Through the years, parents have asked me many questions regarding details of a surgical procedure for their child. How long will it take? Where will the incision be? Will there be stitches or staples? Will there be much pain after surgery? When can we go home? I have tried to answer them as well as I could on the basis of my experience. My knowledge of the surgical or diagnostic procedure gives confidence to families whom I meet a short time before the induction of anesthesia. Such knowledge also helps me to better care for patients.

Some of the same considerations apply to surgeons. Unless the patient is related to an OR nurse, a PACU nurse or an anesthesiologist, the family will generally meet their surgeon before any other member of the perioperative team. Parents often are more fearful of anesthesia than of surgery. Gone are the days when a surgeon did not need to understand anesthesia techniques. This issue was crafted to answer some of the questions that a surgeon or his or her patients might have regarding pediatric anesthesia. Reports have hit the lay press regarding neurodevelopmental outcomes and the safety of anesthesia in infants. With the improvement of anesthetic monitors and medications, the age that is recommended for elective operations has progressively diminished. Is there more to safety in these patients than the technical ability to put them to sleep and wake them up?

Post-operative pain control often begins in the OR. We have more than twenty years of experience with caudal blocks in pediatric patients. When, why and how are these blocks done? These are not the only blocks used for pediatric urologic surgery. Other modalities may improve the comfort of the patient immediately after a procedure and/or extend the duration for many hours after that.

We hope that this edition of Dialogues in Pediatric Urology sheds light on contemporary anesthetic risks and acute and chronic pain management concerns for your patients and their families.

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Northwestern University’s Feinberg School of Medicine, Chicago

You walk into a room to evaluate a one year old with a communicating hydrocele. The parents hand you two articles about the neurobehavioral complications of general anesthesia in infants and toddlers. “Can we wait until after he turns two?” Perhaps fine to wait in this case, but what about hypospadias?

Are there new concepts in regional blocks to offer better postoperative pain relief?

How do NSAIDs benefit urology patients? Are they safe? And when should they be administered?

Is there a child with chronic pelvic pain in your practice? Is there a different way to help this child?

As pediatric urologic surgeons, we interact with our colleagues in anesthesiology several times per week. We may take their expertise for granted, as they have allowed us to safely bring younger and younger patients to the table for both routine and complex procedures. Institutional preferences and protocols are in place, and mutual decision-making is often limited to out of the ordinary patients.

This edition of Dialogues was conceived to ensure that we are fully utilizing the expertise of our colleagues in the care of our patients. Dr. Dsida and his contributing authors have put together a collection of excellent articles, and we anticipate that you will find several things useful to your clinical practice.
Regional Anesthesia: The “Single Shot Caudal” and Beyond

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The “single shot caudal” epidural injection is perhaps the most common regional anesthetic technique employed in pediatric urology cases. It can be used for procedures as diverse as circumcision, hypospadias repair, hydrocelectomy, orchidopexy, ureteral reimplantation, and pyeloplasty. Its popularity stems in part from the readily palpable landmarks at the base of the sacrum and the relative ease of caudal block insertion in infants and children versus adults [Figures 1 and 2].

Dosing of Drugs Used in Caudal Injections

Dosing formulae have been developed using age, weight, and the number of spinal segments to be blocked. Weight is a better correlate in predicting spread and is more commonly used. Volumes of 0.5-1 ml/kg will achieve blockade to the L1 and T6 dermatomes, respectively. Bupivacaine, usually in a concentration of 0.125%, is the most commonly used local anesthetic. In theory and often in practice, this dilute solution will result in a “differential nerve blockade”, whereby transmission via the smaller diameter A-delta and C nerve fibers that carry pain signals is blocked. The larger diameter nerve fibers carrying sensation and motor function are largely spared, so that a child can often feel and move his lower extremities with diminished or absent pain. Duration of postoperative analgesia with bupivacaine, ropivacaine, and levobupivacaine is on average 4-8 hours [Table 1].

A number of different additives have been combined with local anesthetics in an attempt to prolong analgesia. The alpha-2 agonist clonidine is the most commonly used of these additives. Doses of 1-2 mcg/kg clonidine will enhance analgesia by 2-3 hours or more. Epi-nephrine, used primarily as an indicator of intravascular injection, can also be used to extend analgesia. Because epinephrine also slows the systemic absorption of local anesthetic, it has the ancillary benefit of...

