Postoperative Pain in Children

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Abstract

Postoperative pain therapy is an important component of medical practice to improve the quality of postoperative care in all patients. However, postoperative pain management in children is a challenge for clinicians because of the differences in perception, expression of pain comparison to adults. Infants and older children possess different pharmacodynamics and responses to drugs thus confounding the issue. Evolving new technologies and drugs increase the treatment options but on the other side appropriate management selection gets harder. In this review, our knowledge about the mechanisms and management options of postoperative pain in children are reviewed in the light of new developments on the subject.

Keywords: Pain; Children

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The International Association for the Study of Pain defines pain as an unpleasant sensory or emotional experience associated with, or described in terms of, actual or potential tissue damage [1]. Postoperative pain, with nociceptive attributes, is an acute pain that begins with surgical trauma and reduces as the tissue heals [2,3].

Pathways and physiologic mechanisms develop in the late fetal and newborn stage. From the sixth week of gestation there is an afferent link between sensory fibers and neurons. The first nociceptors develop in the perioral region in the 7th week of intrauterine life and cover the body surface by the 17th week. Myelination begins in the 19th week. Spinothalamic and spinoreticular tracts become functional in the third trimester. Pain sensation is similar to adults by age 2, while pain definition completes by ages 2 to 7 [4,5].

The receptors specific to pain sensation are called nociceptors. Nociceptors transform mechanistic, thermal and chemical energy into electrical signals and action potential. These signals are sent to the spinal cord via the primer afferent fibers. Endogenous algogens released from tissue damage activate the nociceptors [6-10]. Transmission of the stimuli from the nociceptors to the upper centers and sensation of pain follows a four-stage path. The energy form that stimulated the transduction nociceptors is changed to electrical energy. Pain sensation is transmitted to the upper centers by the transmission nociceptors through the unmyelinated A-δ and myelinated C fibers. Modulation of pain stimuli starts at the spinal cord with neural factor changes. Perception, together with the stimulus sent by the spinal cord to the upper centers, combines with the person's previous experience and is felt as pain [11].

The first path to the upper centers is made of two types of afferent nerve. The thick myelinated A-α with roots in the mechanoreceptors stimulates the low-threshold A-β fibers. This alerts the cortex with information about touch, heat, position and localization [6-8]. The thin myelinated A-δ and unmyelinated C fibers with roots in the specific pain receptors in the free nerve endings are sensitive to thermal, mechanistic and chemical stimuli (polymodal). After the primary neuron enters the dorsal horn of the spinal cord it branches and synapses with the secondary neuron [6,8,12,13]. The grey matter of the dorsal horn is split into 10 laminae by cell type, afferent connection and histochemical characteristics. The neurons that synapse with the pain fibers are located in lamina I, II and V [6,10-14]. Most of the axons of the secondary neuron cross the anterior white comissure passing from the middle line to the front diagonal and in the white matter of the opposite anterior horn they comprise the vertically rising anterolateral spinothalamic tract. The third row of spinothalamic tract neurons synapse with the ventral posterolateral nucleus, the reticular formation, the perisegaductal grey matter and the nucleus raphes magnus. While the ascending fibers from the ventral posterolateral nucleus of the thalamus to the somatosensory areas of the parietal cortex postcentral gyrus I and II and the sylvian fissure synapse with the fourth neuron to detect and localize pain, the fibers from the intralaminar and medial nucleus of the thalamus to the anterior cingulate gyrus mediate the emotional component of pain [12] (Figure 1).

The nerve system produces two different responses to the nociceptor warnings related to tissue damage. These are characterized by lowering of the threshold values in the terminal afferent receptors to increase peripheral sensibility and stimulation of spinal neurons to increase central sensitization. Modulation of post-traumatic pain occurs in the peripheral nociceptors, the spinal cord of the central nervous system or the supraspinal structure [9,10]. Pain stimuli inhibit neuronal activity in the segmental spinal cord and supraspinal centers. According to this theory, known as the gate control theory, pain is initially controlled by the spinal cord [6,10,14,15]. Other inhibitory neurotransmitters systems descend to the spinal cord segments via the dorsolateral spinal tract. These include the corticospinal, tectospinal, visuo-spinal and medullary nucleus tracts. Serotonin, norepinephrine and enkephalins are neurotransmitters along the inhibitory path. This system is known as the endogenous spinal opioid chain [6,9,10].

Untreated pain caused by surgical trauma produces very important physiopathologic changes in children similar to those in adults.

