Pediatric Regional Anesthesia: Drawing Inferences on Safety from Prospective Registries and Case Reports

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Two articles in this month's *Anesthesia & Analgesia* address safety of regional anesthesia and analgesia in pediatrics.[1,2] At first glance, one is very reassuring, the other is frightening. In this Editorial, we will recommend a middle ground. Practitioners of pediatric regional anesthesia should be careful and vigilant but can be confident that many types of complications can be made extremely rare by adopting some recommended practice patterns.

Over the past 30 years, pediatric applications of postoperative regional anesthesia and analgesia have expanded rapidly.[3] There is now a substantial body of studies regarding techniques, pharmacokinetics, and clinical outcomes. Age-related trends in local anesthetic pharmacokinetics have been characterized, and safe dosing guidelines have been established.[4]

Most regional anesthesia in adults is performed awake or with doses of sedatives and analgesics that maintain verbal responsiveness, permitting patient reporting of paresthesias, severe pain with needle movement or injection, immediate symptoms of systemic local anesthetic effect, and progression of sensory and motor blockade over the minutes after injections. Textbooks, review articles, and consensus documents often strongly criticize performing most types of major peripheral or neuraxial blocks in adults under deep sedation or general anesthesia.[5]

In contrast, most, but not all, regional anesthesia in children is performed under either deep sedation or general anesthesia. Advocates of pediatric regional anesthesia have cited a series of retrospective and prospective safety studies to support their contention that the widespread practice of performing regional anesthesia under general anesthesia is safe.[6–8]

Polaner et al. report on the first 3 years of prospective registry data from PRAN, the Pediatric Regional Anesthesia Network, a consortium of North American pediatric centers. This report has a number of strengths. The data collection and analysis plan was generally thoughtfully constructed. There is a good degree of detail and new information regarding how procedures are performed and regarding most adverse events. The methodology for data gathering is likely to be fairly complete for intraoperative serious adverse events and for events occurring during patients' inpatient stay. There are several scenarios that could potentially lead to underreporting of peripheral nerve injuries, most notably partial nerve injuries in nonverbal or nonambulatory children that might evade detection by parents and physicians. For example, a thoracic nerve root or an intercostal nerve injury following thoracic epidural or thoracic paravertebral block might not be detected in a preverbal child. In addition, for a patient in a cast, a deficit might not be apparent until days to weeks postoperatively. The methodology for postoperative surveillance in this registry is likely to omit some cases with delayed detection.

Despite these possible sources for underreporting, the PRAN investigators make a good case for the overall very good safety of pediatric neuraxial and peripheral blocks as performed by clinicians in these hospitals.

In contrast to the conclusion of the PRAN investigators that "nothing really bad happened," Meyer et al. showed admirable courage and forthrightness in reporting on 4 cases of neurologic injury following epidural anesthesia in children. All 4 cases involve care by experienced anesthesiologists with extensive experience in pediatric epidural analgesia and acute and chronic pain management.

Based on the incomplete information available in this case report, we would tend to agree with the authors' general contention that there was "absence of proof of medical negligence." A more important question, which the authors have addressed in their discussion, might be phrased as follows: "Based on these cases and other available knowledge, do we have ways to modify our practice to prevent similar complications in the future?" We consider the 4 cases in this light, taking advantage of "20–20 hindsight."

Among the 4 cases, case 1 was perhaps the most frightening, because the patient was healthy and uncomplicated, the epidural catheter placement proceeded uneventfully at a lumbar level below the terminus of the spinal cord, the duration of general anesthesia was short, and there were no hemodynamic clues intraoperatively to raise concerns. The test dose was appropriate (0.1 mL/kg).

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Even though the loading dose of local anesthetic contained epinephrine, it should be noted that this 4 mL dose was fractionated, and that for a 15 kg child, it was a comparatively small loading volume (0.26 mL/kg). Typical epidural loading volumes for lumbar or caudal epidural anesthesia in infants and toddlers are often >3-fold higher, or roughly 0.8 to 1 mL/kg. Aside from the use of epinephrine in this low-volume loading dose, everything about the case was "textbook." We are forced to invoke very rare mechanisms, such as direct injury to a low-lying arterial variant supplying an anterior spinal artery, unrecognized intravascular injection of air, or epinephrine-induced anterior spinal artery spasm. As reviewed previously by Neal, there is overall very little evidence for neuraxial epinephrine inducing spinal cord ischemia or other harm in humans.[9]

