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REVIEW ARTICLE

Recent trends in the management of acute pain in children

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The author provides practitioners with a summary of recent trends in the management of acute pain in children. This review encompasses pharmacologic techniques as they pertain to two common acutely painful conditions in children: postoperative and procedural pain. In the area of postoperative analgesia, reviewed are the use of regional anesthesia, spinal opioids, α-agonists, preemptive analgesia, and patient-controlled analgesia. In the area of procedural pain, current standards for safety guidelines and several recently introduced sedative and analgesic medications are discussed. The author emphasizes that the proper and safe alleviation of acute pain in the pediatric population is not only feasible but is currently the standard of care in the United States.

(Key words: Anesthesia pediatric, regional; pain acute, pediatric; patient-controlled analgesia; opioids; spinal opioids; benzodiazepines; propofol; local anesthetics; eutectic mixture of local anesthetics [lidocaine and prilocaine]; analgesia, preemptive; ketorolac).

In the past decade, the awareness of the deleterious effects of pain has increased dramatically,[1] and practitioners' reluctance to treat pain in children has decreased. In general, pediatric patients are no longer deprived of analgesics for fear of overmedication, addiction, or ignorance of their appreciation of pain. In many large children's centers, anesthesiology and pediatric departments have organized formal pain services to serve as consultants on complex cases, as well as to provide education for house officers on analgesic techniques. The purpose of this review is to discuss some of these recently developed techniques. The review encompasses mainly pharmacologic strategies as they pertain to two common acutely painful conditions in children: postoperative and procedural pain. It is not intended to be a comprehensive overview of pain management in this population, but rather a brief, and timely, review of some modern innovative strategies.

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Postoperative pain

In the 1980s, several published studies reported that children received less postoperative analgesics than their adult counterparts.[2-4] These observations provided the impetus for the present-day concern for postoperative pain control in children. Various methods exist with which to ensure a pain-free postoperative course in the tiniest infants or following the most complex surgical procedures. In addition to traditional methods (such as administering parenteral analgesics on demand), regional analgesia or anesthesia, and patient-controlled analgesia (PCA) are effective in children.

Although generally underused, regional anesthesia is the simplest and most efficacious method. One technique is to administer a single injection of local anesthetic intraoperatively. Alternatively, if it is decided that analgesia should continue for an indeterminate period postoperatively, a small catheter is secured in the region of the nerves providing innervation to the surgical site, and a continuous supply of local anesthetic is infused. Either method can be used for peripheral or central axis analgesia.

Peripheral nerve blocks

Local anesthetic can be administered indirectly as a field block before skin incision or directly onto the nerves intraoperatively. There are few surgical procedures in which this method of postoperative analgesia *cannot* be used. A long-acting local anesthetic, such as bupivacaine hydrochloride, will usually provide 4 to 12 hours of anesthesia, depending on the nature of the surgery and the location of the block. The inclusion of epinephrine (1:200,000)

will increase the duration of analgesia. Bupivacaine is an amide local anesthetic that is administered in doses up to 2.5 mg/kg. Lower doses are used in neonates and small infants because of their relative deficiency of alpha$_1$-acid glycoprotein, a serum protein that binds to local anesthetics. Because of this relative deficiency, neonates are more likely to exhibit local anesthetic toxicity at lower doses than older children.[5] Toxicity is manifested by central nervous system excitation (seizures) and cardiovascular collapse. Techniques of commonly used pediatric nerve blocks are described in detail in two excellent reviews.[6,7]