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Received April 05, 2012; Accepted June 25, 2012; Published June 30, 2012


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Effective treatment of postoperative pain decreases surgical mortality and morbidity rates and has been shown to promote quicker healing [4,16,17]. Untreated postoperative pain, especially in thoracic and upper abdominal surgeries, decreases respiratory motion and the cough reflex and prevents expectoration of secretions. The risk of atelectasis and postoperative pulmonary complications increases. Surgery increases plasma release of β-endorphins, adrenocorticotropic, vasopressin, catecholamine, growth hormone, glucagon, cortisol aldosterone and other corticosteroids, while depressing insulin release. This results in exhaustion of carbohydrate and fat stores, while increasing the levels of lactate, pyruvate, ketone bodies, glycerol and free fatty acids. Plasma amino acids, nitrogen excretion and 3-methylhistidine/creatinine level increases are related to protein destruction. In children this response is 3 to 5 times greater than in adults but the duration is shorter. Severe pain results in sympathetic stimulation of catecholamine release and systemic increases in vascular resistance, heart rate and myocardial oxygen consumption. Inadequate treatment of pain can result in arrhythmia. Increased sympathetic activity can reduce blood flow to the extremities and increase the risk of deep vein thrombosis. Catecholamine release linked to pain reduces gastrointestinal motility and splanchnic blood flow. There is a linear relationship between postoperative pain and anxiety in children. Higher levels of anxiety and fear increase the pain level and need for analgesics. Psychological distress due to being away from family and the hospital stay when combined with untreated pain can cause psychological problems in children [4,5,16,17].

**Evaluation of Pain in Children**

Evaluating and measuring pain in children is hard due to differences in perception, interpretation and self-expression processes. When choosing methods of pain evaluation the child’s age, general situation and knowledge of pain should be considered. Measurements should be systematically repeatable. None of the methods for measuring pain in children is a single standard pain measurement and does not provide enough information on the different components of pain. If possible, the gold standard of pain measurement is the best method of determining personal expression. The younger the child the harder it is to evaluate pain. For babies and small children behavioral and biological readings are used. The most commonly used technique for evaluating pain in children who cannot talk is completely subjective and insufficient, based on intuition and clinical experience. Children above the age of three, depending on their developmental stage, can use words to inform about localization, strength and nature of their pain. Preschool children can use various scoring systems. However it is difficult to distinguish which results are due to pain, hunger or anxiety. In school-age children and adolescents Visual Analogue Scales (VAS) can be used [4,5,16,17].

Tests of personal expression evaluate the cognitive characteristics of pain. Facial scales play an important role. The child indicates which face illustrates the degree of their pain. Facial scales are easily understood by children, are easy to use and have perfect psychometric properties. Children under the age of 5 use 1-4 cards, 5-8 year olds can use word- or graphic-based scales. Pain thermometers, colored analogue scales and VAS are trusted and valid evaluation methods in children above the age of 5 [4,5,17].

Biological parameters such as heart rate, blood pressure, and blood cortisol levels can be used to measure pain in children [5,17].

There are scales which use various behaviors such as crying, facial expression, verbal expression, touch, body position and motor activity as a basis for pain measurement [5,17].

Scales which combine behavioral and biological parameters to measure pain in children are available. In children under 3, facial appearance, body position, motion, crying, sleep pattern and skin color are combined with vital sign data on arterial blood pressure, heart rate, respiration rate and peripheral oxygen saturation in a single scoring system to provide an almost true evaluation. Neonatal Pain Scale (NIPS), Children’s Hospital Of Eastern Ontario Pain Scale (CHEOPS; crying, face, verbal expression, position, touching sensitive area, leg position), and Objective Pain Scales (OPS; blood pressure, crying, movement, agitation, verbal evaluation and body motion) are commonly used [4,5,17].

Basic principles of pain treatment are applied to pediatric patients with very little change. Preventing postoperative pain begins before the operation and continues throughout the duration of surgery and the postoperative period [18-22]. Certain rules need to be followed when applying analgesia to children, a care system related to pain level should include choice of medicine, appropriate dose intervals, timely drug administration based on the half-life, and preferably oral administration of drugs. It is emphasized that special drugs may be chosen according to the operation undergone the child’s age group and pain level [18-22].

According to pain level the following techniques are recommended as pediatric postoperative pain treatment strategies; mild pain - non-steroidal analgesics (NSAID); moderate pain - NSAID, NSAID and opioid combination, IV opioids (continuous infusion, PCA, continuous interval administration of opioids) and regional anesthetic; severe pain - IV opioids and regional anesthetics [18-22].

