POSTOPERATIVE ANALGESIA IN CHILDREN: AN UPDATE

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Introduction

Acute pain is one of the most common adverse stimuli experienced by pediatric population as a result of surgery, illness, any injury and necessary medical procedure. Pain is associated with increased anxiety, avoidance, somatic symptoms, and increased parent distress and may lead to long term effects[1].

Despite the magnitude of these effects, the acute pain has on a child is often inadequately assessed and treated. Numerous myths, insufficient knowledge among caregivers, and inadequate application of knowledge contribute to the lack of effective management[2]. Fear of adverse reactions and toxic effects often contributed to the inadequate use of analgesics.

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage[3]. Several experts suggest that the neonate's expression of pain does not fit within the strict definition of the International Association for Study of Pain because of the requirement for self-report. This lack of ability to report pain contributes to the failure to recognize and treat pain aggressively during infancy and early childhood[3]. Because neonates cannot verbalize their pain, they depend on others to recognize, assess, and manage their pain. Therefore, health care professionals can diagnose neonatal pain only by recognizing the neonate's associated behavioral and physiological responses.

A large scale survey reported that 40% of pediatric surgical patients experienced moderate or severe postoperative pain and that 75% had insufficient analgesia[4]. The structural components necessary to perceive pain are already present at about 25 weeks gestation whereas the endogenous descending inhibitory pathways are not fully developed until mid-infancy[5]. Opioid and other receptors are much more widely distributed in fetuses and neonates[6]. Fetuses subjected to intrauterine exchange transfusion with needle trans-hepatic access will show both behavioral signs of pain as well as a hormonal stress response[7]. Significant pain stimulation without proper analgesia, for example during circumcision, will not only cause unacceptable pain at the time of the intervention but also produces a 'pain memory' as illustrated by an exaggerated pain response to vaccination as long as six months following the circumcision[8]. Both neonates and infants are able to mount a graded hormonal stress response to surgical intervention and adequate intra- and postoperative analgesia will not only modify the stress response but has also been shown to reduce morbidity and mortality[9-10].

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The following guidelines are designed to support quality health care and effective management of acute intraoperative and postoperative pain management. Objective of present guidelines are to recognize pain in children, minimize moderate and severe pain safely in all children, prevent pain if possible, bring pain rapidly under control and to continue pain control after discharge from the hospital.

Assessment Tools

Recognition and assessment of pain is the first and most important step in successful pain management. Pain should be assessed on a regular basis using self-report, behavioral observation and physiologic measures, bearing in mind the age of the child and his or her communication capabilities. There are many different scales that can be used in different age groups. It is of importance to use a scale that is feasible in the clinical setting[11].

- Children eight year of age and above can generally use visual analogue pain scales used by adults, which involve rating the intensity of pain on a horizontal scale.

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- For children from three to eight years old, self reported measures use either face scales (series of photographs or drawings of faces showing increasing degree of distress) or color-analogue scales (rulers with increasing intensity of red color signifying increasing intensity of pain). Good agreement was reported between the results obtained with a photographic face scale and those obtained with a color-analogue scale among three to seven year old children[12].

- Behavioral observational scales are the primary methods of pain assessment for neonates, infants, and children under four years of age or for children with developmental disabilities[12]. Such scales may score facial expressions, limb and trunk motor responses, verbal responses, crying or combinations of behavioral and autonomic measures. Some of these scales record "distress", which reflects fear and anxiety as well as pain. Behavioral scales may under represent the intensity of persistent pain, as compared with

self-reports.

- Physiological indexes of pain are useful and include changes in heart rate, respiratory rate, blood pressure, oxygen saturation, vagal tone, palmer sweating, and plasma cortisol or catecholamine concentrations although they may be nonspecific. For example, tachycardia may be caused by hypovolemia or hypoxemia, rather than pain. Thus, pain assessment in neonates, infants, and children less than four years of age and in children with major disabilities remains a challenge.

Techniques of Pain Control

Combination of pharmacological and non pharmacological techniques have proven to be useful in managing pain in children.

