofascial trigger points than in sites that were outside of a trigger point but still within the endplate zone [12].

Studies have found that development of trigger points is dependent on an integrative mechanism in the spinal cord. When the input from nociceptors in an original receptive field persists (pain from an active trigger point), central sensitization in the spinal cord may develop, and the receptive field corresponding to the original dorsal horn neuron may be expanded (referred pain). Through this mechanism, new "satellite trigger points" may develop in the referred zone of the original trigger point [11].

4. Mechanisms of Action of Trigger Point Injections

Noninvasive measures for treatment of trigger points include spray and stretch, transcutaneous electrical stimulation, physical therapy, and massage. Invasive treatments include injections with local anaesthetics, corticosteroids, or botulinum toxin, or dry needling [13–18].

Hong reported that with either lidocaine injection or dry needling of trigger points, the patients experienced almost complete relief of pain immediately after injection if local twitch responses were elicited. On the other hand, they experienced only minimal relief if no such response occurred during injection. Hong has suggested that nociceptors (free nerve endings) are encountered and blocked during trigger point injection if local twitch response can be elicited [19].

The mechanism of action of trigger point injections is thought to be disruption of the trigger points by the mechanical effect of the needle or the chemical effect of the agents injected, resulting in relaxation and lengthening of the muscle fibre. The effect of the injectate may include local vasodilation, dilution, and removal of the accumulated nociceptive substrates. Botulinum toxin A has been used to block acetylcholine release from the motor nerve ending and subsequently relieve the taut band [6].

While the relief of local pain could easily be explained by the relaxation of the muscle fibre, the relief of referred pain could not be explained without attributing it to a peripheral nerve blockade. However, little has been said in the literature regarding the mechanism of trigger point injection in this respect.

5. Could the Application of Ultrasound Solve the Mystery of Trigger Points?

5.1. Direct Visualization of Trigger Points. As mentioned above, the most common physical finding of a trigger point is palpation of a hypersensitive bundle or nodule of muscle fibre of harder than normal consistency. Attempts to confirm the presence of myofascial trigger points using imaging have been demonstrated by magnetic resonance elastography [20]. For ultrasound, earlier studies have failed to find any correlation between physical findings and diagnostic ultrasound [21]. This may be attributed to poorer quality of ultrasound imaging in earlier dates.

Recently, Sikdar et al. have tried to use ultrasound to visualize and characterize trigger points. They found that trigger points appeared as focal, hypoechoic regions of elliptical shape, with a size of 0.16 cm [22]. This is promising as ultrasound can provide a more objective diagnosis of trigger point. Even if visualization of individual trigger point is difficult due to the small size, some advocate the use of ultrasound to guide proper needle placement in muscle tissue and to avoid adipose or nonmusculature structures during trigger point injections [23].

5.2. Injection of Peripheral Nerves. Trigger point injections have been implicated in patients with headache, low back pain, and various other musculoskeletal and systemic disorders. Some of these injections may involve injectate deposition directly to the nerves supplying the region. Indeed, entrapment, compression, or irritation of the sensory nerves of local regions has been implicated in various conditions.

5.2.1. Greater Occipital Nerve. Entrapment of the greater occipital nerve is often implicated as the cause of cervicogenic headache, and the characteristic occipital headache can be reproduced by finger pressure over the corresponding occipital nerve over the occipital ridge [3, 24–26]. This referral pattern of pain coincides with that of the properties of a trigger point, and it could explain the mechanism of referred pain for trigger points.

Simons has considered that the effect of greater occipital nerve injection is due to the release of the entrapment by relaxation of semispinalis muscle [7]. However, injection of local anaesthetics with or without steroid over the occipital nerve has been found to result in alleviation of occipital headache [27]. In migraine headaches, local injection of local anaesthetics or botulinum toxin type A to the greater

occipital nerve has been demonstrated to provide relief of the condition [24].

There are several techniques of ultrasound-guided blockade of greater occipital nerve. The classical distal block technique involves placing the transducer at the superior nuchal line, while for the new proximal approach, the transducer is placed at the level of C2, and the greater occipital nerve lies superficial to the obliquus capitis inferior muscle [28, 29].

5.2.2. Abdominal Cutaneous Nerve. Kuan et al. showed that local injection of anaesthetics or steroid can treat some patients with lower abdominal pain presenting with trigger points in the abdomen, thus avoiding diagnostic laparoscopy and medications [30].

Trigger points over the abdominal wall may in fact be entrapped cutaneous nerves. Peripheral nerve entrapment (e.g., ilioinguinal-iliohypogastric nerves, thoracic lateral cutaneous nerve) has been suggested to cause lower abdominal pain [31, 32].

