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MANEGMENT OF PAIN IN NEONATES, INFANTS AND SMALL CHILDREN

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Abstract

Effective pain management in neonates, infants, and young children is a critical clinical and ethical imperative. The immature yet functional nociceptive system in this population, characterized by underdeveloped inhibitory pathways and a tendency for wind-up hyperexcitability, means they experience pain intensely and are vulnerable to its detrimental short-term physiological effects and potential long-term neurodevelopmental sequelae. This review underscores the role of frequent, objective pain assessment using validated, age-appropriate tools to guide therapy. It advocates for a proactive, multimodal approach that integrates non-pharmacological interventions—such as sucrose, breastfeeding, skin-to-skin contact, and distraction—as first-line strategies. For more significant pain, a tailored pharmacological strategy is essential. This involves a stepped approach utilizing non-opioid analgesics (e.g., paracetamol, NSAIDs, metamizole), judicious opioid administration, and adjuncts like ketamine and dexmedetomidine. The paper highlights the importance of locoregional anesthetic techniques (e.g., caudal, epidural, and peripheral nerve blocks) in providing superior intraoperative and postoperative analgesia while minimizing systemic drug exposure. Dosing must account for profound age-related pharmacokinetic and pharmacodynamic differences. Ultimately, successful pediatric pain management requires a paradigm shift towards preemptive and multimodal analgesia, meticulous assessment, and interdisciplinary collaboration to ensure patient safety, alleviate suffering, and improve outcomes.

Key words: *multimodal analgesia, pediatric, postoperative analgesia,*

Introduction

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." (1). For children who cannot verbally articulate this experience, this definition underscores the subjective nature of pain and the clinician's responsibility to infer its presence. Untreated pain in the pediatric population, particularly neonates, is not merely a matter of transient discomfort. It triggers a cascade of detrimental physiological stress responses, including cardiorespiratory effects such as hypertension, tachycardia, increased intracranial pressure, and desaturation; metabolic effects, such as catabolism, hyperglycemia, and lactic acidosis; suppression of immune function; and behavioral changes, such as sleep disturbances, feeding difficulties, and irritability. Furthermore, repeated painful experiences in early life can lead to altered pain perception, making children more sensitive to pain later in life, and can potentially contribute to long-term neurodevelopmental

impairments. (2) Therefore, proactive and effective pain management is a moral and clinical imperative to mitigate both short-term harm and long-term sequelae.

Neurophysiology of Pain in Children

Understanding pain processing in young children and youth is crucial for effective intervention. The nervous system of a neonate is immature but fully capable of transmitting nociceptive signals. (3)

- Nociception is intact: By the 24th gestational week the anatomical structures for pain transmission (peripheral receptors, spinal cord tracts, thalamus) are developed. However, the descending inhibitory pathways, which modulate and dampen pain signals, are underdeveloped until later in infancy. This results in a relative imbalance in which excitatory signals dominate, meaning that neonates may experience pain more diffusely and intensely than older individuals for a given stimulus.
- Wind-Up Phenomenon: Repeated painful stimuli can lead to "wind-up," a state of spinal cord hyperexcitability where the response to subsequent stimuli is amplified. This underscores the importance of pre-emptive analgesia.
- Pharmacokinetic and Pharmacodynamic Differences: Key differences profoundly impact drug dosing:
- Body Composition: Higher total body water and lower fat and muscle mass affect the volume of distribution for water-soluble (e.g., morphine) and lipid-soluble drugs.
- Hepatic Metabolism: Immature enzyme systems (e.g., cytochrome P450, glucuronidation) prolong the half-life of many drugs (e.g., morphine, midazolam).
- Renal Excretion: Lower glomerular filtration rate (GFR) delays the clearance of drugs and their active metabolites (e.g., morphine-6-glucuronide).
- Blood-Brain Barrier: More permeable in neonates, allowing greater drug penetration to the CNS and increasing the risk of toxicity.

Pain Assessment

Accurate assessment is the cornerstone of effective pain management. (4) Since self-report, the gold standard, is impossible in pre-verbal children, clinicians must rely on behavioral and physiological cues. Assessment must be done frequently, at least three times per day, documented, and used to guide therapy. Pain is considered a vital sign and is measured accordingly.

Pain Assessment Tools for Neonates and Infants

These tools combine behavioral and physiological indicators.

- Premature Infant Pain Profile (PIPP/PIPP-R): A well-validated tool for both preterm and term neonates. It scores seven indicators: gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow. The total score characterizes pain as none, minimal, moderate, or severe.

- Neonatal Infant Pain Scale (NIPS): A simple, fast tool useful in clinical settings. It assesses facial expression, crying, breathing patterns, arm movements, and leg movements. Scores range from 0 (no pain) to 7 (maximum pain).
- FLACC Scale: The most widely used tool in children approximately 2 months to 7 years old. It scores five categories: Face, Legs, Activity, Crying, and Consolability. Each category is scored 0-10, for a total of 0 (no pain) to 10 (severe pain). A revised version (r-FLACC) allows parents to provide input on behaviors specific to their child (e.g., "my child grabs his ears when in pain").