Non pharmacological

A variety of non pharmacologic pain prevention and relief techniques have been shown to effectively reduce pain from minor procedures in neonates. These include use of oral sucrose/glucose, breastfeeding, nonnutritive sucking, "kangaroo care" (skin-to-skin contact), facilitated tuck (holding the arms and legs in a flexed position), swaddling, and developmental care, which include limiting environmental stimuli, lateral positioning, the use of supportive bedding and physical therapy. These measures have been shown to be useful in preterm and term neonates in reducing pain from a heel stick, venipuncture, and subcutaneous injections and are generally more effective when used in combination[13].

Pharmacological

Analgesics can be administered through different routes depending on the age, type of procedure, presence of intravenous line, patient preference and severity of pain.

Oral route

Oral route is the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal

Table 1
Maximum local anesthetic doses in infants and children

Drugs	Dose mg/kg	Continuous epidural analgesia (CEA) mg/ml
Lidocaine (plain)	5	Not available
Lidocaine (epinephrine)	7	Not available
Bupivacaine	2: < 3 months 3: child dose	1 (0.5-1.25)
Levobupivacaine	2	Not available
Ropivacaine	2	1 (0.5-1.25)

dysfunction, those who require a very rapid onset of analgesia and those who are unable to utilize or tolerate the oral route.

Intravenous route

Analgesics are administered as single or intermittent boluses or as a continuous infusion. For prolonged use, continuous infusion is preferred to avoid large variations in plasma concentration. The safety and efficacy of patient-controlled analgesia for children as young as six years is supported by controlled trials[12]. Nurse-activated patient-controlled analgesia is now widely used for infants[9] as a convenient way to prevent delays in relieving episodic pain.

Activation of the button for patient-controlled analgesia by parents (parent-controlled analgesia) is widely accepted in palliative care. However, its use for postoperative pain is controversial because of the potential for either overdosing or under dosing, subjects who have not received opioids before.

Rectal route

Rectal route is particularly useful in immediate postoperative period where patient is not allowed to take oral medication.

Regional (Table 1)

Regional analgesia includes Local infiltration, Peripheral nerve blocks and Central nerve blocks (spinal, epidural, Caudal). The most common regional block in pediatric patient is caudal block.

Non Steroidal Anti Inflammatory Drugs (Table 2)

There are mainly four categories of drugs which are effective in pain management. These are non opioids (Paracetamol, Non steroidal anti-inflammatory drugs, and clonidine), opioids (Morphine, Meperidine, and Tramadol), local anesthetics and adjuvant drugs.

Table 2
Recommended doses of non-steroidals for pediatric patients[4,11,14,15]

Drugs	Dose	Interval (hours)	Maximum daily dose
Acetaminophen	5-15 mg/kg PO	4-6	Children:< 100mg/kg/day Infants: 75mg/kg/day Newborns: (< 32 wks PCA):60 mg/kg/d (28–32 wks PCA): 40 mg/kg/d
Ibuprofen	4-10 mg/kg PO	6	< 40mg/kg/day
Naproxen	5-10 mg/kg PO	8-12	20 mg/kg/day
Diclofenac	1-2 mg/kg PO	8-12	Not available
Ketorolac	0.3-0.5 mg/kg I/V	6-8	< 2mg/kg/day

Acetaminophen (Paracetamol)

Acetaminophen is the most widely prescribed analgesic used for mild type of all pains. It lacks the troublesome side effects of other NSAIDs. Its effects are mediated by central cyclooxygenase III (COX-III) inhibition. Acetaminophen can be given orally or rectally. Acetaminophen is metabolized in the liver primarily by glucuronidation and sulfation[14].

The recommended oral dosage is 10 to 15 mg per kilogram every four hours for children[15]. Rectal administration produces delayed and variable uptake; single bolus dose of 35 to 45 mg per kilogram generally produces therapeutic plasma concentrations, with prolonged clearance. Subsequent rectal doses should be smaller (e.g., 20mg per kilogram), and the interval between doses should be extended to at least six to eight hours.