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Maximum Dose (mg/kg)</th>
<th>Duration of Action (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>2.5</td>
<td>3-6</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>3</td>
<td>2-4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>20</td>
<td>1-1.5</td>
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Table 1 - Maximum dose of local anesthetic agents and anticipated duration of action.
decreasing the risk of local anesthetic toxicity. The opioids fentanyl, morphine, and hydromorphone represent another class of drugs that are used synergistically to enhance, and in the cases of morphine and hydromorphone, lengthen pain relief. Repeating the caudal at the conclusion of a case of several hours duration (a “double shot” caudal), at half of the initial volume of 1 ml/kg 0.125% bupivacaine, has also been shown to significantly prolong blockade.9

Caudal epidural catheters

For those patients undergoing more extensive procedures such as ureteral reimplantation, pyeloplasty, bladder exstrophy repair, or complex bladder reconstruction, continuous infusion via an epidural catheter can provide another means to allow extended pain relief. In infants and children up to approximately five years of age it is possible to successfully thread catheters from the caudal epidural space to lumbar and lower thoracic levels.10,11 The goal in placing these catheters is to have the catheter tip terminate in the middle of the desired dermatomes to be blocked. Tip location can be verified by fluoroscopy with use of contrast media, electromyography, or more recently ultrasound. Local anesthetic and additive solutions similar to those used in adult catheters are used in infants and children. Drug dosages and infusion rates, however, are decreased in neonates and infants less than 3-6 months of age. This is because of decreased plasma protein binding and consequently higher free (unbound) fractions of drug, and because of differences in pharmacokinetics in children relative to adults.

Patient-and Parent/Nurse-controlled Epidural Analgesia

Patient-controlled analgesia with intravenous opioids is well established in children, and this concept has been extended to epidural analgesia as well. In a study of pediatric patients undergoing surgical procedures anticipated to cause moderate to severe postoperative pain, patient-controlled epidural analgesia (PCEA) was used in 128 children (132 procedures) as young as 5 years of age.12 90% of patients achieved satisfactory analgesia with no patients requiring treatment for sedation or respiratory depression. Similarly, the concept of parent/nurse-assisted intravenous analgesia has also recently been extended to epidural analgesia. This has been done to optimize dosing flexibility and pain relief given in infants and children unable to self-activate the demand dose button.13 Results comparable to the patient-controlled epidural analgesia group were obtained, with effective analgesia in 86% of patients and no patient needing treatment for sedation or respiratory depression. This technique was employed in patients as young as 5 months of age.

Risks Associated with Caudal Blocks

Though caudal injections and catheters are routine procedures, there are rare but significant complications that can occur. Prior to injection of the local anesthetic solution, the epidural needle is inspected and then aspirated for blood or cerebrospinal fluid (CSF). The presence of CSF indicates a sub-

arachnoid needle tip location. If the larger volume of local anesthetic used in an epidural injection is directly instilled into the subarachnoid space, a “total spinal” could result with a complete sensory and motor blockade, and possible hypotension or bradycardia. Since a negative aspirate may not guarantee correct needle tip position, a “test dose” is typically given using a small volume of local anesthetic and an intravascular marker such as epinephrine in a concentration of 1:200,000 (5 mcg/ml). A 10 beat/minute increase in heart rate, 15% increase in systolic blood pressure or 25% increase in electrocardiographic T wave amplitude during the 60 second test dose observation time is indicative of an intravascular injection, requiring needle repositioning and retesting.14 More recently ultrasound has been employed to ensure correct needle tip location and local anesthetic solution injection. In addition to being able to visualize the needle tip, one will see “tenting” of the dura mater or epidural space with injection.

The primary concerns with intravascular injection of large volumes of local anesthetic are neurotoxicity and hemodynamic collapse. Neurotoxicity such as seizures from local anesthetic overdose can be treated with barbiturates, benzodiazepines or propofol, although seizure activity can be masked under general anesthesia. The most successful treatment for local anesthetic-induced arrhythmias and cardiotoxicity is the use of lipid emulsion, which some now consider first line therapy [Figure 3].15 The mechanism is unclear but the emulsion may act as a “lipid sink” and bind local anesthetic molecules. Epinephrine, a front line drug in the treatment of cardiovascular collapse, may actually impair lipid resuscitation in usual resuscitation doses.16 A recent pediatric case report described the use of lipid emulsion for successful resuscitation from ropivacaine/lidocaine-induced ventricular arrhythmias following posterior lumbar plexus block in a child.17 There is a growing consensus that lipid emulsion be immediately available where regional anesthesia is being performed.

(continued on next page)
These complications, while obviously serious, are fortunately quite rare. A study of complications of single-dose caudal epidural blockade reported an intravascular injection prevalence of 1:25,100.\textsuperscript{18} A more recent prospective national pediatric epidural audit of over 10,000 epidurals revealed a 1:2,000 incidence of serious complications with a 1:10,000 incidence of sequelae at 12 months.\textsuperscript{19} No deaths or cardiac arrests were reported. A recent case series of 3 urology patients aged 14 months – 5 years, who received 100 times the intended dose of caudal clonidine due to a pharmacy error, reported only somnolence, but no respiratory depression, desaturation, or hemodynamic instability.\textsuperscript{20}