**Pharmacologic Methods**

**Non-Steroidal Anti-Inflammatory Drugs (NSAID)**

NSAIDs have well known analgesic, anti-pyretic and anti-inflammatory effects. Their pharmacodynamic and pharmacokinetic properties are the same in children and adults. Their effect is due to
Commonly Pediatric Postoperative Pain Treatment Strategies

1. Pharmacologic Methods

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Table 1: Commonly Pediatric Postoperative Pain Treatment Strategies.

Acetaminophen: It is a para-aminophenolic derivative. Acetaminophen has approximately equal levels of analgesic effect with aspirin. It is the most commonly used analgesic for infants and children, effectively and safely used for newborns. The incomplete development of the hepatic metabolic system of newborns means less production of toxic metabolites from the drug. Its antipyretic effects are similar in strength to aspirin but its anti-inflammatory effect is very low. Antipyretic and analgesic effect is related to PG synthesis and release being inhibited from the hypothalamus and spinal cord dorsal horn. The lack of anti-inflammatory effect is due to peroxide rich environments preventing COX inhibition [23,24].

Acetylsalicylic acid: It is a wide range of uses in pain treatment for children. Oral doses are similar to acetaminophen. Acetylsalicylic acid can be used in a dose range of 65 to 100 mg/kg in 4-6 divided doses per day. Daily maximum dose is 60 mg/kg. Elimination half-life reaches adult levels after the first year. The relationship between its use for high body temperature and Reye's syndrome, high gastrointestinal (GIS) side effects, and platelet dysfunction have significantly reduced its use for children [16,17,22,25].

Ibuprofen: It is preferred in liquid form for mild to moderate pain in children. Doses are 5-10 mg/kg. Daily maximum dose is 40 mg/kg/day [16,17,22,25].

Ketorolac: It is structurally linked to zomepirac and tolmetin. Single dose studies show that it provides equal analgesia to opioids but may affect renal function. Peak plasma concentration is reached 30-60 minutes after oral or parenteral administration. More than 99% ketorolac binds with plasma protein. Ketorolac is metabolized in the liver, conjugates and is excreted by the kidneys. It may be used for continuous intravenous infusion or PCA at a dose of 0.5 mg/kg IV/IM. Daily maximum dose is 2 mg/kg/day. Side effects such as nausea, GIS bleeding, platelet dysfunction and development of interstitial nephritis limit the use of this agent [16,17,22,25].

Dexamethasone: Ketoprofen is a S+ enantiomer of dexamethasone, and a preferred analgesic with rapid and safe effect profile [25].

Diclofenac: Diclofenac is used commonly to treat mild to moderate post-operative pain. Diclofenac is versatile and may be used during and post operation via oral, intramuscular, intravenous or rectal routes. Intramuscular use of diclofenac should be avoided as it can cause long-term pain. A preparation of oral diclofenac with misoprostal is available. Pediatric dose is 2 to 3 mg/kg/day orally in divided doses 2 to 4 times daily. Daily maximum dose is 200 mg/day. Side affects of diclofenac similar other NSAIDs. On the other hand, diclofenac is among the better tolerated NSAIDs. Mostly gastrointestinal (GIS) side effects can be observed [25].

Indomethacin: Indomethacin is a potent NSAID. May cause many serious side effects. Indomethacin contrindicated children under 2 years of age. Indomethacin may be administered orally, intravenously or rectally. Pediatric dose is 1 to 2 mg/kg/day in 2 to 4 divided doses. Maximum daily dose 4 mg/kg [25].

Opioids

Opioids are the most commonly used analgesic group for moderate to severe pain at any age. They provide good pain relief with a wide confidence interval. They should be used with caution in children younger than two months due to a high risk of respiratory depression.
Side effects such as nausea, vomiting, urinary retention, hallucinations, somnolence, dizziness, and intestinal obstruction are no higher in children than in adults (Table 1) [16,17,22,25].

It is possible to administer opioids intramuscularly, intravenously or subcutaneously in child patients. Intramuscular administration is rarely used due to children’s fear of injections. Oral administration is not chosen for reasons including postoperative ingestion difficulties, delayed effectiveness, nausea, vomiting and delayed GIS emptying. Intravenous administration is used most commonly. Continuous intravenous infusion and patient-controlled pain relief methods may be chosen for children. However for moderate to severe pain, transdermal or transmucosal routes may be tried as alternatives to the IV route. Epidural and intrathecal routes provide widespread and long-term pain relief, but close monitoring is required due to possible side effects such as respiratory depression [16,17,22,25].

