REVIEW ARTICLE

Combined use of neuraxial and general anesthesia during major abdominal procedures in neonates and infants

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Summary
With the advent of ultrasound and improvements in equipment, the applications of regional anesthesia in the pediatric population have continued to expand. Although frequently used for postoperative analgesia or as a means of avoiding general anesthesia in patients with comorbid conditions, the adjunctive use of regional anesthesia during general anesthesia may effectively decrease the intraoperative requirements for intravenous and volatile agents, thereby providing a more rapid awakening and earlier tracheal extubation. More recently, the limitation of the requirements for volatile and other anesthetic agents may be desirable, given concerns regarding the potential impact of these agents on neurocognitive outcome in neonates and infants. Several authors have demonstrated the potential utility of combining a neuraxial technique (spinal or epidural anesthesia) with general anesthesia in neonates and infants undergoing intraabdominal procedures. We review the literature regarding the combined use of neuraxial and general anesthesia in neonates and infants during major abdominal surgery, discuss its potential applications in this population, and review the techniques of such practice.

Introduction
During the neonatal period and infancy, exposure to certain anesthetic and sedative agents has been shown to increase the incidence of neuronal apoptosis in animal models, which may lead to long-term cognitive and behavioral deficits (1–9). The true impact of such effects in humans remains controversial, given that these data have been obtained from retrospective and case-controlled studies as well as conflicting studies, which demonstrate no impact on outcome (10–20). However, given these concerns, best clinical practice may dictate means to avoid or limit such problems, pending the outcome of prospective, randomized trials. As the majority of the studies have demonstrated that the effect of anesthetic and sedative agents on neurocognitive outcome is dose and duration dependent, techniques to decrease the requirements for these agents may be of interest.

Major abdominal surgery in neonates includes the repair of congenital pyloric stenosis (CPS), gastroschisis, omphalocele, congenital diaphragmatic hernia (CDH), necrotizing enterocolitis (NEC), small bowel obstruction (SBO), Meckel's diverticulum, and malrotation of the intestine. One means of limiting the requirements for and hence the exposure to volatile and intravenous anesthetic agents is to use neuraxial anesthesia as an adjunct to general anesthesia. Several authors have demonstrated the potential utility of combining a neuraxial technique (spinal or epidural anesthesia) with general anesthesia (GA) in this patient population during intraabdominal procedures. In the majority of cases, the intent of such a practice is to limit the intraoperative need for opioids and the impact of surgery on postoperative ventilatory function, thereby facilitating early tracheal extubation. However, these techniques may also effectively decrease the dose requirements of general anesthetic agents. We review the literature regarding the combined use of neuraxial and general anesthesia in neonates and infants for major abdominal surgery, discuss its potential applications in this population, and present potential techniques for such practice.
The problem of apoptosis

Apoptosis is programmed cell death inherent in each living cell of the human body including the neurons in the brain. Multiple animal model studies in rats and primates have shown that prolonged neonatal exposure to volatile anesthetic agents, ketamine, benzodiazepines, and propofol results in a dose-dependent increase in neuronal apoptosis (1–9). As noted above, the exact impact of these processes on human neurocognitive development remains controversial and unproven, while regional anesthetic procedures in the pediatric population have been well reported to be a safe practice (21,22).

Apoptosis is a natural process that occurs in redundant neurons during neuronal synaptogenesis during a pre- and postnatal time frame in humans (sixth month of gestation to 24 months after birth; 7). Apoptosis degrades and recycles cell components in an organized manner, preventing collateral damage of surrounding cells with cell death occurring without initiation of a surrounding inflammatory cascade. There are three different pathways by which apoptosis is mediated including the extrinsic caspase pathway, intrinsic caspase pathway, and the caspase-independent pathway. Although each has a different trigger, there can be overlap between pathways (6). Conversely, necrosis is ‘accidental death of cells and living tissue’, which leads to neuronal death with damage to contiguous tissue secondary to the inflammatory reaction that ensues (1,8). Various anesthetic and sedative agents have been shown to accelerate apoptosis by activating GABA and/or blocking NMDA receptors, thereby depressing neuronal activity and inducing apoptosis, leading to neurotoxicity in a dose- and exposure-time-dependent manner (23). These studies have been conducted using various in vitro and in vivo neuronal models including humans (24–31). Although the anesthetic and sedative agents have multiple effects acting via different receptor systems, their action as NMDA receptor antagonists and GABA agonists and how these actions relate to apoptosis and neurotoxicity are of primary concern. It is these effects that are thought to pertain to the long-term cognitive and behavioral effects on term neonates exposed to certain anesthetic and sedative agents during general anesthesia.