Ultrasound-guided blocks for ilioinguinal and iliohypogastric nerves have been practised widely in anaesthesia [33–35]. Recently, ultrasound-guided transversus abdominis plane (TAP) block is also commonly used to provide postoperative pain relief for patients undergoing laparotomy [35–38].

By placing the ultrasound probe about 5 cm cranial to the anterior superior iliac spine, the ilioinguinal and iliohypogastric nerves can be found between the transverse abdominal and the internal oblique muscle [39]. For TAP block, the transducer can be placed in a transverse plane between the iliac crest and the anterior axillary line. Local anaesthetics can be deposited between the transversus abdominis muscle and the internal oblique muscle [40].

5.2.3. Dorsal Ramus of Spinal Nerve. Low back pain is a common chronic pain syndrome; however, in most cases, a specific diagnosis cannot be established. Trigger point injections have been found to relieve myofascial low back pains. However, there has been lack of evidence in the literature to support its efficacy. This could be attributed to the heterogeneity in the diagnosis and technique of localization of trigger points in low back pain. Most of the studies employed subjective localization of trigger points, and the techniques of localization and injection of trigger points were not well described.

Miyakoshi et al. demonstrated that CT-guided total dorsal ramus block was effective in the treatment of chronic low back pain in a group of patients with overlapping facet syndrome with myofascial syndrome with pain originating from myofascial structure, facet joint, or both [41]. They demonstrated that a single injection of a larger volume of local anaesthetics over the conventional target point for medial branch block, which was the junction of the L5 superior articular process and the transverse process, was effective to block the medial, intermediate, and lateral branches of the lumbar dorsal ramus, with significantly better pain reduction compared to conventional trigger point injection. The findings in this study shed light to the possibility of relief of myofascial pain syndrome by a single nerve injection. It may explain the poor results of pure intramuscular injections in controlled studies, in contrast to the better results with uncontrolled studies and case reports, in which some of the results may be attributable to accidental nerve injection using the conventional blind injection techniques.

For ultrasound-guided medial branch block, the transducer is first placed longitudinally to find the respective transverse process and localize the lumbar level. Then the transducer can be rotated into a transverse plane to delineate the transverse process and the superior articular process of the adjacent facet joint. The bottom of the groove between the lateral surface of the superior articular process and the cephalad margin of the respective transverse process was defined as the target site [42].

Ultrasound-guided technique may be adapted to perform injection of the lower back, targeting at the dorsal rami of the lumbar spinal nerves to increase the efficacy of injection.

5.2.4. Lumbar Plexus. There have been case reports on the use of trigger point injection for treatment of pain that was remote from the site of trigger points. Interestingly, Iguchi et al. used trigger point injection for the amelioration of renal colic. In their paper, they described the injection technique as follows. Trigger points were located over the paraspinal region at around L3 level. A long needle (23-gauge 6 cm) was inserted deep into the trigger points, and 5–10 mL of 1% lignocaine was injected [43]. Such injection was in fact into the psoas muscle, and the effect could be attributed to a lumbar plexus block.

Lumbar plexus block with ultrasound guidance has been described. A curved transducer can be placed in the transverse plane at L2–L4 level for the lumbar plexus block. This transverse view should show the psoas muscle without the transverse process. The target of the needle tip is within the posterior 1/3 of the psoas muscle bulk [40].

5.2.5. Pudendal Nerve. Langford et al. reported the effective use of levator ani trigger point injection in the treatment of chronic pelvic pain. Trigger points were identified by manual intravaginal palpation, and the trigger points were injected with a large volume (up to about 20 mL) of a mixture of local anesthetics and depot steroid. The effect of such injection might in fact be caused by the concomitant pudendal nerve block [44].

Pudendal nerve blockade with ultrasound guidance can be performed via the transgluteal approach. The probe is placed transverse to the posterior superior iliac spine and moved caudally until the piriformis muscle is seen. The probe is then moved further caudad to identify the ischial spine, in which the pudendal nerve will be seen lying medial to the pudendal artery [29].

6. Other Advantages of Ultrasound in Trigger Point Injections

Trigger point injections are commonly performed in clinics as an outpatient procedure. Serious complications, although

of rare occurrence, have been reported (e.g., pneumothorax, haematoma, intravascular injection of local anaesthetics, and intrathecal injections) [45]. Direct visualization of surrounding soft tissues and important structures can reduce the risk of such complications. Moreover, ultrasound allows real-time imaging of the spread of the injectate around the relevant structures and increases the success rate of injection.