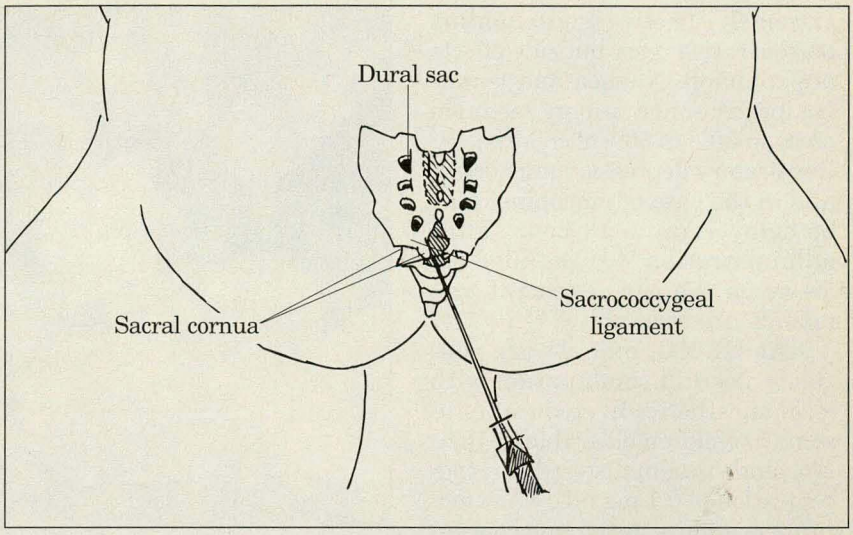

Figure 1. *This illustration demonstrates the anatomic landmarks for insertion of local anesthetic or an epidural catheter into the epidural space via the caudal canal. (Drawing courtesy of Steven Allis.)*

Central axis blocks

The central axis consists of the spinal cord and spinal nerves that emanate from the cord. The two approaches to the central axis are via the subarachnoid and epidural spaces. These can be accessed anywhere from the cervical to the caudal vertebrae, depending on the purpose of the block. Traditionally, local anesthetics are used to provide anesthesia, but opioids are also commonly administered, and alpha$_2$-agonists, such as clonidine, are being used as well.

The epidural route is generally chosen over the subarachnoid route for postoperative pain management. Theoretically, it is safer to leave an indwelling catheter in the epidural space rather than the subarachnoid space where accidental overdose might lead to respiratory arrest, and where infection can potentially cause meningitis. Furthermore, recent reports[8] of cauda equina syndrome following continuous subarachnoid anesthesia in adults prompted the US Food and Drug Administration to place a safety alert (May 29, 1992) on the use of spinal microcatheters pending further investigation.

Technically, the easiest approach to the epidural space in small children is via the caudal canal. The landmarks are prominent, and little chance of accidental dural puncture exists. Local anesthetic or opioids (or both) are injected into the epidural space through the sacrococcygeal ligament, which is found between the sacral cornua *(Figure 1)*. A dilute solution of bupivacaine (0.25% or 0.125%) with epinephrine (1:200,000) is commonly administered; it provides 4 to 8 hours of pain relief below the level of blockade. A single injection of 0.5 mL/kg (0.125 mg/kg) will provide analgesia to regions innervated below the 10th thoracic dermatome. This dosage is generally sufficient for lower extremity and groin procedures. For abdominal procedures, 1 mL/kg (0.25 mg/kg) will provide analgesia to innervations as high as the sixth thoracic dermatome. Alternatively, a catheter is placed in the epidural space and is secured to the child's back for use postoperatively *(Figure 2)*. It is possible to thread the catheter cephalad to the desired level needed for sufficient analgesia, even to a high thoracic level.[9] Typically at the University of Rochester Medical Center (URMC), a dilute solution of bupivacaine hydrochloride (0.125% or 0.0625%) is infused at an initial dose of 0.3 mg/kg to 0.4 mg/kg per hour.

Side effects, such as unintentional subarachnoid blockade or urinary retention, are uncommon, but transient or permanent nerve damage is extremely rare. The extent of motor blockade will vary directly with increasing concentration and dose of local anesthetic used. Reports of seizures in pediatric patients receiving continuous bupivacaine infusions prompted a reevaluation of the maximal toxic doses in this age range.[10,11] Although little data exist on the pharmacokinetics of continuous epidural bupivacaine infusions in children, doses should probably be limited to less than 0.5 mg/kg per hour.[12]

Spinal opioids

Opioids administered into the epidural or subarachnoid space will result in central analgesia. Fentanyl citrate and morphine are most commonly used. Fentanyl is lipophilic and is absorbed rapidly into the spinal cord and epidural vessels, resulting in early onset of analgesia and a relatively short duration of action (45 to 90 minutes). Water-soluble, morphine accumulates in the spinal fluid where it is transported cephalad to the brain. Its onset of action is approximately 1 to 2 hours, and it provides up to 24 hours of pain relief. Spinal opioids are

extremely effective in attenuating postoperative pain, but side effects are common. Nausea and vomiting, pruritus, and urinary retention occur in 30% to 50% of children.[13,14] Respiratory depression may occur, and in the case of morphine, may be delayed up to 18 hours after administration.[15,16] Detailed reviews on the use of central axis opioids are available.[17,18]

At URMC, opioids are routinely used in combination with local anesthetics in epidural infusions in children older than 1 year. Morphine is administered in a concentration of 0.1 mg/mL, while fentanyl is administered in a concentration of 2.5 μg/mL. Subarachnoid morphine, 0.1 mg to 0.2 mg, is administered when the surgical procedure is extensive, and the child will be recovering in the intensive care unit with careful respiratory monitoring. An example of this is following anterior or posterior spinal fusion for scoliosis.