The use of regional anesthesia in conjunction with general anesthesia would allow for a significant reduction in the requirements for volatile anesthetic agents and decrease the total dose of intravenous anesthetic agents while maintaining surgical anesthesia. Although the major impetus for such trials and strategies has been to provide effective analgesia while limiting the need for systemic opioids as a means of achieving early tracheal extubation, this approach could become a favorable alternative to the traditional general anesthetic technique with the goal of reducing the overall exposure to potentially neurotoxic agents in neonates.

Regional anesthesia in the neonate and infant

When initially introduced into clinical practice, the role of regional anesthesia was as a means of avoiding general anesthesia in patients with comorbid conditions that were thought to increase the risks of morbidity and mortality during general anesthesia. These initial reports included the use of spinal anesthesia in the early 1900s when the conduct of general anesthesia in neonates and infants was fraught with the potential for perioperative complications (32). The use of regional anesthesia in neonates and infants decreased as the safety of general anesthesia increased. These techniques saw a resurgence during the 1980s as a means of avoiding general anesthesia in the former preterm infants who were shown to have an increased risk of apnea following exposure to commonly used volatile anesthetic agents including halothane and isoflurane (33–38). The vast majority of these cases included the former preterm infant undergoing surgical procedures below the umbilicus, predominantly herniorrhaphy, for which spinal or caudal anesthesia was well suited. In 1986, Ecoffey et al. (39) described epidural anesthesia combined with nitrous and oxygen in infants and children for urologic and upper abdominal surgery. Other investigators even demonstrated the potential for the use of neuraxial techniques (spinal anesthesia) during major surgical procedures including closure of gastrochisis without the need for endotracheal intubation and general anesthesia (40). Although they reported anecdotal success, the obvious risks entailed of providing spinal anesthesia without airway control for small neonates and infants during major abdominal procedures limited the widespread acceptance of the technique.

These same investigators were also the first to combine a neuraxial technique (spinal anesthesia) with endotracheal intubation and general anesthesia during thoracotomy for ligation of a patent ductus arteriosus (41). The study cohort included 14 neonates with a postconceptional age ranging from 28 to 41 weeks and a weight of 650–2965 g. Following endotracheal intubation and controlled ventilation (11 of the 14 patients had required endotracheal intubation prior to the procedure), hyperbaric tetracaine (1.2–3.35 mg·kg$^{-1}$, mean dose of 2.4 mg·kg$^{-1}$) was injected into the lumbar intrathecal space and the neonate placed in Trendelenburg position. The goal was to achieve a high spinal
anesthetic as demonstrated by a lack of upper extremity movement. There was a decrease in blood pressure of 15–20 mmHg in one of the 14 patients associated with a decrease in heart rate from a mean of 180–125 b-min⁻¹. Seven patients required no other anesthetic agents while the other seven required supplementation with isoflurane, fentanyl, midazolam, or nitrous oxide. Of the three patients who did not require endotracheal intubation prior to arriving to the operating room, tracheal extubation at the completion of the procedure could be performed in two patients.