**Tramadol:** Tramadol’s chemical name is cis-2-[(dimethylamino) methyl]-1-(3-metoxyphenyl) cyclohexanol hydrochloride [26,27]. As a phenylcyclohexanol derivative, it is structurally similar to codeine, affects the central nervous system, has weak opioid agonist properties and is a synthetic analgesic. Its affect comes from 35% opioid and 65% non-opioid mechanisms. Uptake, inhibition and increase in release of neuronal 5-hydroxytryptamine (5-HT) and noradrenalin are responsible for non-opioid mechanisms. Tramadol’s effectiveness is not fully antagonized by naloxone, but is blocked by alpha-2 adrenoreceptor and serotonin antagonists, supporting this mechanism. In a racemic mixture of two pharmacologically active isomers, the D-isomer has 170 times higher affinity for μ-receptor and is six times more potent than the parent compound [26-28].

Tramadol may be administered by oral, rectal, IM, IV and epidural routes. Bioavailability in oral use is above 80%. In plasma about 17% binds to protein. Peak plasma levels are reached 2-3 hours after administration. Elimination half-life is not related to dose and is an average of 6.3-7.4 hours. A study on the pharmacokinetic properties of tramadol in drop form for 2-7 year old children found that after oral administration the elimination half-life was 3.6 ± 1.1 hours, serum clearance was 5.6 ± 2.7 mL.kg⁻¹.dk⁻¹ and volume distribution was 4.1 ± 1.2 L.kg⁻¹. M1 metabolite peak plasma levels were reached 4.5 ± 1.5 hours later, with a half-life of 5.8 ± 1.7 hours. These kinetic parameters were interpreted as similar to late adults [26,27,29].

Tramadol is metabolized by cytochrome-P461 in the liver. Excretion is 90% in urine and 10% in fecal matter. The metabolite, O-desmethyltramadol, has weak analgesic effects. Increased age, severe liver and kidney disease reduce uptake 1.5-2 times and increases plasma levels. Eighty per cent passes the placenta. There is no depressive effect on the fetus. It can be used in children above one year in age [26,27].

Its gravimetric effect is about 10 times lower than morphine. It has no potential to cause euphoria, dysphoria, tolerance or addiction. The risk of abuse is low. This is explained by the combined effective mechanism [26-29].

Tramadol has minimal effects on respiration, heart rate and blood pressure. The most common side effects are nausea, vomiting, malaise, dry throat, fatigue, sedation, central nervous system irritation, orthostatic hypotension, increased sweating and tachycardia. Overdose and intoxication findings are the same as other opioids. These are summarized as myosis, nausea, vomiting, coma, convulsions, respiratory depression, respiratory arrest and cardiovascular collapse [26,27]. A multi-centered and prospective study on the effects of tramadol overdose found hypertension and convulsions linked to an adult dose of at least 500 mg, while coma and respiratory depression were linked to a dose of at least 800 mg. The researchers reviewed the data from 127 cases of tramadol poisoning and found patients suffered from the following problems: 30% from lethargy, 15% nausea, 13% tachycardia, 10% agitation, 8% convulsion, 5% coma and hypertension and 2% respiratory depression [30]. In the postoperative period pediatric cases can be administered 1-2 mg.kg⁻¹ orally [31], 1.5 mg/ kg intravenously every 6 hours or 0.2-0.6 mg.kg⁻¹.hour continuous IV infusion [32]. Tramadol in drop form may be used in doses of 1.5-3 mg/ kg [33-35].

**Morphine:** It can be used at a dose of 0.1-0.15 mg/kg every 4 hours intramuscularly. At intervals 0.05-0.1 mg/kg intravenous dose can be used. For continuous intravenous injection, 10-15 mcg/kg/hour is recommended for children less than 3 months and 10-50 mcg/kg/hour for children above 3 months [16,17,22,25].

**Meperidine:** It may be used at a dose of 1 mg/kg every four hours. Chronic use can cause convulsions due to accumulation of normeperidine, a degradation product of meperidine. It should be used with care in chronic cases [16,17,22,25].