Also meriting discussion are the risks of infection, hematoma, and nerve root injury. As with local anesthetic toxicity, these events are exceedingly rare. In the national pediatric audit noted above, two epidural abscesses and one case of meningitis were noted over a five year period.\textsuperscript{19} Epidural hematoma may occur spontaneously or in the presence of a traumatic needle placement in a patient with a clinically significant coagulopathy or thrombocytopenia. As such, an epidural injection is contraindicated in these patients. The usual time-course for the onset of symptoms from an epidural abscess is 2-5 days, whereas that from an epidural hematoma tends to be more acute. The primary distinction in presentation between these two is the presence of fever and laboratory values indicative of infection and inflammation with an epidural abscess [Table 2]. With regards to nerve root injury, prospective studies have demonstrated a prevalence of 1 in 5000 in infants younger than three months of age.\textsuperscript{21} Among older infants and children there were six instances in 10,633 children, with all six having complete resolution of symptoms within one year.\textsuperscript{19} Although epidural injection or catheter placement in adults is typically done prior to induction of anesthesia, it is routine and accepted practice in infants and children to do so under general anesthesia. This is done to ensure immobility, and therefore safety, in patients who are unable or unwilling to cooperate with positioning and needle insertion.\textsuperscript{22}

### Alternatives to Epidural Analgesia

One of the pediatric urology populations largely exempt from epidural analgesia is the patient with spinal dysraphism, such as myelomeningocele. Although epidural analgesia has been used in select cases, the congenital spinal anomalies usually preclude epidural catheter placement. A useful alternative in these patients is the use of ultrasound-guided transversus abdominis plane (TAP) blocks. The fascial plane between the internal oblique and transversus abdominis contains the lower six thoracic and upper lumbar abdominal afferent nerve fibers. This plane can be readily identified in most children using ultrasound guidance or, in its absence, a “pop” technique with a blunt regional anesthesia needle. The TAP block provides highly effective postoperative analgesia in the first day following major abdominal surgery in adults.\textsuperscript{23} More recently an ultrasound-guided technique has been described in children.\textsuperscript{24} Ultrasound-guided placement of bilateral TAP catheters has been shown to provide extended analgesia and a significant opioid-sparing effect in children undergoing bladder augmentation surgery.\textsuperscript{25}

### Improved Outcomes with Epidural Analgesia?

Outcome studies of epidural analgesia versus intravenous opioids in adults undergoing major surgery have generally shown superior analgesia in the epidural group with less gastrointestinal, pulmonary and cardiovascular morbidity, but no difference in overall mortality. Comparable outcome data in pediatric regional anesthesia is relatively lacking. A recent Cochrane Database Review analyzed caudal epidural block versus other methods of postoperative pain relief for circumcision in boys.\textsuperscript{26} The analysis was limited by small numbers and poor methodology, but did not show an advantage of caudal epidural analgesia over dorsal penile nerve block, topical anesthesia or parenteral opioids. Further study is needed using different surgical models such as hypospadias repair, ureteral reimplantation, and pyeloplasty. A more expansive pediatric meta-analysis of regional anesthesia is pending.\textsuperscript{27}

\textit{Intraoperatively, the benefits of an epidural blockade are tangible. Often less inhalational agent, less or no opioid medication and potentially less or no muscle relaxant are needed to achieve excellent surgical conditions. This can translate to earlier awakening and extubation from anesthesia.}

\textsuperscript{\textit{Table 2 - Signs and symptoms of an epidural or spinal abscess and hematoma (Adapted from Coté CJ, Lerman J, Todres D. A Practice of Anesthesia for Infants and Children 4th ed. Polaner DM, Suresh S, Coté CJ. Regional Anesthesia. Chapter 42. 2009: 883)}}
Non-narcotic Agents for the Treatment of Urologic Pain

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Introduction

Children with pain of urologic origin are unique in that the pain signals from the pelvic structures are often transmitted via the sympathetic nervous system. Because of this, children with pathology involving the kidneys, bladder, ureters and urethra may experience a visceral-type pain that is diffuse and not easy to localize. Unlike pain from the skin and soft tissues, urogenital pain is not always responsive to treatment with opioids and can be associated with gastrointestinal upset such as nausea and vomiting. Non-steroidal anti-inflammatory drugs (NSAIDs) provide excellent relief for mild to moderate postoperative pain and work as an adjunct to reduce opioid-related side effects. NSAIDs can be particularly efficacious for certain types of urologic pain, including bladder spasms and pain associated with kidney stones.

Pharmacology of NSAIDs

With tissue disruption and lysis of cell membranes, fatty acids are released and metabolized to prostaglandins, which result in local inflammation and pain through the stimulation of the free nerve endings of A-delta and C fibers. NSAIDs, acetylsalicylic acid, and salicylates inhibit the enzyme cyclooxygenase, blocking prostaglandin formation. Recent pharmacokinetic and pharmacodynamic data have provided pediatric clinicians with ample information to suggest appropriate dosing guidelines for the pediatric population (Table 1). The role of cyclooxygenase (COX) inhibitors in the treatment of acute pain includes their use as the sole agent for mild pain, their combination with opioids for oral administration in moderate pain, and their addition to parenteral opioids and regional anesthetic techniques for severe pain. In the latter situation, their use does not eliminate the need for opioids, but rather provides adjunctive analgesia and a reduction in opioid requirements. As the majority of opioid-related adverse effects are dose-related, modalities that decrease total opioid consumption may decrease opioid requirements. In the latter situation, their use does not eliminate the need for opioids, but rather provides adjunctive analgesia and a reduction in opioid requirements.