Various other investigators have demonstrated several potential advantages of using neuraxial anesthesia in combination with general anesthesia in neonates and infants. These have included decreased intraoperative requirements for volatile agents, opioids and neuromuscular blocking agents, control of the surgical stress response, earlier tracheal extubation, improved postoperative analgesia, and decreased length of hospitalization (42–44). Other investigators have described specific techniques of epidural catheter placement at various levels (45–47). In majority of cases, the caudal or lumbar epidural block was placed after the induction of anesthesia merely for the purpose of providing postoperative analgesia without specific emphasis on its intraoperative effects. The remainder of this paper will focus on reviewing those reports that specifically entail the use of neuraxial anesthesia in combination with general anesthesia during abdominal procedures in neonates and infants with a focus on its impact on the perioperative course including intraoperative anesthetic requirements.

Regional anesthesia combined with general anesthesia

Various authors have reported the successful combination of a neuraxial technique with general anesthesia in neonates and infants (Table 1; 45,48–55). Early experience with this combination for major abdominal surgery in neonates and infants was reported by Bosenberg et al. in 1988 (45). The authors performed a three-phase study, which included a first phase that demonstrated the feasibility of the passing a catheter from the caudal to the thoracic levels in cadaver specimens. This was followed by demonstration of the technique in piglets and finally in a cohort of 20 neonates and infants, ranging in age from 4 weeks to 5 months, undergoing biliary tract surgery. In 19 of 20 cases, the catheter was placed within one vertebrae of the desired thoracic dermatome (T₉). In one patient, the tip of the catheter was at T₁₂, but successful anesthesia was achieved with a larger dose of local anesthetic. The epidural catheter was dosed with 0.5 ml·kg⁻¹ of 0.25% bupivacaine. Successful intraoperative anesthesia was achieved in all 20 patients as demonstrated by minimal changes in heart rate and blood pressure during surgical incision with maintenance anesthesia of 70% nitrous oxide in oxygen. No adverse effects were noted. The same investigators subsequently reported their experience with the combined use of general and epidural anesthesia in a retrospective cohort of 240 neonates (48). As opposed to their previous study, the catheter was placed directly at the lumbar or thoracic level.

Lumbar epidural anesthesia was been combined with general anesthesia in a cohort of 20 neonates and infants during abdominal procedures including duodenal–jejunal–ileal atresia repair, volvulus, and soave pull through for Hirschsprung’s disease (49). The patients ranged in age from 4 h to 35 days and in weight from 1.3 to 4.5 kg. The lumbar epidural catheter was placed at the L₁₋₄ or L₄₋₅ interspace and dosed with 0.8 ml·kg⁻¹ of 0.25% bupivacaine with epinephrine (1 : 200 000) and fentanyl (1–2 μg·kg⁻¹). Epidural anesthesia was judged successful in all patients as demonstrated by the lack of hemodynamic response to surgical incision during maintenance anesthesia of 0.5% isoflurane. The epidural catheter was also used to provide analgesia for the initial 2–3 postoperative days.

A low-lying caudal epidural catheter has also been used as an adjunct to general anesthesia during abdominal surgery in neonates (50). This prospective study included a cohort of 25 infants ranging in age from 1 to 28 days and in weight from 2.2 to 4.9 kg. Surgical procedures included exploratory laparotomy, closure of gastroschisis or omphalocele, colostomy, ileostomy takedown, and bladder extrophy repair. A short 22- or 24-gauge intravenous cannula was placed into the caudal epidural space through the sacrococcygeal ligament and dosed with a bolus of 1–1.5 ml·kg⁻¹ of 3% chloroprocaine followed by an infusion of 1–1.5 ml·kg⁻¹·h⁻¹. No response to surgical incision was noted with maintenance anesthesia of 0.2% isoflurane or 70% nitrous oxide. Tracheal extubation was accomplished in the operating room in 23 of the 25 patients. Tracheal extubation was not performed in two patients due to concerns of bleeding in one and residual neuromuscular blockade in the other. No complications were noted in the patients. The authors chose chloroprocaine due to the need to use a larger volume, given the low-lying catheter and previous studies demonstrating its rapid metabolism (56).