Pain Assessment for Verbal Children

- Wong-Baker FACES Pain Rating Scale: For children as young as 3 years old. The child points to one of six faces that best represents their pain, from a smiling "no hurt" face to a crying "worst hurt" face.
- Visual Analog Scale (VAS) & Numeric Rating Scale (NRS): For older children (e.g., >8 years). The VAS is a 10 cm line where the left end is "no pain," and the right is "worst pain imaginable." The NRS asks the child to rate their pain from 0 (no pain) to 10 (worst pain).

Non-Pharmacological Management of Pain

Non-pharmacological interventions are effective, safe, and should be used as first-line for minor procedures and as adjuncts to medications for more significant pain. They provide comfort, reduce anxiety, and block pain transmission through competing sensory input.

Interventions for Neonates and Young Infants

- Sucrose/Breastfeeding: The most evidence-based intervention. Sweet-tasting solutions (24% sucrose or glucose) administered orally via pacifier or syringe 2 minutes before a procedure provide potent analgesia. The mechanism is believed to be the release of endogenous opioids. Breastfeeding is equally, if not more, effective, combining sucrose, skin-to-skin contact, sucking, and smell.
- Non-Nutritive Sucking (NNS): Providing a pacifier for sucking can have a calming and analgesic effect.
- Facilitated Tucking/Swaddling: Holding the infant contained in a flexed position (facilitated tucking) or swaddling provides comfort and promotes physiological stability.
- Kangaroo Care (Skin-to-Skin Contact): Placing the diaper-clad infant skin-to-skin on the parent's chest regulates heart rate, oxygen saturation, and reduces behavioral pain responses.

Interventions for Infants and Young Children

- Distraction is a powerful tool. It can include blowing bubbles, watching videos, listening to music, interactive toys, or using interactive apps.
- Parental Presence and Involvement: A parent's voice, touch, and presence are profoundly calming. Coaching parents to be actively involved (e.g., holding, singing, assisting with distraction) reduces the child's and the parent's anxiety.

- Other Techniques: For older children, guided imagery, deep breathing exercises ("blow out the birthday candles"), and hypnosis can be highly effective.

Pharmacological Therapy

When pain is anticipated to be more severe, pharmacological agents are necessary. The key principle is to use a multimodal approach and combine drugs from different classes (e.g., opioids, NSAIDs, local anesthetics) to target pain pathways synergistically (5,6). This allows the use of lower doses of each drug, minimizing side effects. Analgesics should be administered by the clock, on a scheduled basis, to maintain therapeutic levels and prevent "breakthrough" pain, rather than "as needed". We should also use preemptive analgesia, which means administering analgesia before a painful procedure (e.g., pre-operative analgesia) to prevent wind-up and reduce total analgesic requirement.

What is the anesthesiologist's responsibility? Is it just to cover the intraoperative needs for analgesia, or the whole perioperative period? The answer to these questions is to be provided by every institution itself, depending on many factors. However, close communication between the anesthesiologist, surgeon and pediatrician is necessary.

Let us divide the perioperative period for practical reasons of explaining analgesia.

1. *Preoperative.* This is usually administered as preemptive analgesia by itself or with premedication. Paracetamol 10-15 mg/kg per os or Ibuprofen 10mg/kg per os.
2. *Intraoperative.* After induction of anesthesia, the rectal route can be used to give paracetamol 40-60mg/kg or i.v 10-15 mg/kg, or metamizole i.v 10-15 mg/kg. Of course, the opioids are the mainstay in general anesthesia, and usually fentanyl is used 1-3mcg/kg, depending on the surgery, its length, the extubation plan, the child's condition, the surgeon's expertise, etc. Furthermore, morfium, sufentanyl and remifentanil can also be used. As an adjunct to the opioids, a dose of 0,5mg/kg i.v of ketamine is used.

Locoregional Anesthesia

The primary use of regional techniques in pediatric anesthesia has been to supplement and reduce the requirement for general anesthetics and to provide better postoperative pain management. Blocks range in complexity from relatively simple peripheral nerve blocks (e.g., penile block, ilioinguinal block); to brachial plexus block, sciatic nerve block, femoral nerve block, and TAP (transversus abdominis plane) block; to central blocks (e.g., spinal or epidural techniques). Regional blocks in children (as in adults) are often facilitated by ultrasound guidance, and less commonly by nerve stimulation.

Spinal anesthesia is a safe and valuable technique in infants and children, particularly ex-premature babies, undergoing short lower abdominal or urological surgeries. Its key benefit is reducing life-threatening respiratory complications associated with general anesthesia. Dosing is primarily based on **milligrams per kilogram (mg/kg)** of body weight, not on a fixed volume. Infants and children usually experience minimal hypotension from sympathectomy.