Single rectal doses of 20 mg per kilogram produced safe plasma concentrations in preterm neonates. Daily cumulative acetaminophen doses by the oral or rectal route should not exceed 100 mg per kilogram per day for children, 75 mg per kilogram for infants, 60 mg per kilogram for term and preterm neonates beyond 32 weeks of postconceptional age, and 40 mg per kilogram for preterm neonates from 28 to 32 weeks of postconceptional age[12].

Acetylsalicylic acid (Aspirin)

Because of its association with Reye's syndrome, aspirin is now used only rarely in pediatric patients suffering from rheumatologic conditions[14] can be prescribed as 10-15mg/kg PO[4].

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are used for the management of mild to moderate pain. They are used alone or in combination with opioids. Main advantage of NSAIDs is lack of respiratory depression and sedation. Their mechanism of action is through the inhibition of cyclooxygenase (COX), the enzyme responsible for metabolizing arachidonic acid. When arachidonic acid is released from traumatized cell membranes, it is metabolized by COX to form prostaglandins and thromboxanes, which in turn sensitize peripheral nerve endings and vasodilate vessels, causing pain, erythema, and inflammation. There are two COX isoenzymes. The constitutive form of COX (COX-1) is present throughout the body and the prostaglandins and thromboxanes that are produced are essential for functions such as gastric mucosa protection, renal blood flow regulation, and platelet aggregation. Potential complications of COX-1 inhibition include gastric ulceration, bleeding, altered renal function, and bronchoconstriction. COX-2 is called an ''inducible COX'' and is present only in traumatized cells or inflamed tissue. Most NSAIDs are nonselective COX inhibitors, but the potential attraction of selective COX-2 inhibition in the reduction of side effects is apparent. Presently, the future of COX-2 inhibitors in children is uncertain[14]. Ibuprofen can be administered 6-8 hours interval in doses of 8mg/kg PO and 20mg/kg rectally[15]. Ketorolac in doses of 0.4 to 1.0 mg/kg is useful for mild to moderate pain in children when parenteral administration is required[15].

OPOIDS (Tables 3, 4, 5)

Opioids are morphine like substances. The term opoid is derived from opium (from the Greek term for juice) which is extracted from the poppy plant. Opioids are used for moderate to severe nociceptive pain. Opioids bind to pre- and postsynaptic cell membranes in the central nervous system through the specific opioid receptors, resulting in neuronal inhibition by decreasing excitatory neurotransmitter release from presynaptic terminals or by hyperpolarizing the postsynaptic neuron. Opioid receptors are classified as mu, kappa, delta, and sigma. The mu receptor is further subdivided into subclasses mu1, which mediates supraspinal analgesia and dependence, and mu 2, which mediates respiratory depression, intestinal dysmotility, sedation, and bradycardia. Opioids are classified as agonists, partial agonists, agonist-antagonists, and antagonists. Examples of the mu1 agonists include morphine, hydromorphone, meperidine, methadone, fentanyl, sufentanil, remifentanil, codeine, oxycodone, and hydrocodone.

Table 3
Recommended single doses of opioids for pediatric patients[4,11,14,15]

Drugs	Single dose	Interval (hours)	Potency (relative to morphine)
Codeine	0.5-1 mg/kg PO	4-6	Not available
Meperidine	0.5-1.0 mg/kg I/V	2-3	0.1
Morphine	0.05-0.15mg/kg I/V 0.3mg/kg PO	2 3-4	1
Fentanyl	0.5-1 mcg/kg I/V	1-2	50-100
Tramadol	1-2 mg/kg I/V		0.1
Nalbuphine	25-50 mcg/kg I/V	2-4	

Table 4
Recommended continuous infusion dose of opioids for pediatric patients[4,11,15]

Drugs	Continuous infusion rate doses
Meperidine	0.1 0.3 mg/kg/hr
Morphine	10-40 mcg/kg/hr
Fentanyl	0.5 mcg/kg/hr
Nalbuphine	10-15 mcg/kg/hr

Table 5
Recommended PCIA dose of opioids for pediatric patients

Drugs	Bolus dose mcg/kg	Lockout interval min	Continuous infusion mcg/kg/hr	1 hour limit mcg/kg/hr
Morphine	20	8-10	0-20	100
Fentanyl	0.5	6-8	0-0.5	25
Nalbuphine	20	8-10	0-20	100

Agonist-antagonist opioids, which are agonists at one receptor type and antagonists at another receptor, include nalbuphine and pentazocine. Analgesia by agonist-antagonists is mainly kappa & sigma-mediated, with antagonism or partial agonism at the mu receptor.