Due to its excellent safety profile and lack of significant side effects, acetaminophen is the most commonly used analgesic agent in pediatric practice. In fact, due to the developmental differences in metabolism in infants and young children, this drug appears to have a lower potential for toxicity in children than adults. Hepatic toxicity can result when the toxic metabolite of acetaminophen, NAPQI, is produced in such high quantities that there is not enough glutathione peroxidase (GSH) to bind to it. Infants and children produce high levels of GSH as a part of hepatic growth and this seems to provide a protective effect. In a recent study comparing weaning to adult rats after a toxic dose of acetaminophen was administered, the weaning rats demonstrated a 24-fold increase in GSH/NAPQI conjugate production and significantly less histopathologic damage.

Pharmacokinetic studies in children greater than 1 year of age of both the oral NSAID ibuprofen and the intravenous NSAID ketorolac (continued on next page)
have demonstrated similar pharmacokinetic and pharmacodynamic profiles to that observed in adults. In addition, no differences in pharmacokinetics were found among the various age groups (1-3 yr, 4-7 yr, 8-11 yr, and 12-16 yr) and dosing every 6 – 8 hours appears to be safe and effective. Though there is limited pharmacokinetic data regarding NSAIDs in children less than 1 year of age, several recent studies have demonstrated that the pharmacokinetics of a single dose in the perioperative period is quite similar to older children and adults.

Adverse Effects

For the pediatric urologist, there are three major concerns with the use of NSAIDs for pain relief: 1) the effect on platelet function and the potential for increased perioperative bleeding, 2) the effect on renal blood flow and 3) the decreased protective effect on the gastric mucosa and possibility of gastric upset and bleeding. The effects on bleeding are directly related to the lack of the protective effect of prostaglandins on platelet function. Inhibition of the homeostatic cyclooxygenase-1 enzyme can lead to increased postoperative bleeding, especially with the potent intravenous non-steroidal agent ketorolac. Rusy et al. randomized 50 children undergoing adenosin sulfatectomy to receive either ketorolac (1 mg/kg) or acetaminophen (35 mg/kg rectally) following anesthetic induction. Patients receiving ketorolac had significantly more blood loss (2.67 versus 1.44 ml/kg) and required more surgical interventions to control bleeding during the surgical procedure, but did not demonstrate increased bleeding postoperatively. Since there are many other hemostatic factors in the coagulation cascade, the tendency toward increased bleeding with non-steroidal agents tends to be mild and easily controlled. Blood loss was not increased with the use of ketorolac after two types of potentially high-blood loss procedures including congenital heart surgery and spinal fusion. In a retrospective analysis, there was no difference in the need for surgical re-exploration in infants and children following surgery for congenital heart disease who received ketorolac compared to case-matched controls. In a subsequent prospective, randomized trial in the same population, there was no difference in median chest tube output (13.3 versus 16.5 mL/kg/day) when comparing patients randomized to ketorolac or placebo.

Of additional concern to pediatric urologists is the fact that NSAIDs, due to their inhibition of the production of homeostatic prostaglandins that regulate normal renal blood flow, can cause acute tubular necrosis and renal failure. Numerous studies in children have indicated that renal failure is extremely rare after NSAID administration except in patients with pre-existing renal dysfunction, during concomitant administration of other nephrotoxic agents, or in the presence of hypovolemia. In fact, studies of the long term treatment of arthritis in children with NSAIDs have demonstrated a paucity of renal effects compared to adults. Even in young children, NSAID administration has been found to be quite safe. In a prospective trial of 27,065 febrile children less than 2 years of age, the children were randomized to receive acetaminophen (12 mg/kg), ibuprofen (5 mg/kg) or ibuprofen (10 mg/kg) for the treatment of fever. There was no statistical difference in adverse effects, including acute GI bleeding, acute renal failure, anaphylaxis, Reye’s syndrome, asthma, bronchiolitis, and vomiting/gastritis among the 3 groups. A similar review of the short-term use (48 hours) of the more potent intravenous agent ketorolac, in over 1700 children at Children’s Hospital Boston, demonstrated a low rate of complications. Four children (0.2%) demonstrated hypersensitivity reactions (urticaria and/or bronchospasm), two children (0.1%) had evidence of renal impairment (though both had other underlying problems that could account for the renal insufficiency) and one child (0.05%) had melena at the completion of a 48 hour course of the drug. Most recently, Moffett et al. reported no adverse renal or hematologic effects in their retrospective review of ketorolac use in 53 children less than 6 months of age who received at least one dose of ketorolac following surgery for congenital heart disease. In their study, the greatest increase in serum creatinine from baseline was 0.3 mg/dl.