**Adjuvants**

**NMDA antagonists:** In central sensitization physiopathology NMDA receptors play an activation role in the important wind up phenomenon. Agents that affect NMDA receptors may prevent wind up and central sensitization. Non-competitive antagonists such as ketamine and dextromethorphan are used clinically. Dextromethorphan strongly potencializes the effects of morphine and increases its effective duration. Ketamine is becoming popular as a preemptive analgesic given intravenously at sub-anestheic doses, and is gaining new areas of indication [19,20,22]. Ketamine doses of 0.5-1 mg/kg can be repeated every 3-5 minutes. Although preferred for sedation and pain relief, its secretion enhancing properties should not be forgotten [25].

**Other Antinociceptive Drugs**

Serotonergic, acetylcholinergic and GABAergic antagonists have an antinociceptive effect on the spinal cord [22]. Clonidine, an alpha-2 adrenergic receptor agonist, has a use in anesthesia and pain relief due to its sedative, hemodynamic and analgesic properties. Erbay et al. [36] found that oral clonidine given to children in premedication provided good sedation reduced the hemodynamic response to intubation and significantly reduced the need for analgesics in the postoperative period.

**Regional Methods**

All regional block techniques used in adults may be used for children. Regional techniques in children for postoperative pain relief are generally administered after induction of general anesthetic or sedation. In the pediatric population regional techniques combined with general anesthetic reduce consumption of intraperoperative analgesics and volatile anesthetics, reduce the stress response to surgery and encourage fast and painless recovery from surgery. The surgical location and type are important in choosing a method (Table 1) [37,38].

**Central blocks**

The most popular type of block for pediatric patients is a caudal block. Caudal blocks have high efficency for lower abdominal, perineal and lower extremity surgeries. For sacral level analgesia 0.5 ml/kg 0.25% bupivacaine ± 1:200,000 epinephrine; for lumbar and lower thoracic
level analgesia 1 ml/kg 0.25% bupivacaine ± 1:200,000 epinephrine; and for mid-thoracic level analgesia 1.25 ml/kg bupivacaine ± 1:200,000 epinephrine should be used. Side effects of caudal block include nausea, vomiting, weakness, urinary retention, and dural puncture. Epidural block provides enough analgesia for thoracic, abdominal, perineal and lower extremity surgeries. The preemptive analgesic effect of epidural blocks applied to thoracic and abdominal surgeries is trivial [22,25,37,38]. For lumbar or thoracic epidural analgesia in children of 3-36 months 0.75 ml/kg 0.5% bupivacaine ± 1:200,000 epinephrine; for older children 0.5 ml/kg bupivacaine ± 1:200,000 epinephrine; and for continuous infusion 0.08 ml/kg/hour 0.25% bupivacaine doses are recommended. Close monitoring is recommended due to the risk of the catheter dislodging and infection [25,37,28].

Peripheral blocks

Peripheral nerve blocks are used in operations because they provide more specific and longer term analgesia [22,25,37,28]. Ilioinguinal and iliohypogastric nerve blocks are efficient methods of pain relief after operations including inguinal herniotomy, varicocele and orchidopexy. Penile nerve block is used for postoperative pain relief after circumcision and hypospadias interventions. Ilioinguinal and iliohypogastric nerve block dose is 0.4 ml/kg 0.5% bupivacaine + 1:200,000 epinephrine. For dorsal penile block the dose is 2 injections of 1 ml 1% lidocaine, 0.25% or 0.5% bupivacaine with 0.2 ml/kg 1% lidocaine or 0.5% bupivacaine applied in the subpubic area. Femoral block requires an effective dose of 0.2 ml/kg 0.5% bupivacaine or 0.3 ml/kg 1% lidocaine [25,37,38]. Tramadol, due to its local anesthetic properties, may be used in peripheral block and infiltration anesthesia [39,40].

Local infiltration

It can be used alone for small interventions in cooperative children, or for postoperative analgesia after surgeries requiring general anesthetic [37,38]. Best results have been obtained at tonsillectomy operations. Ropivacaine administered to the tonsillar area before the operation has been shown to be effective in postoperative pain treatment [41]. Central sensitization at the brain stem level due to vagal stimulation of the sensory inputs to the brainstem has also been shown to be effective in postoperative pain treatment [41].

Intravenous Patient-Controlled Analgesia (PCA)

Though experience of PCA is low, research indicates PCA is a preferred method. PCA use is limited by factors such as age and emotional development but may be used on patients above 5 years of age. It can also describe as parent-or nurse-controlled analgesia. For local infiltration 0.5-1 ml/kg 0.25% bupivacaine is one of the recommended agents [19,20,22,25,37,38].

References


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