7. Future Directions

The nonspecific diagnosis and lack of objective clinical measurements for trigger points mean that the evidence for the effectiveness of trigger point injection remains heterogenous. There is so far no strong evidence for the effectiveness of trigger point injections, and many physicians consider trigger point injections a little more than, if not equivalent to, placebo effects.

With the advancement of ultrasound technology, the quality of scans for soft tissues and musculature has improved dramatically. Future studies may focus on more objective diagnostic criteria of trigger points using ultrasound imaging. For the technique of trigger point injections, real-time visualization of trigger points, relaxation of locally contracting muscles, and visualization of surrounding tissues or important structures may improve the outcome and minimize complications of such treatments.

Moreover, efficacy of some of the trigger point injections traditionally performed may be related to some kind of peripheral nerve blocks, the implication which is yet to be explored.

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Review Article

Transforaminal Blood Patch for the Treatment of Chronic Headache from Intracranial Hypotension: A Case Report and Review

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This case report describes the successful treatment of chronic headache from intracranial hypotension with bilateral transforaminal (TF) lumbar epidural blood patches (EBPs). The patient is a 65-year-old male with chronic postural headaches. He had not had a headache-free day in more than 13 years. Conservative treatment and several interlaminar epidural blood patches were previously unsuccessful. A transforaminal EBP was performed under fluoroscopic guidance. Resolution of the headache occurred within 5 minutes of the procedure. After three months without a headache the patient had a return of the postural headache. A second transforaminal EBP was performed again with almost immediate resolution. The patient remains headache-free almost six months from the time of first TF blood patch. This is the first published report of the use of transforaminal epidural blood patches for the successful treatment of a headache lasting longer than 3 months.

1. Introduction

Headaches secondary to intracranial hypotension or cerebrospinal fluid hypovolemia have been well documented for over 100 years. Dr. Bier experienced such a headache first hand in 1898 which lead to the first report of what is now known as postdural puncture headache (PDPH) [1, 2]. Forty years later Dr. Schaltenbrand described spontaneous intracranial hypotension (SIH) [3] which has recently become a more recognized cause of severe persistent headache. PDPH and SIH are very similar in mechanism, symptomatology as well as treatment. A relative decrease in intracranial pressure is thought to cause irritation of pain sensitive structures such as the meninges and bridging veins. Patients typically present with a postural occipital-frontal headache that resolves in the supine position and is greatly exacerbated by sitting or standing. The headaches can be associated with neck pain, nausea, vomiting photophobia, and cranial nerve palsies [4–6]. In severe cases, SIH has been associated with dementia, encephalopathy, paralysis, coma, and even death [7–9]. In 2004 the International Classification of Headache Disorders, 2nd edition provided specific diagnostic criteria for SIH [10]. These criteria are shown in Table 1. Conservative therapy including bed rest, oral hydration, increased salt intake along with intravenous fluid, caffeine, and the use of an abdominal binder have all been recommended [4, 6]. Refractory cases of both PDPH and SIH typically resolve with the use of an epidural blood patch (EBP). Dr. Gormley described this technique in 1960 and it remains the treatment of choice when conservative management has been ineffective [4, 6, 11]. Traditionally, EBP is performed by placing a needle in the epidural space through an interlaminar approach and injecting 10–30 mL of sterile autologous blood. At times the traditional interlaminar

Table 1: Diagnostic criteria for headache due to spontaneous spinal CSF leak and intracranial hypotension according to the International Classification of Headache Disorders, 2nd edition, 2004 [10].

(A) Diffuse and/or dull headache that worsens within 15 min after sitting or standing, with at least one of the following and fulfilling criterion D:
(1) Neckstiffness
(2) Tinnitus
(3) Hypacusia
(4) Photophobia
(5) Nausea
(B) At least one of the following:
(1) Evidence of low CSF pressure on MRI (e.g., pachymeningeal enhancement)
(2) Evidence of CSF leakage on conventional myelography, CT myelography or cisternography
(3) CSF opening pressure <60 mm H_2O in sitting position
(C) No history of dural puncture or other cause of CSF fistula
(D) Headache resolves within 72 h after epidural blood patching

approach is either impractical due to surgical scar or local infection. We present a case of successful treatment of chronic headache secondary to SIH using a transforaminal epidural blood patch (Figures 1 and 2). Using a transforaminal approach allowed for placement of blood directly at the presumed site of CSF leak when an interlaminar approach was not practical because of a previous laminectomy.