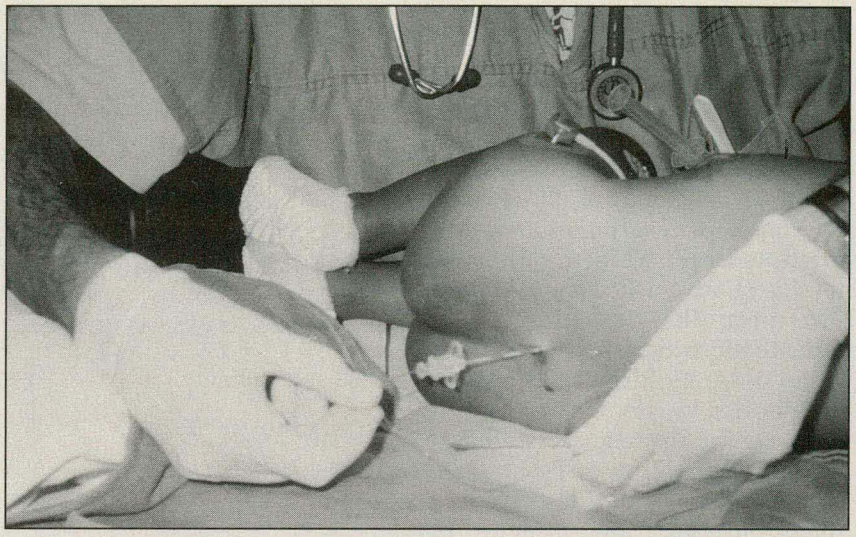

Figure 2. *While the infant is anesthetized, an epidural catheter is inserted through a large-bore needle that is placed into the caudal canal using sterile technique. The catheter is taped to the infant's back and used postoperatively to administer local anesthetics.*

Alpha-agonists

Recently, extensive investigation has been undertaken regarding the use of alpha$_2$-agonists, such as clonidine, administered into the central axis. Spinally administered clonidine causes sedation and analgesia without the marked respiratory effects of opioids. Although the exact mechanism of analgesia is not completely understood, it appears that clonidine binds with alpha$_2$-receptors in the spinal cord and results in inhibition of neurotransmitter release. At the level of the dorsal root neuron, alpha$_2$-agonists inhibit substance P release in the nociceptive pathway. When added to epidural bupivacaine, clonidine, 1 μg/kg, increases the degree and duration of postoperative analgesia in children.[19] Intravenous (IV) administration of clonidine can cause sedation that may be mediated by its effect on the locus ceruleus, a small, discrete nucleus of noradrenergic cells in the brain stem.[20] Once further investigations are completed, alpha$_2$-agonists will undoubtedly play an important role in the pharmacologic arsenal of perioperative analgesia.

Preemptive analgesia

Peripheral tissue injury, such as that due to surgical trauma, results in peripheral and central sensitization—changes in the way the nervous system responds to subsequent painful stimuli. Peripheral sensitization is a decrease in the threshold of nociceptor afferent terminals. Central sensitization is an increase in the excitability of spinal neurons. The combination of these two phenomena following surgical trauma results in a state of hyperexcitability and a decreased pain threshold postoperatively.[21] Initiating the administration of analgesics postoperatively is often ineffective as the nervous system is already modified when the damage is done. This knowledge has led to the theory that preemptive analgesia—blocking the painful stimuli before they arise—may prevent or attenuate postoperative pain by preventing peripheral and central sensitization. Clinical studies in adults have thus far substantiated this theory,[21] but further investigation is needed in this area to delineate optimal management.