Though rare, administration of NSAIDs has also been associated with gastritis and gastrointestinal bleeding. Prostaglandins have a protective effect on the gastric mucosa that can be disrupted when prostaglandin inhibitors are administered. Gastrointestinal effects tend to be mild in children, with an incidence of GI bleeding reported as 17 per 100,000 in one large study of the use of ibuprofen in young children. In order to prevent this complication, prophylactic treatment with ranitidine is frequently used at Children’s Hospital Boston to reduce GI upset when intravenous ketorolac is administered postoperatively.

Treatment of mild to moderate perioperative pain with oral NSAIDs

Because they are available in several preparations suitable for use in pediatric patients of all ages (tablets, capsules, chewable tablets, elixirs, and infant drops), acetaminophen and ibuprofen are the most commonly prescribed NSAIDs for children. Acetaminophen is also available in suppository form and sustained release tablets. Acetaminophen remains a cornerstone in the perioperative setting due to its strong safety profile and lack of platelet effects, raising no additional concerns of increased intraoperative or postoperative bleeding. Studies in preterm neonates and infants have even provided useful guidelines for treatment with acetaminophen in neonates as young as 28 weeks gestational age. Specific dosing guidelines for these drugs can be found in Table 1.

There are several options for the timing of the administration of these agents in the perioperative setting. Acetaminophen (15 mg/kg) or ibuprofen elixir (10 mg/kg) can be combined with the oral premedication agent midazolam. This technique allows the medication to achieve a plasma concentration that will provide effective analgesia by the time of awakening, and also masks the unpleasant taste of the intravenous preparation of midazolam when it is given orally. An alternative to preoperative administration is placement of an acetaminophen suppository (40 mg/kg) following anesthetic induction. A third option is postoperative administration of either ibuprofen or acetaminophen once the child complains of pain in the recovery room. This combination technique can also be used for outpatients with acute pain. This latter option is less desirable in the perioperative setting since the onset of activity of any of these agents following oral or rectal administration is 20-30 minutes.

When prescribing acetaminophen for administration at home, it is important to ensure that the infant or child is not receiving acetaminophen. (continued on next page)
nophen in other forms, such as in over-the-counter cold medicines. Given that there are several different acetaminophen preparations available with numerous manufacturers, it is equally important to know the amount of acetaminophen or ibuprofen in each specific product. Unfortunately, the most common cause of acetaminophen toxicity in patients less than 10 years of age remains inadvertent parental overdosing.16

Parenteral NSAIDs for postoperative pain

Even when the choice is made to escalate pain therapy to include parenteral opioids, the prostaglandin synthesis inhibitors can be used to lower postoperative opioid requirements and thereby decrease opioid-related adverse effects. Although initial clinical trials suggested that ketorolac was as effective as opioids in treating acute pain, its practical clinical role is similar that of other NSAIDs as an adjunct to opioid analgesia.17 Vetter and Heiner demonstrated that a single intravenous dose of ketorolac administered just prior to the completion of a surgical procedure as a supplement to morphine PCA decreased morphine requirements, lowered pain scores, and decreased the incidence of adverse effects during the initial 12 postoperative hours.

NSAIDs for Pain of Urogenital Origin

Urogenital pain is often visceral in nature and may be transmitted to the central nervous system via capsaicin-sensitive C-fibers. Disruption and inflammation of the lining of the urogenital tract can lead to a rapid increase in local prostaglandin production, which is known to profoundly increase C-fiber activity. This increase in C-fiber neural activity has been correlated with several specific types of episodic urologic pain, including bladder spasms and renal colic.

NSAIDs for Bladder spasms

Bladder spasms are acute spasmodic pains arising from the bladder, which are common after bladder inflammation or surgery. Though the precise mechanism for bladder spasms is not known, studies have demonstrated that bladder hyperactivity triggered by C-fiber afferents may play an important role. These C-fiber afferents are abundant in the urinary bladder, where they are involved in the regulation of both normal and pathological voiding reflexes. Neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) are synthesized in response to inflammation or injury and can produce edema and neutrophil accumulation and promote contraction of the ureter, bladder dome, trigone and urethra. These abnormal contractions are thought to be the source of the bladder spasm pain that children experience after bladder surgery.

The bladder is a well known site of local prostaglandin synthesis after outlet obstruction, inflammation, and mucosal injury. Prostaglandins are one of the most potent sensitizers of C-fiber neural transmission, and the reduction in their synthesis by nonsteroidal anti-inflammatory agents can suppress the development of bladder spasms. We were able to show in a randomized, double-blind, placebo-controlled fashion that the intravenous NSAID ketorolac is quite effective in reducing the pain associated with bladder spasms after ureteral reimplantation surgery.18 In our experience, the routine use of ketorolac postoperatively after ureteral reimplantation surgery has allowed for significantly better pain control in the perioperative period and improved patient outcomes.

NSAIDs for Kidney Stones

According to a recent study, the incidence of urolithiasis in children has been steadily increasing over the last 20 years, accounting for 1 in 685 hospital admissions to pediatric hospitals. Though the reasons for this rising incidence are unclear, there appears to be a higher incidence of ureteral stones in children with obesity, diabetes and hypertension. Certain food contaminants such as melamine have also been associated with a high incidence of urinary calculi. Ureteral stones can be extremely painful and children may require hospitalization for IV hydration, nonsteroidal anti-inflammatory agents and opioid analgesics.