For each of the other cases, the situation appeared more complicated, and in hindsight, one could identify clues that should in the future raise our concern or suggest practice changes. Case 2 involved multiple factors that could reduce spinal cord perfusion pressure, including prolonged surgery, extreme Trendelenberg position, episodic reductions in arterial blood pressure and elevations in central venous pressure. Infusion of a comparatively high volume of epidural solution, partially in boluses and partially via infusion in a patient with epidural lipomatosis[10] and reduced spinal canal compliance could have resulted in a "neuraxial compartment syndrome."[11] It is common for patients to have degrees of sensory and motor block following epidural-light general anesthesia. Nevertheless, in our view, this case and related cases illustrate the need for standardized protocols for examination of patients in the postanesthetic care unit and early identification of those with greater impairments than would be expected from the intraoperative dosing. In our view, particularly when combined epidural-general anesthesia is used for prolonged surgery, there is a strong case to be made for intraoperative use of more dilute solutions of local anesthetics, e.g., bupivacaine 0.1% or ropivacaine 0.1% to 0.15%. With these dilute solutions, if a patient has complete sensory block of the lower body or cannot move the legs at all in the postanesthetic care unit, the immediate response should be to stop the infusion and reassess frequently. Failure to demonstrate regression of block/deficits over the next 2 hours should be assumed to represent a potential neurologic emergency, and should result in urgent spine magnetic resonance imaging (MRI) and neurosurgical consultation. In this case, surgery was very prolonged and the patient arrived in the postanesthetic care unit late in the day. Initial recognition of dense motor impairment occurred 5 hours later and, despite prompt attention at that time, neurosurgical intervention did not occur until the next day. Whether more rapid decompression might have resulted in greater sparing of spinal cord functioning is a conjecture but unproven. Epidural lipomatosis is underappreciated as a risk factor, and clinicians should regard morbidly obese patients and those receiving high-dose corticosteroids as potentially at increased risk.[12]

Case 3 involved a lumbar paravertebral catheter placement and infusion, several lumbar epidural catheter placements, several changes in epidural solution, and use of a large number of epidural medications, including bupivacaine, ropivacaine, fentanyl, clonidine, chloroprocaine, and butorphanol. The pattern of deficits, the neurologic examination, and the reported results of MRI give a confusing picture, which might even involve a combined effect of a neuritis involving the cauda equina and lumbosacral nerve roots along with a persistent inflammatory effect of the previous lumbar paravertebral sympathetic catheter infusion leading to impairments in sympathetic innervation to the urinary and anal sphincters and to the branches of the right lumbar plexus, including the right genitofemoral nerve.

The use of epidural butorphanol is controversial. The formulation was apparently preservative-free, and there have been previous adult and pediatric clinical trials of its use.[13] The histologic effects of butorphanol were regarded as benign following epidural administration in dogs but neurotoxic following intrathecal administration in sheep. The cumulative numbers of patients in published clinical trials and case series for epidural butorphanol are relatively small and insufficient to define confidence limits on the risk for neurotoxicity in humans. Concerns regarding off-label administration of neuraxial drugs have been highlighted previously by Professors Eisenach, Shafer, and Yaksh.[14] Several other drugs commonly used in the epidural space are not labeled for such use (e.g., fentanyl), but there is a much more extensive body of animal and human literature supporting their safety. In addition, most drugs that are labeled for epidural use do not have pediatric labeling for that route of administration. If there are toxicities that are age-specific, based on what is known about peripheral nerve development, it seems probable that these would apply to infants and toddlers, but that adolescents should respond in a manner similar to adults. Animal models have been developed to examine age-dependence of systemic and local toxicities of peripheral and neuraxial local anesthetics and other analgesics.[15,16]

Case 4 involved direct thoracic placement under general anesthesia, severe hypotension after a test dose and again after an intraoperative loading dose, followed by apparent signs of high spinal anesthesia after a repeat dose in the postanesthetic care unit. The authors interpret the report of the MRI as most consistent with a vascular pattern of injury. From the available information presented, including neurologic examinations and responses to multiple local anesthetic injections, the catheter location appeared subarachnoid, and we cannot exclude direct contact of the needle or catheter with the thoracic spinal cord. In considering this case, as well as cases reported previously by Flandin-Blety and Barrier,[17] we agree with the authors that severe hypotension following a test dose or loading dose in an anesthetized child should be taken seriously and not immediately ascribed to hypovolemia. In our view, clinicians should avoid repeat dosing in an anesthetized patient, or, in selected cases, should consider use of low volume contrast epidurography prior to any repeat local anesthetic dosing.

Prompt recognition of deficits improves outcome in the setting of epidural hematoma and epidural abscess and other sources of epidural mass effect, including epidural

Table 1. Provisional Recommendations for Epidural Anesthesia in Anesthetized Children

1. Limit epinephrine dosing to the test dose (0.5 μg/kg in 0.1 mL/kg).
2. Prevent or promptly treat severe hypotension.
3. Consider severe hypotension following test dosing or loading dosing of an epidural catheter under general anesthesia to be due to subarachnoid placement unless demonstrated otherwise.
4. Consider severe hypertension following test dosing or loading dosing to possibly indicate a painful response to intraneural placement.
5. Perform loss-of-resistance with saline, not air.
6. Consider selective use of Tsui's nerve stimulation technique or fluoroscopy, as well as ultrasonography for infants, for cases of direct thoracic puncture under general anesthesia.
7. Inject epidural loading doses slowly in anesthetized patients.
8. Use dilute local anesthetic solutions for intraoperative epidural infusions.
9. In the postanesthetic care unit, document the degree of sensory and motor blockade. If blockade appears dense, stop the infusion and observe for clear regression. If there is no regression at all over the next 3 h, consider emergent spine magnetic resonance imaging and neurosurgical consultation as appropriate. Note that wire-wrapped epidural catheters must be removed prior to magnetic resonance imaging.
10. Consider patients receiving high dose corticosteroids and/or morbid obesity as at increased risk for epidural lipomatosis and reduced spinal canal compliance.

tumor. However, none of these 4 cases involved hematoma, abscess, or tumor.