A partial agonist such as buprenorphone exerts less than full response at a receptor site.

Opioid antagonists include naloxone and naltrexone.

Side-effects common to opioid agonists include respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention, ileus, and constipation. Less common effects are dysphoria, hallucinations, seizures, and myoclonic movements. Opioids can be used as oral, sublingual, transdermal, intranasal, and rectal routes[3].

Morphine

Morphine is the standard opioid with which all other opioids are compared[16]. It has a rather poor oral bioavailability (25-40%), which necessitates a larger oral dose when converting from i.v. to enteral administration[11]. It can be given through multiple routes (intravenous, oral, subcutaneous, intrathecal, epidural, and intra-articular). Morphine is metabolized in the liver to morphine-3-glucuronide (inactive) and morphine-6-glucuronide (active), which are both excreted by the kidneys. Generally, the elimination half-life is longer and the clearance is decreased in newborns compared with older children and adults. This difference is especially pronounced in preterm neonates. In addition, less morphine is protein bound in neonates, allowing a greater proportion of unbound

morphine to penetrate the brain, thus increasing the risk for respiratory depression. The elimination half-life and clearance reach adult values within 2 months of age[16].

Recommended single intravenous dose is 0.08-0.1 mg/kg while epidural and caudal are given as 50 mcg/kg and 120-150 mcg/kg respectively[15]. If morphine is given by PCA, start with bolus dose of 20 mcg/kg, lockout interval 5 min with or without background infusion 4 mcg/kg/h (especially first 24 h)[4].

Pethidine (Meperidine)

Meperidine is a synthetic opioid derived from phenylpiperidine. It has 1/10th the analgesic potency of morphine and is metabolized in the liver by hydrolysis and N-demethylation. It has an elimination half-life of approximately three hours. It offers no advantage over morphine in terms of side effects. The primary metabolite, normeperidine, can cause hallucinations, agitation and seizures, when meperidine is used for an extended period[11]. It can be used intramuscularly & intravenously. It is used in single doses for postoperative shivering[17] Meperidine should also not be used in conjunction with monoamine oxidase inhibitors or in patients with hyperthyroidism[14].

Recommended intravenous dose is 1-1.5 mg/kg with 2-3 hour interval after titration while usual intramuscular dose is 0.8-1 mg/kg with 3-4 hour interval[15].

Fentanyl

Fentanyl is a synthetic opioid that is 100 times more potent than morphine. It is highly lipophilic, resulting in significant brain penetration. Fentanyl has a short duration of action because of redistribution out of the plasma into body tissues[14]. Metabolism is through glucuronidation in the liver to inactive metabolites that are excreted by the kidney. Because of its potency, hemodynamic stability, and brief duration of action in small doses, fentanyl is an attractive analgesic for short painful procedures in children, especially in an intensive care unit setting[16]. Fentanyl can be given through multiple routes: intravenous, epidural, intrathecal, nasal, transmucosal, and transdermal. With repeated dosing or with prolonged infusions, fentanyl may accumulate in the body and leads to longer duration of action.

Transmucosal fentanyl permits rapid onset of analgesia for brief, painful procedures in hospitalized children in whom intravenous access is not available. Transmucosal is more efficient than oral administration because it bypasses the hepatic first pass metabolism of the oral route, which reduces the availability of fentanyl by 25% to 33%[14].