As with the bladder, dense networks of fibers expressing substance P and C-reactive protein are found in the smooth muscle layers of the upper urinary tract, with greatest density in the upper ureter and kidney. Smooth muscle distension most likely activates these fibers and can cause severe visceral-type pain, generally referred to as renal colic.
Treatment modalities that are the most effective for this type of pain generally involve the use of non-steroidal anti-inflammatory agents and antiemetics. Though opioid analgesics can be helpful in reducing distress, they tend to be less effective than non-steroidal anti-inflammatory agents and can exacerbate the nausea and vomiting associated with this type of visceral pain. Though ultimately speeding the resolution of the nephrolithiasis, minimally invasive techniques like ureteroscopy and stent placement can initially lead to a significant increase in pain in the postoperative period. Judicious use of intravenous steroids and NSAIDs may not only decrease postoperative pain for these patients but potentially reduce the severe nausea and vomiting that often accompanies this type of pain.

Other Options: Tramadol

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. The drug is marketed as a racemic mixture of dextro- and levo-enantiomers and is classified as a phase IIb analgesic in the WHO pain ladder of analgesia. It is a centrally acting analgesic and has been recommended for mild to moderate pain control. The opioid effect of the drug is due to its partial affinity to the dextro-enantiomer of the Mu receptor. Tramadol is rapidly absorbed after oral administration with a bioavailability of 65% due to a first pass metabolism after GI absorption. Tramadol is administered orally in a dose of 1 to 2 mg/kg with a maximum dose of 50 mg administered every 6 hours. It is important to remember that tramadol cannot be used in patients who are on MAO inhibitors or on serotonin inhibitors since they can develop serotonin syndrome. (EDITOR’S NOTE: This potentially life-threatening situation occurs due to acute excess serotonergic activity in the central nervous system and peripherally. It can be related to overdose of one agent or combined effects of prescription and some recreational agents. Cognitive, autonomic and somatic symptoms can occur, including but not limited to agitation, hallucinations, coma, sweating, extreme hyperthermia, hypertension, tachycardia, gastrointestinal symptoms, tremors and myoclonus.) Tramadol has been used effectively for postoperative pain control, as well as for chronic pain relief in children.

Conclusions

Pain of urogenital origin is often visceral in nature and is more responsive to local anesthetics and nonsteroidal anti-inflammatory agents than opioid analgesics. Research is ongoing into the mechanisms of urogenital pain and the safety and effectiveness of the various treatment modalities.

References


Suggested Reading

Clinical Anesthetic Neurotoxicity In Children-An Update
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An estimated 6 million children receive anesthesia each year in the US. According to the Nationwide Inpatient Sample, 1.5 million infants under the age of 12 months undergo surgery as inpatients annually. Modern anesthesia provides amnesia, analgesia, immobility, and autonomic control in surgical settings, and optimal conditions for imaging studies and diagnostic procedures. It is because of these benefits and a presumed high level of safety that the use of anesthesia has increased exponentially and is administered to younger and younger children. However, the mounting evidence in animal studies of neuronal apoptosis in vitro and long-term neurodevelopmental deficits in vivo challenges the safety to exposing infants to anesthesia and makes the issue of anesthetic neurotoxicity an urgent matter of public health.

The initial discovery that NMDA antagonists induced neuronal apoptosis in the developing rat brain was noted by Ikonomidou et al in 1999. (Editor’s Note: N-methyl d-aspartate antagonists, e.g.: ketamine, nitrous oxide, PCP, dextromethorphan and synthetic opioids meperidine and tramadol.) In 2003, anesthetic agents were also implicated in rats, and over the next few years, almost all commonly used anesthetics have been shown to cause neurotoxicity. The effects were initially found at postnatal day 7, during the period of peak synaptogenesis in the rat brain, but not at postnatal day 14. Later discoveries however indicate that the effects of anesthetics on the developing brain are not limited to merely apoptosis. Anesthetics were also found to affect dendritic spine density at postnatal days 15 and 30. Overall, the preclinical data provide convincing evidence that anesthetics adversely affect the developing brains in rodents and non-human primates. Moreover, these anesthetic effects are dose-dependent, occur during a window of vulnerability, and are mediated through multiple pathways to induce injury.

In addition to the cellular effects, even more disconcerting is the finding that there are long-term functional deficits. However, while ample histologic evidence exists, functional studies are more limited and have only been documented and reported in rats and mice. Of note, while the histological injury from anesthetic exposure in the developing brain has been consistently demonstrated, evidence of abnormal neurobehavioral outcome has not been found in all cases.

While definitive functional outcome studies are still lacking, the current evidence has been sufficiently alarming and has generated a great deal of interest among the media, the public, and parents. In response, in April 2007, the FDA convened a scientific advisory committee meeting to discuss whether specific recommendations for changes in the use of anesthetic agents in children were needed. The consensus at the time of that meeting was that insufficient data from clinical studies existed to warrant a change in clinical practice.