Patient-controlled analgesia

Patient-controlled analgesia has become the preferred method for controlling acute pain in a variety of settings.[22] Its main advantage is that a constant blood level of opioid can be attained that is specific for the individual patient's pain threshold. Peak levels of opioids are generally avoided, and the amount of maximum opioid that can be delivered is limited by a computer-controlled infusion device. As such, PCA avoids intermittent cycles of pain and is an inherently safe technique. The child may control the frequency of the opioid dose, but the physician decides the amount of that dose, the minimum interval between doses, and the maximal hourly dose. The use of PCA may enable children to benefit psychologically by maintaining self-control over their analgesic needs during the period of hospitalization—a critical time of loss of self-control.[23]

Berde and colleagues[24] studied 82 children and adolescents between the ages of 7 and 19 years who underwent orthopedic procedures. The patients were randomly assigned to receive either intramuscular (IM) morphine, intermittent PCA

morphine, or intermittent PCA morphine plus a continuous background morphine infusion for postoperative analgesia. The authors reported that patients who received the PCA regimens had a higher quality of pain control and greater satisfaction than those who received IM injections, without a higher incidence of opioid-related complications.

There is no lower age limit with which to restrict the use of PCA, as long as the child understands the principles of its use, as well as that pain relief following a bolus dose will not occur immediately; and has the physical capability to push the button on demand. In general, children older than 7 or 8 years will comprehend the use of this device, but each child should be evaluated individually. Physicians must ensure that the patient's nurse and family are fully educated in the use of PCA, and that only the patient is allowed to push the button, thus preserving an inherent safety feature. Nurse-controlled analgesia has been described for children who are delayed developmentally or who are unable to physically push the button and may be an acceptable alternative for selected patients.[25]

Procedural pain

Procedural pain is the acute suffering during invasive medical procedures. Common examples include injections with needles and reduction of fractured bones. Procedural pain is most commonly encountered in the emergency department, but may also occur in pediatric subspecialty clinics where painful procedures (such as bone marrow aspiration) are commonly performed. In the not-too-distant past, physicians were either unconcerned about acute pain in children and thus used little more than restraint devices for physical containment, or were content to heavily sedate children with agents, such as chloral hydrate, or the "lytic cocktail" (meperidine hydrochloride, promethazine hydrochloride, prochlorperazine), which are fraught with side effects or long durations of action. Unfortunately, there is no "magic bullet"—that is, one medication that is easy to administer, contains both analgesic and anxiolytic properties, and carries little risk of adverse effects. In general, the preferred method is a combination of sedatives that enables one to take advantage of their desirable properties while avoiding adverse effects. Whichever drugs or combination thereof is chosen, the practitioner should always adhere to stringent safety guidelines, such as those published by the American Academy of Pediatrics (AAP).[26]

AAP guidelines

In 1987, the AAP published guidelines that intended to set the standard of care with regard to requirements for monitoring and personnel during sedation of children. These guidelines were subsequently revised in 1992.[26] The AAP recognizes that there are two general states of sedation that may be achieved via anesthetics: conscious and deep sedation (*Table 1*). The AAP's recommendations for monitoring and personnel are based on the level of sedation achieved (*Table 2*).

Opioids

Opioids are traditionally incorporated into analgesic regimens because of their ability to provide potent analgesia without unconsciousness. For many years, the lytic cocktail was commonly used to sedate children during painful procedures. This regimen has recently fallen out of favor because of its long duration of action and propensity for potentially harmful side effects.[27,28] Therefore, practitioners have sought a reliable, safe opioid that is easily titratable. Morphine and meperidine are not desirable because of their relatively long durations of action.

Fentanyl citrate is a synthetic opioid approximately 100 times more potent than morphine. It has gained popularity because of its rapid onset and short duration of action (30 to 40 minutes). A large retrospective study using 2 μg/kg to 3 μg/kg confirmed its safe use in children during repair of facial lacerations.[29] Fentanyl is also available in a lollipop form called an orulet.[30,31]

Alfentanil hydrochloride is a synthetic opioid agonist related to fentanyl. Less potent than fentanyl,

Table 1
Definition of Sedative States*

■ **Conscious sedation**

A medically controlled state of consciousness that:

- □ allows protective reflexes to be maintained;
- □ retains the patient's ability to maintain a patent airway independently and continuously; and
- □ permits appropriate patient response to physical stimuli or verbal commands ("Open your eyes.").