Transdermal fentanyl provides a consistent analgesic effect for selected patients, such as children with severe pain due to cancer. Transdermal fentanyl administration is available in patches of 25, 50, 75, and 100 mg/h for use lasting 2 to 3 days. It has a long onset time but also a long duration that persists after the patch is removed[14]. Fentanyl can be given intravenously as a single bolus of 1-1.5 μg/kg or infuse continuously at 2-4 μg/kg/hr[15].

Codeine

Codeine is used to treat moderate pain[11]. Codeine is a mu agonist and a derivative of morphine. It is a commonly used oral opioid most often combined with acetaminophen in liquid or tablet form. Codeine is 0.10 times as potent as morphine. Its bioavailability is 60% after oral administration, with an onset time of 20 minutes and an elimination half-life of 2.5 to 3 hours. Codeine is metabolized in the liver and then excreted in the urine[18]. Five to ten percent of codeine is metabolized by O-demethylation in the liver by a P-450 oxidase pathway (CYP2D6) to produce morphine. This conversion is necessary for analgesia to occur after codeine administration. When the codeine and acetaminophen combination is used, care must be taken to stay within safe dosage ranges of acetaminophen[14]. Recommended doses: 0.5-1 mg/kg PO with 4-6 hr interval[15].

Nalbuphine

Nalbuphine is a kappa agonist and a mu antagonist. It has an analgesia equivalent to morphine up to a dose of approximately 200 mg/kg, at which point it has a ceiling effect of analgesia. Kappa mediated side effects of sedation, dysphoria, or euphoria are likely at higher doses. Nalbuphine is metabolized mainly in the liver and has a half-life of approximately 5 hours. It is usually given intravenously. When given orally, it has

a bioavailability of only 20% to 25%. Care is needed when using nalbuphine in opioid-dependent children in order not to induce opioid withdrawal[14].

Naloxon

Naloxone is antagonist at all opioid receptors. It is used for opioid induced side effects, like respiratory depression. It also is used in smaller doses for pruritis (1-2 mcg/kg IV). Naloxone is metabolized in the liver and has an elimination half-life of 60 minutes[14].

Tramadol

Tramadol a synthetic cyclohexanol, 4-phenyl-pipridine chiral racemic analog of codeine, is a centrally acting analgesic that possesses weak affinity for the mu opoid receptor and modifies transmission of nociceptives impulses through inhibition of monoamines (norepinephrine and serotonin) reuptake, but not production. Tramadol is approximately 1/10 as potent an analgesic as morphine[15]. In general, tramadol is a safe and effective analgesic for mild to moderate pain in children[19]. The recommended dose of tramadol is 1 to 2 mg/kg (maximum 100 mg) every 6 hours, with a maximum daily dose of 8 mg/kg/d or 400 mg/d[14].

Ketamine

Ketamine is a phencyclidine derivative and a dissociative anesthetic. It is a potent analgesic in subanesthetic doses and is often used for short painful procedures in children in the emergency room and ICU settings. It can be administered intravenously, orally, rectally, and intramuscularly[14]. In the postoperative period a low-dose continuous infusion can offer an improved pain situation while minimizing side effects. Because of increased secretions and possible dysphoric effects, ketamine is often combined with an anticholinergic agent and a benzodiazepine. The analgesic effects of ketamine are mediated by NMDA receptor antagonism. Oral bioavailability is 20% to 25%. Ketamine is highly lipid soluble, with rapid redistribution. Ketamine is N-demethylated in the liver by the cytochrome P-450 system Intravenous doses of 0.25 to 0.5 mg/kg can produce intense analgesia for 10 to 15 minutes, although the elimination half-life is 2 to 3 hours. A dose of 1 to 2 mg/kg IV may be needed for more painful procedures such as fracture reduction.

Conclusion

Despite several advances in assessment and management of acute pediatric pain, significant number of children still suffer from moderate to severe pain in the postoperative period. There is a need for education and training of care provider, evidence based research, development of easily applicable assessment tool and effective treatment of pain by pharmacological and non pharmacological means. Institutions should develop and implement guidelines and protocols for pediatric pain prevention, assessment and management according to local environment.

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