Since 2007, five clinical studies have been published. All studies have been retrospective cohort studies. Two of these studies derived their data from the Olmsted County Birth Cohort, and both used evidence of learning disability as an outcome measure. They found that while maternal exposure to general anesthetics during labor and delivery did not have an effect on the child, multiple exposures to anesthesia and surgery before age 4 did increase the incidence of learning disability. While the Olmsted County birth cohort provides a large sample of 5320 study subjects with available medical and anesthesia records, one criticism is that the demographics of the cohort do not reflect that of the overall US population. In addition, since the anesthesia exposure occurred between 1976 and 1982, the types of anesthetics used at that time are no longer commonly used today. The outcome of “learning disability,” calculated as the discrepancy between IQ and actual achievement in language, math, and verbal ability is also broad measure and may not detect subtle differences in one area.

DiMaggio et al used the NYS Medicaid dataset and constructed a birth cohort of 383 children undergoing inguinal hernia repair during the first 3 years of life. This cohort was compared to an age-matched sample with no history of anesthesia exposure. The outcome measure was evidence of a diagnosis of developmental delay or behavior problems based on ICD-9 coding. While the exposed cohort was found to have a 2.3 fold incidence of adverse outcome, this study also had several limitations. In this study of a large administrative database, the specific anesthetic exposure also could not be confirmed, the outcome measure was prone to misclassification, and the Medicaid sample of patients could be considered at higher risk of disability due to a low socioeconomic status. In addition, although hernia surgery does not have a known association with abnormal neurocognitive function, it could possibly be a confounding element.

Kalkman et al performed a study in a limited number of patients who had received anesthesia for urologic surgery at 0-6 years old and who were subsequently evaluated with parental reports of the Child Behavior Checklists (CBCL) at 12-15 years of age. Although they found what appeared to be an association between exposure prior to 24 months of age and abnormal behavior, the study was not powered to achieve statistically significant results.

Bartels et al studied 1143 monozygotic twin pairs using the Young Netherlands Twin Registry to examine the effects of anesthetic exposure on long-term neurocognitive function. The outcome measure used was educational achievement and teacher reports of the Child Behavior Checklists (CBCL) at 12-15 years of age. While they found that exposure prior to the age of 3 significantly reduced educational achievements, there was no difference between twin pairs discordant for anesthesia exposure. However, similar to other studies employing retrospective analysis of existing data, this study did not have standardized neuropsychological outcome measure and lacked specific exposure data.

All of the clinical studies to date have provided perhaps more questions than answers. Their major limitations include the lack of specific outcome measures and the variability of anesthetic exposure. While clinical guidelines still cannot be made from the available data, these studies underscore the need for more definitive answers.

The challenges in designing prospective studies to address this...

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research question include the neurodevelopmental outcome to be evaluated, as well as the window of vulnerability to be examined. While academic performance or a diagnosis of a behavioral disorder can give a crude measure of neurodevelopmental impairment, subtle findings may be missed. Direct, standardized, age-specific neuropsychological assessment is essential. While it is difficult to determine the exact susceptibility period based on the available studies, the time of synaptogenesis appears to be a vulnerable period in animal models. In humans, synaptogenesis in the primary sensorimotor cortex begins at birth and is not completed in the prefrontal cortex until the age of 2-3 years.14-16

The two large-scale studies proposing to perform prospective data collection on neuropsychological function are the GAS study and the PANDA (Pediatric Anesthesia and NeuroDevelopment Assessment) study. The GAS study is a multi-center randomized trial that will enroll 600 children to compare general sevoflurane anesthesia with regional anesthesia for infants undergoing inguinal hernia repair. The children will be followed for five years, and evaluation will be performed at age 2 years and 5 years. The PANDA study is also a multisite study that will involve eight US study sites. It is an ambi-directional, sibling-matched cohort study that will enroll a total of 1,000 children or 500 sibling pairs. The period of anesthesia exposure will be before 36 months of age, and the exposure is limited to a single episode of general anesthesia for inguinal hernia repair in ASA I and ASA II patients. The study will perform an extensive neuropsychological battery in children between age 8 and 15 years. Because the PANDA study will have a comparison group without anesthesia exposure, its results will specifically address the effects of anesthesia/surgery exposure. Therefore, the results from the PANDA study will be applicable to otherwise healthy children undergoing elective surgery.

In conclusion, there is insufficient evidence at this point to change current clinical management. Research to further elucidate this question is underway and if anesthesia is found to result in no adverse outcome, millions of children and parents could be offered reassurance. If, however, anesthesia is found to cause a neurodevelopmental deficit, alternate strategies in anesthesia delivery, timing of surgery, comorbidities, and protective measures must be considered.