In a review of the experience of the French Language Society of Pediatric Anesthesia, Giaufre et al. evaluated 24 409 anesthetics, which included regional blockade (21,22,57). The majority (89%) were performed during general anesthesia. This included 363 full-term neonates
Combined neuraxial and general anesthesia in neonates and infants during abdominal surgery

Table 1 Combined general and neuraxial anesthesia in neonates and infants during abdominal surgery

<table>
<thead>
<tr>
<th>Authors and reference</th>
<th>Cohort description</th>
<th>Technique and dosing</th>
<th>Findings</th>
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<tr>
<td>Bosenberg et al. (45)</td>
<td>20 neonates and infants ranging in age from 4 weeks to 5 months and in weight from 2.7 to 6.5 kg. Thoracic epidural catheter threaded from caudal space. Bolus dosing of 0.5 ml kg⁻¹ of 0.25% bupivacaine. Demonstrated efficacy of placing a thoracic epidural catheter from the caudal space. In 19 of 20 cases, the catheter was placed within one vertebrae of the desired thoracic dermatome (T₃). No change in HR or BP in response to surgical incision during maintenance anesthesia of 70% nitrous oxide in oxygen.</td>
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<td>Bosenberg (48)</td>
<td>248 epidurals in 237 neonates ranging in age from 2 h to 35 days and in weight from 0.9 to 5.8 kg. Lumbar and thoracic epidural anesthesia (direct placement). Initial bolus of 0.5 ml kg⁻¹ (thoracic) or 0.7 ml kg⁻¹ (lumbar) followed by intermittent doses (0.1 ml kg⁻¹) as needed of 0.25% bupivacaine. Satisfactory intraoperative anesthesia was achieved in all patients. No opioids administered. Intermittent bolus doses of 0.2% used to continue postoperative analgesia. Complications included dural puncture (1), intravascular catheter migration (1), and self-limited seizure (1).</td>
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<td>Murrell et al. (49)</td>
<td>20 neonates and infants ranging in age from 4 h to 35 days and in weight from 1.3 to 4.5 kg. Lumbar epidural catheter. Bolus dose of 0.8 ml kg⁻¹ of 0.25% bupivacaine with epinephrine (1 : 200 000) and fentanyl (1–2 µg kg⁻¹). No hemodynamic response to surgical incision during maintenance anesthesia of 0.5% isoflurane. Postoperative epidural infusions were used to provide analgesia for the initial 2–3 postoperative days.</td>
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<td>Tobias et al. (50)</td>
<td>25 neonates ranging in age from 1 to 28 days and in weight from 2.2 to 4.9 kg. Caudal epidural catheter uses a short intravenous cannula. Bolus dose of 1–1.5 ml kg⁻¹ followed by an infusion of 1-1.5 ml kg⁻¹ h⁻¹ of 3% chloroprocaine. No hemodynamic response to surgical incision during maintenance anesthesia of 0.2% isoflurane or 70% nitrous oxide. Twenty-three of the 25 infants underwent tracheal extubation in the operating room.</td>
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<td>Tobias (51)</td>
<td>Anorectoplasty in a 3-week-old, 3.6 kg infant with single ventricle physiology, pulmonary atresia, and PGE-dependent pulmonary blood flow. Spinal anesthesia with 1 mg kg⁻¹ of tetracaine and 5 µg kg⁻¹ morphine. No change in hemodynamic parameters following surgical incision during 0.2% isoflurane.</td>
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<td>Courreges et al. (52)</td>
<td>45 neonates and infants ranging in age from 1 to 87 days old and in weight from 2.6 to 6.3 kg for major abdominal surgery. Thoracic and lumbar epidural catheters. Bolus dosing of 0.5 ml kg⁻¹ of 0.25% bupivacaine with epinephrine (1 : 200 000). No hemodynamic response to surgical incision during maintenance anesthesia of 0.5–1% isoflurane or halothane. Postoperative analgesia provided by a continuous infusion of 0.125% bupivacaine or 0.25% lidocaine infusion at 0.2 ml kg⁻¹ h⁻¹ for 6–72 h. No complications noted.</td>
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<td>Van Niekerk et al. (53)</td>
<td>20 neonates and infants ranging in age from 1 to 62 days old and in weight from 0.52 to 2.75 kg for abdominal surgery. Epidurography confirmed placement lumbar or thoracic catheter from caudal approach. No hemodynamic response to surgical incision during maintenance anesthesia of 0.3% isoflurane. Complications included intravascular catheter migration (1), catheter curled (1), and catheter migration into muscle (1).</td>
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<td>Vas et al. (54)</td>
<td>20 neonates ranging in age from 18 h to 34 days and in weight from 1 to 3.4 kg for TEF repair and major abdominal surgery. Eighteen lumbar and two caudal epidural catheters. Dosing included a bolus of 0.25% bupivacaine at 0.1–0.2 ml kg⁻¹ segment⁻¹. Repeat dose at 90 min of 0.25% bupivacaine at 0.05-0.1 ml kg⁻¹ segment⁻¹. No hemodynamic response to surgical incision during maintenance anesthesia of nitrous/oxygen and 0.25–1% halothane. Nineteen of 20 underwent tracheal extubation in the operating room. No complications noted.</td>
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<td>Raghavan et al. (55)</td>
<td>22 neonates with an average gestational age of 36 week and weight ranging from 1.5 to 3.1 kg for gastroschisis repair. Lumbar and caudal catheter, single-shot caudal. Anesthesia was maintained with low dose of a volatile. Decreased need for postoperative ventilation requirement (23% vs 88% with GA only).</td>
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HR, heart rate; BP, blood pressure; TEF, tracheoesophageal fistula; GA, general anesthesia; PGE, prostaglandin E.