■ **Deep sedation**

A medically controlled state of depressed consciousness from which the patient is not easily aroused. It may:

- □ be accompanied by a partial or complete loss of protective reflexes; and
- □ includes the inability to maintain a patent airway independently and respond purposely to physical stimuli or verbal commands.

*Data from the American Academy of Pediatrics.[26]

alfentanil has an extremely short duration of action because of its small volume of distribution. However, it tends to accumulate when large doses are used over prolonged periods. In IV doses of 10 μg/kg to 25 μg/kg, alfentanil hydrochloride provides adequate analgesia for short, painful procedures, such as fracture reduction performed in the emergency department. Patients can be discharged sooner than when they are receiving other opioid agents. Remifentanil is an ultrashort-acting opioid that is due to be released in the near future. It differs from alfentanil in that it does not accumulate after repeated doses and thus promises to be the ideal analgesic for painful procedures of indeterminate duration. Regardless of their onset or offset times, all opioid agents have a similar profile of side effects, the most important being respiratory depression. Other common side effects of opioids include pruritus, nausea, vomiting, and urinary retention.

Ketorolac tromethamine

A recently introduced nonsteroidal anti-inflammatory agent, keterolac tromethamine is one of the few parenterally administered analgesics in its class. This agent was first touted as an alternative to opioids for postoperative analgesia; however, its ability to equal the analgesic effects of morphine are unsubstantiated.[32,33] Ketorolac will ultimately be used for postoperative pain management as a supplement to opioid analgesia to decrease unwanted opioid effects, such as vomiting and respiratory depression.[34,35] Ketorolac inhibits platelet aggregation by inhibition of prostaglandin synthetase. However, no study has shown a clinically meaningful increase in perioperative bleeding with its use. At URMC, ketorolac tromethamine (1 mg/kg) is administered during most pediatric surgeries to supplement regional and intravenous analgesics.

Benzodiazepines

Benzodiazepines are frequently incorporated into sedative regimens because of their ability to cause anxiolysis and anterograde amnesia. Diazepam, lorazepam, and midazolam hydrochloride are commonly used, but diazepam and lorazepam are undesirable for use during short procedures because of the drugs' relatively long durations of action. Another undesirable property of diazepam is its propensity to cause significant pain when injected intravenously. Because of these concerns, midazolam is usually the first-line agent for sedation of children. Its onset and duration are predictably short; its safety profile is excellent, and because it is water-soluble, no pain occurs on injection. It can be administered by the oral (0.5 mg/kg), nasal (0.3 mg/kg), or IV (0.05 mg/kg) routes. However, it is not recommended as the sole agent, because it does not reliably produce a cooperative motionless child (at safe doses), and it is not an analgesic. As no oral formulation is available, the IV solution is used orally in doses up to 0.75 mg/kg.[36,37] Although midazolam tastes extremely bitter, the oral route, nonetheless, remains the most practical option.

Table 2
Guidelines for Monitoring and Personnel*

■ **Conscious sedation**

Personnel

Practitioner. Responsible for treatment of patient, administration of all sedative drugs, and managing complications. Must be trained in Pediatric Basic Life Support (PBLS); training in Pediatric Advanced Life Support (PALS) strongly encouraged.

Support person. Responsible for monitoring physiologic parameters during sedation and assist in resuscitation. Training in PBLS strongly recommended.

Monitoring

- ☐ Continuous pulse oximetry and heart rate
- ☐ Intermittent respiratory rate and blood pressure

■ **Deep sedation**

Personnel

Practitioner. Responsible for treatment of patient, administration of all sedative drugs, and managing complications.

Support person. Responsible for continuous monitoring of patient's vital signs, airway patency, and adequacy of ventilation.

- ☐ At least one of the personnel must be trained in PBLS and airway management; training in PALS strongly recommended.