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References

Chronic Pain Management in Urology

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Chronic pain is defined as pain that persists for greater than three weeks. In general, postoperative pain is of shorter duration. However, work done in animals has demonstrated the presence of central sensitization that leads to increased activity of un-myelinated C-fibers leading to persistent pain.1 There are two major pain descriptors: nociceptive pain, where pain is directly related to tissue injury, and neuropathic pain, in which pain is persistent and may not be related to immediate injury. Patients with chronic pain may exhibit allodynia, which is pain out of proportion to the nociception (e.g., touching with a feather that can cause severe pain) and hyperalgesia, or increased pain sensitivity. The most common pain problems in urology patients that may become persistent are: 1) ilioinguinal neuralgia and 2) abdominal pain and hyperalgesia secondary to surgery.

Advances in pain management in pediatrics over the last 2 decades allow for better analgesia with decreased side effects. A pediatric pain clinic uses a multidisciplinary approach to pain control and includes an anesthesiologist, a child psychologist, physical therapist, nurse practitioner, and other ancillary staff including biofeedback therapy as well as massage therapy.2 All patients are encouraged to fill in a questionnaire prior to their clinic appointment that deals with issues regarding pain, as well as issues related to school attendance, family dynamics, etc. All radiological imaging is reviewed with the team prior to the patient’s first visit. The initial visit can take a longer time, since much of pain management in children is based on cognitive-behavioral modulation.

Psychological Intervention

Psychological intervention is part of cognitive management in children. A comprehensive evaluation of the child, along with separate interviews with the family, may allow a better understanding of the issues. Interventions that are offered at the pain center include visual guided imagery and relaxation techniques. In addition, biofeedback therapy is routinely offered for all patients in the clinic.

Physical Therapy Intervention

Physical therapy is an integral part of managing pain in children. Measures used in urology patients include a transcutaneous electric nerve stimulation (TENS) unit. Stimulating the C-fibers, one is able to decrease the firing of the larger A-delta fibers. Other physical therapy measures, including abdominal strengthening exercises, are used for improving pain relief.

Pharmacological Intervention

Common pharmacological interventions include the use of tricyclic antidepressants and anticonvulsants. Opioid therapy is usually limited to cancer pain management or, in some instances, for allowing patients to participate in physical therapy.

Tricyclic antidepressants are commonly used as an initial intervention for chronic pain relief in children. Although the mechanism of action is not clear, there is data to demonstrate the efficacy of this class of drugs for pain relief.3 It is imperative to perform an electrocardiogram in children prior to initiation of these drugs. Treatment may be contraindicated in children who already have EKG abnormalities, since prolongation of the QT interval may occur with treatment. (Editor’s Note: Several urologic medications, such as some anticholinergics and alpha-blockers, may also prolong the QT interval.) Nortriptyline, the pro-drug of amitriptyline, is used more frequently in our institution since patients experience less somnolence than with amitriptyline. If sleep is an issue with the child’s chronic pain, then the judicious use of amitriptyline may be indicated.

Anticonvulsant therapy has been used for children with chronic pain for several decades. The introduction of gabalins (pregabalin and gabapentin) has revolutionized the management of pain.4 Blockade of the voltage-gated calcium channel can lead to better pain relief in children, but these agents may be associated with increasing somnolence and weight gain, which may be a consideration when dealing with teenage females.

The use of selective serotonin norepinephrine reuptake inhibitors (SNRI), a new class of drugs for pain management, has been demonstrably good in adolescents, especially those with co-morbidities such as depression and generalized anxiety states.5 Duloxetine (brand name Cymbalta) has been used with good success in our center.

Nerve Blocks

This is a new category of intervention that is now being offered for pediatric urology patients. The most common problems associated with urology patients are persistent abdominal pain and persistent groin pain. If using the above paradigms to manage pain is unsuccessful, the use of nerve blocks is considered at our center. We have performed serial ilioinguinal nerve blocks using ultrasound guidance6 (Figure 1) and transversus abdominis plane (TAP) blocks using US guidance with significant improvement in pain symptoms (Figure 2).7

Complementary Therapies

According to the National Center for Complementary and Alternative Medicine, 1 out of 3 adults and 1 in 8 children seek alternative and complementary therapy to help treat disease or symptoms of disease.8 Acupuncture or acupressure is one such therapy. In traditional Chinese medicine, it is taught that the body’s energy or Qi (pronounced “chee”) circulates the body in meridians. If the energy is disrupted or obstructed, an imbalance of energy results causing disease or symptoms. Pelvic pain is a symptom that can be treated with acupuncture. There are a variety of avenues to utilize in acupuncture, just as there

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are different modalities to administer a medication (ie: IV, PO, IM, inhaled, intrathecal, epidural). Firstly, there are different meridians, such as the principal and the curious meridians. The curious meridian of Chong Mo has data showing that it is beneficial in treating pelvic pain symptoms. Additionally, there are several microsystems that acupuncturists specialize in, such as hand, scalp, and auricular microsystems. For example, specific points can be needled on the ear to correspond with symptoms the patient experiences in the urologic system. Data is emerging on the effective use of acupuncture to treat a myriad of conditions from back pain to infertility. It is a promising non-pharmacologic modality to treat pain since side effects are minimal.

References