and 1849 1- to 6-month-old infants who received neuraxial blockade with general anesthesia, which included volatile anesthetic agents, benzodiazepines, ketamine, propofol, and methohexitol. The primary purpose of the study was to access adverse effects, and therefore, the ability of the neuraxial technique to decrease the dose or eliminate the need for anesthetic agents was not addressed.

Although several other investigators have outlined the use of epidural anesthesia in neonates and infants, many of these have included only descriptions of the placement technique or provided anatomic information regarding the epidural space in neonates and infants. As such, they are not included in this review. Additional studies discussing the intraoperative effects of neuraxial anesthesia combined with general anesthesia in this population are outlined in Table 1.

Adverse effects

As with any procedure, adverse effects may occur with regional anesthesia in this population. With regional anesthesia, adverse effects may be related to the placement of the needle and catheter, the medications
infused, or physiologic effects of the medications (sympathectomy). Of greatest concern is the risk of potential injury to spinal cord during placement. Although not advocated in the adult population, the placement of neuraxial anesthesia in the anesthetized patient is common practice in the pediatric-aged patient including the neonate (58). This practice is well within the accepted standard of care and large-scale databases such as the pediatric regional anesthesia network (PRAN) has demonstrated the safety of these practices (57,59,60). However, others advocate advancing a catheter from the caudal space to the higher levels (lumbar and thoracic) to avoid the need for direct placement at the thoracic level, thereby avoiding the risk of spinal cord trauma. Despite these concerns, large-scale studies regarding the safety of regional anesthesia in the pediatric-aged patient have failed to report any major, permanent neurologic sequelae of these practices (57–59). However, there remains anecdotal reports outside of these databases of significant morbidity, which although not conclusively linked to the regional anesthesia technique still limits the enthusiasm of some practitioners regarding the use of regional anesthesia (61,62). Additional work into the specific etiology of such problems is needed to further increase the safety of these techniques. The advent of ultrasound has been suggested as a means of facilitating not only peripheral, but also neuraxial blockade. Its use in these techniques in patients of all ages is likely to increase (63). Given the risks of bleeding (epidural hematoma formation), neuraxial techniques are contraindicated in patients with coagulation disturbances including qualitative and quantitative platelet disorders. Attention to these details is also necessary during catheter removal (64).