Equipment

- ☐ Electrocardiograph and pediatric defibrillator
- ☐ Intravenous (IV) access immediately available and/or an established IV

Monitoring

- ☐ Continuous pulse oximetry and heart rate, documented every 5 minutes
- ☐ Intermittent respiratory rate and blood pressure
- ☐ Monitor ventilation status via precordial stethoscope or capnograph

*Data from the American Academy of Pediatrics.[26]

Propofol

Propofol is an ultrashort-acting hypnotic that has become the preferred agent for induction and maintenance of general anesthesia. The major advantage of propofol over other hypnotic agents (for

example, thiopental sodium) is its lack of accumulation after multiple doses. Thus, onset and duration are easily controlled. Patients have a rapid, complete return to their baseline mental status soon after propofol infusion is discontinued. In lower dosages, this drug has been used as a sedative agent during painful and radiologic procedures.[38,39] The dose is titrated to effect and is usually given in increments of 0.5 mg/kg to 1 mg/kg. The IV administration of propofol is likely to cause pain or burning at the site of injection, especially in children. The addition of lidocaine (0.2 mg/kg) to the propofol solution can attenuate this effect.[40]

Although safety data are lacking, it appears that propofol use in healthy children carries a wide margin of safety with regard to respiratory and cardiac depression when used at doses effective for conscious sedation.[39] However, respiratory depression is always a hazard when propofol is combined with other sedatives (such as opioids) or when used at higher doses. We have used continuous propofol infusions in children undergoing bone marrow aspiration and lumbar punctures in the outpatient oncology clinic. It is not infrequent that doses up to 15 mg/kg are required over a 30-to-45-minute period in children with malignancies. The children are in a state of deep sedation, and breathe spontaneously with "blow-by" oxygen administered continuously. We have had no complications or episodes of significant oxygen desaturation in more than 1 year of use. Because of its propensity to cause deep sedation, propofol should only be used when the child's fasting status has been ascertained so that children are not at risk for pulmonary aspiration of gastric contents.[26] For this reason, propofol has not been used extensively in the emergency setting.

Eutectic mixture of local anesthetics (EMLA)

Eutectic mixture of local anesthetics (EMLA) cream consists of the local anesthetics lidocaine and prilocaine in concentrations of 2.5% each. When mixed in equal amounts, the pure solid bases of lidocaine and prilocaine form a eutectic mixture—an oil at room temperature. This cream is an oil-in-water emulsion of these two bases that allows effective tissue penetration at low total-drug concentrations. It results in complete dermal anesthesia when applied at least 45 to 60 minutes in advance. As such, it is not suited for use in unanticipated procedures such as venipuncture in the emergency department.

Several investigators have reported the favorable use of this cream in children. In 1982, Ehrenstrom Reiz and colleagues[41] demonstrated that EMLA was superior to placebo in preventing the pain of IV cannulation in children. Halperin and coworkers[42] reported that this cream was effective in eliminating or decreasing pain associated with lumbar punctures and injections into subcutaneous reservoirs in children with cancer. However, not all reports on the use of this agent in children have been favorable. Soliman and coauthors[43] compared EMLA with intradermal lidocaine infiltration in 42 children, aged 7 to 12 years. Assessments were made of patients' responses to a skin "nick" with a 19-gauge needle and intravenous cannulation with a 20-gauge catheter. In addition to finding similar pain scores between the two groups, the authors found no correlation between the level of cooperation and lower pain scores. They also noted that after removal of the cream, the skin retained a greasy quality that made securing the IV catheter difficult.

Transient and minor side effects associated with the cream consist of localized itching, pallor, or erythema. This agent is contraindicated in infants younger than 1 month. These infants are susceptible to prilocaine-induced methemoglobinemia because of their relatively low levels of erythrocyte methemoglobin reductase.[44]

At URMC, this cream is used most often when a child undergoes planned IV catheter insertion, such as before elective surgery or radiologic procedures. Parents are given the cream in advance and are instructed to apply it to their child's skin before leaving home so that enough time has elapsed for it to be effective. The cream is applied to the dorsum of both hands, allowing for "uncooperative" veins. (Most children are conditioned to respond with fear and anxiety at the sight of a needle; first-time recipients are extremely wary. It is unusual to encounter a calm, cooperative child, especially in the younger age groups, who understands that his or her skin is anesthetized.)

Comments

This review has discussed various possible techniques with which to ensure that all practitioners who care for children undergoing surgery or painful procedures do so in a pain-free manner. It is recommended that practitioners who provide acute care to children develop knowledge and experience in at least a few of these techniques. Given the rapid advancement in the understanding of the pathophysiology of pain, and the development of more specific and safer pharmacologic agents and procedures, the alleviation of acute childhood pain is a worthy—and obtainable—goal.

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