Should these cases change our views about safety of pediatric neuraxial anesthesia under general anesthesia, or should our practices be modified? Although these cases are concerning, they still represent very rare events compared to the cumulative denominator from published case series. For cases 1, 2, and 3, it is not clear that the pathologic processes leading to adverse outcomes would have been prevented by the common practice in adults of awake placement and awake initial test dosing and loading doses followed by repeated dosing or infusions during combined epidural anesthesia and general anesthesia. With case 4, there is more reason to implicate placement under anesthesia as possibly contributing to delay in recognition of subarachnoid placement.

For confirmation of needle and catheter location with direct thoracic placement, 3 approaches may be used. Fluoroscopic guidance of needle placement and contrast epidurography can be helpful both to direct the needle and to confirm that the catheter tip location is epidural rather than subarachnoid or entirely outside the neuraxis.[18] Fluoroscopy takes some time, involves radiation exposure, and involves some costs and charges. With midthoracic placement in a lateral position as in case 4, optimal positioning of the patient's arms and careful adjustment of the C-arm is required to obtain anatomically correct and useful lateral and anterior-posterior images and to distinguish an epidural from subarachnoid (myelographic) pattern of contrast spread. Tsui et al.'s nerve stimulation technique involves a wire-wrapped epidural catheter and special adapters that conduct electricity through a column of saline in the catheter, dispersing current through the catheter tip.[19,20] Epidural positioning is confirmed by observing muscle twitches in appropriate territories with currents ranging from roughly 2 to 15 mA. Subarachnoid placement is suggested by bilateral twitches at currents less than or equal to 0.5 mA. Nerve stimulation guidance is not perfect, and there are some technical challenges that can result in false positive and false negative tests, but with practice and attention to technique it can be very helpful in confirming epidural positioning, dermatomal level of the catheter tip, and in avoiding wrong-sided placement in the epidural space. For infants, ultrasound can be used to direct epidural needles and catheters and can confirm the location of injected solutions. Despite our adoption of these practices, we do not claim that available evidence allows estimation of the impact of these techniques on the absolute risk reduction or the numbers-needed-to-harm of pediatric thoracic epidural placements.

Do these cases and the findings of the PRAN registry imply that peripheral and plexus blocks and infusions are safer than epidural analgesia in anesthetized children? In our view, it would be premature to draw this conclusion too strongly. For example, some older case reports and case series and textbook chapters suggested that, in pediatrics, lumbar plexus catheters have higher risks compared to lumbar epidural catheters. However, most of these cases were performed before contemporary use of combined ultrasound and nerve stimulation guidance.[21]

In Table 1, we offer provisional recommendations that might reduce the risk or improve the outcome following rare events such as the cases cited by Meyer et al. We emphasize that these recommendations are provisional and based on clinical impression, not on a solid body of evidence.

The above discussion concerns safety. To evaluate the status of pediatric regional anesthesia at present, it is equally important to assess technical success rates and clinical effectiveness, to properly evaluate risk-benefit ratios. A large number of clinical trials have reported technical success, pain scores, rescue opioid dosing, side effects, and functional recovery parameters. These reflect outcomes under the controlled conditions of a clinical trial. Ideally, a registry like the PRAN database should provide some information about clinical effectiveness in real-world conditions. The data from the PRAN database tell quite a bit about what techniques are used and how safe they appear, but at present there is essentially no information about block success rates, either based on measurement of sensory or motor block, postoperative pain scores, or reduction in rescue systemic analgesic requirements relative to control subjects not receiving regional anesthesia and analgesia. The authors initially attempted to gather data on clinical effectiveness. Shortly after beginning the registry, they found that the participating institutions varied widely in their use of pain measures, documentation of block success, and protocols and practices for postoperative

analgesia. They concluded that their registry and procedures would not provide meaningful data on technical success or clinical effectiveness, so they decided to stop recording these data for the remainder of the study period.

The authors are probably correct that it would have been extremely problematic to draw conclusions about effectiveness without an enormous effort at standardization of measurements and rescue analgesic protocols across these institutions. Nevertheless, it is unfortunate that these "positive outcome data" are not presently available from such a large well-planned and well-executed registry. In the future, we strongly recommend that institutions in this registry adopt consensus-based outcome measures[22] that include multiple domains related to pain, opioid-sparing, side effects, and functional recovery. In summary, the PRAN registry is an important contribution to the study of outcomes of pediatric regional anesthesia. It gives an overall favorable impression regarding the safety of contemporary practices with a larger patient sample than previous studies. The PRAN consortium should be in a strong position to guide future studies of clinical effectiveness of pediatric regional anesthesia.

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