Dosing concerns for local anesthetic agents are of prime importance during regional anesthetic techniques in the neonate and infant. As with other medications, the pharmacokinetics of local anesthetic agents can be quite variable in the neonatal population. The hepatic microsomal enzymes systems, although functional even in the preterm infant, do not attain adult levels until 1–3 months of age. Additionally, decreases in binding proteins (alpha-1-acid glycoprotein) result in a greater free fraction and potentially an increased risk of toxicity (65,66). For single-shot doses, no significant clinical difference exists between neonates and older patients with current recommendations and clinical experience varying from 2.5 up to 3.5 mg·kg\(^{-1}\) of bupivacaine with the higher doses being used when caudal anesthesia is used instead of general anesthesia in the high-risk neonate. During initial bolus dosing, attention to clinical signs suggestive of inadvertent intravascular injection is mandatory to prevent toxicity. These dosing guidelines are particularly relevant when using a low-lying catheter. Although a larger initial bolus dose may be used to achieve surgical anesthesia at a higher level, ongoing use of higher infusions rates will result in toxicity (67,68). In older patients, bupivacaine infusions should not exceed 0.3 mg·kg\(^{-1}\)·h\(^{-1}\) while even lower infusion rates (0.2 mg·kg\(^{-1}\)·h\(^{-1}\)) are recommended in neonates and infants (67). Even within these ranges, bupivacaine accumulates with prolonged infusions (more than 48 h; 69). As noted above, these issues have led some to suggest that chloroprocaine, given its short plasma half-life even in neonates, may be a safer and more effective alternative. Although generally used to provide postoperative analgesia, neuraxial opioids may be combined with the local anesthetic agent for both spinal and epidural techniques. Although this practice may provide effective analgesia, respiratory depression may occur especially with the use of hydrophilic opioids such as morphine. As such, prolonged postoperative monitoring for 24 h is generally recommended.

In addition to providing sensory and motor blockade, some degree of sympathetic blockade will accompany neuraxial anesthesia. In the adult population, sympathetic blockade may result in hypotension or even bradycardia with higher levels (T4 and above). Cardiovascular changes related to spinal anesthesia are generally less frequent and less severe in children than adults (70,71). This is true even following high thoracic spinal anesthesia in neonates and infants including those patients with congenital heart disease (71–73). Should they occur, hemodynamic and cardiovascular changes following spinal anesthesia respond to fluid administration or \(\alpha\)-adrenergic agonists for hypotension and anticholinergic agents for bradycardia.

While the majority of the data has focused on the potential for volatile and intravenous anesthetic/sedative agents to cause neuroapoptosis in the brain, additional studies have demonstrated that these changes may occur throughout the central nervous system including the spinal cord (74). Further work has demonstrated no increased apoptosis with the administration of intrathecal bupivacaine to rates, thereby suggesting a lack of neurotoxicity (75).

**Summary**

Given the deleterious effects of the surgical stress response and its impact on morbidity and mortality, effective anesthetic techniques are mandatory during surgical procedures in neonates and infants (76,77). Recent work has focused on the potential deleterious effects of various volatile and intravenous anesthetic agents on neurocognitive outcome of neonates and
infants. In many of these studies, the effect has been demonstrated to be dose and time related, suggesting that techniques which limit the intraoperative needs to these agents may be beneficial. Regional anesthesia including epidural and spinal anesthesia has been shown to have several potential beneficial effects in this population including earlier tracheal extubation, effective blunting of the surgical stress response, and limiting the need for parenteral opioids. Additionally, many of these reports demonstrate a reduction in the intraoperative requirements for volatile anesthetic agents. Although no reports demonstrate a reduction in the intraoperative requirements for parenteral opioids. Additionally, many of these studies were less than 0.5 MAC (minimum alveolar concentration). There remains a need for further investigation into this combined modality in this group of patients, given the neuronal apoptotic and long-term behavioral and cognitive implications when an abbreviated dose of general anesthesia is not employed. A cooperative effort between neonatologist, pediatric surgeons, and anesthesiologists could further the utility of a combined technique to the benefit of the neonate, not only in the perioperative period, but also potentially long term.

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