2. Case Report

This patient is a 65-year-old male with a history of chronic postural headache for 13 years. The headaches started after sustaining a ground level fall in 1997 shortly after having a L4-L5 laminectomy in 1997 for spinal stenosis. He was eventually seen by a specialist in low pressure headaches and was subsequently diagnosed with spontaneous intracranial hypotension. Computed tomographic melography (CTM) demonstrated a likely CSF leak at L4-L5. The headaches were initially managed conservatively with bed rest, caffeine, increase oral intake, intravenous fluid, and an abdominal binder. These measures provided only minimal temporary relief. Multiple interlaminar epidural blood patches were performed but none of them were effective. The patient also underwent C6–C8 rhizotomy as well as multiple C2-C3 epidural steroid injections. Discouraged and not wanting to consider surgical intervention the patient decided to simply try and cope with the pain. He continued to use acetaminophen, ibuprofen, and oxycodone 40 mg q12 hrs but continued to have daily headaches. Unable to tolerate the headaches any longer the patient once again sought medical intervention in 2010. At that time he was referred to the current authors for evaluation and potential nonsurgical intervention.

At the time of consultation the patient complained of daily dull, achy frontal headache with some radiation to the neck that was significant worse when sitting or standing and resolved when lying supine. His pain was reported to be 9/10 with verbal numeric rating scale (VNRS). The headaches are frequently associated with recent nausea, vomiting, and photophobia. On physical exam he was found to be afebrile, normotensive, and with no gross neurological deficits. Heavily T2-weighted magnetic resonance myelography (MRM) was performed which showed a CSF collection in the posterior epidural space at the level of L5 presumably representing the site of CSF leak. MRM was chosen to help located the exact site of CSF leak because addition lumbar puncture for intrathecal contrast for a CTM could exacerbate the patient's symptoms [12]. The case was discussed with the patient's neurosurgeon and the decision was made to attempt an EBP by entering the bilateral intervertebral foramen. The potential risks and benefits were explained to the patient in great detail.

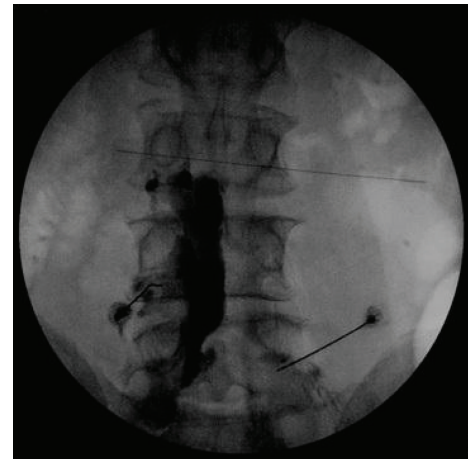

Figure 1: Fluoroscopic image of epidural contrast injected through right L4-L5 foramen.

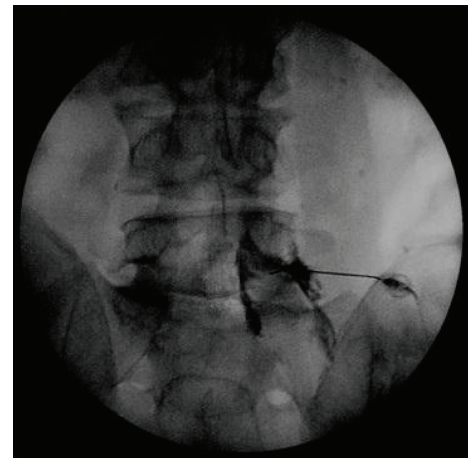

Figure 2: Fluoroscopic image of epidural contrast injected through left L5-S1 foramen.

Table 2: Summary of published case reports of transforaminal EBP.

Author	Age	Sex	Preprocedure diagnosis	Duration of symptoms	Site	Contrast	Quantity of blood injected	Result	Previous interlaminar EBP
Weil	48	M	PDPH s/p Transforaminal ESI	5 weeks	Left L4-L5 L5-S1	No	2 mL each level	Relief within 5 min	Interlaminar EBP not attempted
Slipman	40	F	PDPH s/p Transforaminal ESI	3 months	Left C5-C6	Yes	6 mL	Relief within 15 min	Previous failed Interlaminar EBP ×2
Walega	39	F	SIH	8 weeks	Bilateral C7-T1	Yes	5 mL Left 2 mL Right	Relief time not reported	Previous failed Interlaminar EBP ×2
Bowden	65	M	SIH	13 years	Bilateral L4-L5	Yes	15 mL Bilateral ×2	Relief within 5 min	Multiple previous Interlaminar EBP

3. Procedure Note

After written consent was obtained the patient was brought to the operating room and placed in the prone position. The skin was prepped and draped in the usual sterile fashion and a skin wheal was raised with 3 mL of 1% lidocaine. Under real-time fluoroscopic guidance the L5 pedicle was identified. A 25 gauge spinal needle was inserted but could not be advanced into the L5-S1 intervertebral foramen. After two attempts, the needle was withdrawn and inserted at the level of L4. The needle was then advanced to the 6 o'clock position of the L4 pedicle. Contrast was then injected and epidural spread was identified. 15 mL of sterile autologous blood was then injected into the epidural space. The injection was stopped as the patient began to feel pressure in his lower back but no pain or paraesthesias were reported. On the left side a 25 gauge spinal needle was easily inserted in the 6 o'clock position of the L5 pedicle. After injection of contrast 15 mL of sterile autologous blood was injected. A total of 30 mL of sterile autologous blood was injected. After remaining prone for approximately 5 minutes the patient was moved to the seated then standing position. For the first time in 13 years the patient was able to stand without a headache.

4. Patient Followup

The patient was seen at two weeks and two months for followup and found to be completely headache-free with no apparent complications from the procedure. Three months after the procedure the patient began having slight headaches when he would stand. The headaches were much less severe than before the procedure. They were described as 5/10 on VNRS with frontal "pressure." He denied radiation of pain, nausea, vomiting, and photo- or phonophobia. Treatment options were discussed with the patient and the decision was made to repeat the transforaminal EBP. The procedure was repeated using the exact same technique. 15 mL of sterile autologous blood was injected through the intervertebral foramen at L4 on the right and then an additional 15 mL at L5 on the left. Again, within 5 minutes of the procedure the patient was completely headache-free in both the seated and standing positions. The patient was contacted by phone two months after the second epidural blood patch at which time he reported no return of symptoms.

5. Discussion

An extensive literature review produced only 3 published reports of successful treatment of intracranial hypotension or PDPH using transforaminal epidural blood patch in addition to the current paper [9, 13, 14]. A transforaminal approach was also used by Schievink et al. who reported 4 cases of injection of a fibrin sealant into the epidural space for the treatment of SIH. Two of the 4 patients had a resolution of symptoms one of which had headaches for 8 months [15]. To our knowledge this is the first reported case of successful treatment chronic headache using transforaminal EBP. Each of the published cases is summarized in the Table 1 including patient characteristics, preprocedure diagnosis, duration of symptoms, site, the use of contrast, and the quantity of autologous blood injected. The current case was included in Table 2 for comparison. Of note, no complications were reported in any of the cases. The most common complication of EBP is low back pain. Other reported potential complications of EBP include aseptic meningitis, radicular pain, lumbovertebral syndrome, bradycardia, fever, subdural hematoma, epidural hematoma, and seizures [16].

Two of the transforaminal EBPs were performed for PDPH following transforaminal epidural steroid injection (ESI). The other case was for the treatment of refractory SIH. While each of the cases reported resolution of headache there was a wide range of the quantity of autologous blood injected into the epidural space. Weil et al. had a resolution of symptoms after only 8 total ml of blood injected while the current authors used 30 mL [13]. In 3 of the 4 cases interlaminar EBP had been attempted at least twice. The reason for successful treatment of both SIH and PDPH using a transforaminal approach when previous interlaminar EBP had failed is not exactly clear. We believe this is likely a function of the ability to place blood in close proximity to the dural defect.

A transforaminal approach for the EBP was chosen for the current case to obtain a more direct approach to the dural leak. We felt a direct interlaminar approach at L4-L5 would be unsafe as the integrity of the ligamentum flavum was likely compromised during the laminectomy. The lack of an intact ligamentum flavum would increase the possibility of inadvertent dural puncture and potential worsening of symptoms. An interlaminar approach at a level above or below the defect would likely be ineffective as this had previously been attempted. The two prior EBPs at L2-L3 and through a caudal approach, respectively, were likely ineffective because they failed to reach the site of CSF leak. The spread of epidural blood was likely limited because of postsurgical adhesions. Entering the intervertebral foramen allowed us to avoid possible adhesions and place blood directly at the site of the CSF leak.

Headaches related to intracranial hypotension either from dural puncture or SIH can be severe and very difficult to treat. EBP appears to be the treatment of choice when conservative measures has failed. When EBP does not provide relief patient may benefit from surgical intervention if the site of the CSF leak has been identified [17]. In the case presented the patient suffered from a chronic postural headache for more than 13 years despite medical management and repeated interlaminar EBP. He was referred to clinic as he did not want to consider surgery. The use of a relatively novel approach to a treatment that has been used for 50 years eliminated the patient's headache and restored his quality of life.

6. Conclusion

This case demonstrates that transforaminal epidural blood patch can be an effective in the treatment of chronic headache secondary to intracranial hypotension when traditional interlaminar technique is either impractical or has been previously ineffective.

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