Table 1. Dosage of local anesthetic in spinal anesthesia

Age Group	Typical Weight Range	Recommended Dose (mg/kg) of Isobaric Bupivacaine 0.5%
Preterm & Term Neonates	2 - 5 kg	1,0 mg/kg (0,2ml/kg)
Infants	5 - 15 kg	0,4 mg/kg (0,08ml/kg)
Children (>6 months - 5 years)	>15 kg	0.3 mg/kg, max 5-6mg (0,06ml/kg)

According to Update in Anesthesia. Paediatric spinal anaesthesia. Rachel Troncin and Christophe Dadure

Caudal blocks are reportedly useful after a variety of operations, including circumcision, inguinal herniorrhaphy, hypospadias repair, anal surgery, clubfoot repair, and other subumbilical procedures. Contraindications include infection around the sacral hiatus, coagulopathy, or anatomical abnormalities. The patient is usually lightly anesthetized or sedated and placed in the lateral position. For pediatric caudal anesthesia, 22-gauge needles are used. If the loss-of-resistance technique is applied, the syringe should be filled with saline rather than air, because of the latter's possible association with air embolism. After the characteristic "pop" that signals penetration of the sacrococcygeal membrane, the angle of the needle is reduced, and the needle is inserted only a few millimeters further to avoid entering the dural space or the anterior body of the sacrum. Aspiration is used to detect blood or cerebrospinal fluid. The local anesthetic can then be injected slowly. Failure of a 2-mL test dose of local anesthetic with epinephrine (1:200,000) to produce tachycardia helps to rule out intravascular placement. The most commonly used anesthetics are 0.125% to 0.25% bupivacaine or 0.2% ropivacaine. Morphine sulfate (25 mcg/kg) can be added to the local anesthetic solution to prolong the period of postoperative analgesia in inpatients, but this will increase the risk of delayed postoperative respiratory depression. The required volume of local anesthetic depends on the desired block level, ranging from 0.5 mL/kg for a sacral block to 1.25 mL/kg for a midthoracic block. Single injections usually last 4 to 12 hours. Placement of 20G caudal catheters with continuous infusion of a local anesthetic (e.g., 0.125% bupivacaine or 0.1% ropivacaine at 0.2–0.4 mg/kg/h) or opioid (e.g., fentanyl, 2 mcg/mL at 0.6 mcg/kg/h) allows for prolonged anesthesia and postoperative analgesia. Complications are rare but include local anesthetic toxicity from elevated blood concentrations (e.g., convulsions, hypotension, arrhythmias), spinal block, and respiratory depression. Urinary incontinence is not a problem after a single dose of caudal anesthesia. Lumbar and thoracic epidural catheters can be placed in anesthetized children using a standard midline loss-of-resistance technique or paramedial access. In young children, caudal epidural catheters can be brought into the thoracic position with the tip localized radiographically. Unilateral TAP blocks are most commonly used to provide analgesia after hernia repair. Bilateral TAP blocks can be used to provide effective postoperative analgesia after abdominal surgery where a lower midline incision was made.

3. Postoperative analgesia

Due to practical reasons, we are going to divide postoperative pain management in the PACU room and on the ward. In the PACU room, adequate monitoring allows the use of stronger analgesics and, on the ward, we should be very careful in administering them.

In the PACU room.

We usually give intravenous analgesics, such as: metamizole 10-15mg/kg, fentanyl 0,5-1mcg/kg, morfium 0,025-0,1 mg/kg, tramadol 1-1,5mg/kg and ketamine 0,5mg/kg.

On the ward Paracetamol, metamizole and NSAIDs (nonsteroidal anti-inflammatory drugs) (Table 1) are the first choice drugs for the treatment of postoperative pain (7,8) On the day of surgery, they are usually administered intravenously, and then when the child begins to take fluids and food, the drug is switched to enteral form. For more severe postoperative pain, opioid analgesics are used in the form of boluses or continuous intravenous infusion, but they are not recommended without adequate monitoring of their side effects.

Table 2. Example of a guideline for prescribing analgesia in children

	Dosage Suggestions
Oral NSAIDs	
Ibuprofen	10 mg kg−1 every 8 h
Diclofenac	1 mg kg−1 every 8 h
Rectal paracetamol	
Paracetamol	20–40 mg kg−1 (15 mg kg−1 if< 10 kg) Single loading dose in association with anesthesia; the higher dose is due to poor bioavailability from rectal route of administration
Oral paracetamol	
Paracetamol	10 to 15 mg kg−1 every 6 h (max daily dose: 60 mg/kg)
Intravenous paracetamol	
Paracetamol	loading dose: 15–20 mg kg−1 (Intravenous preparation: 10 mg ml−1) 10–15 mg kg−1 every 6–8 hours
Intraoperative Opioids depending on age of the patient and the type of procedure	
Fentanyl	1–2 micrograms kg−1
Morphine	25 to 100 micrograms kg−1 depending on age, titrated to effect
Sufentanil	0.5–1 micrograms kg−1 bolus, continuous infusion of 0.5–1 micrograms kg−1 h−1
Remifentanil	0.05 to 0.3 micrograms kg−1 min−1
Intraoperative use of Ketamine/S-Ketamine	
Ketamine	0.5 mg kg−1 may be used as adjunct to intraoperative opioids, consider reduced dose (0.25–0,5 mg kg−1) when using S-ketamine, followed by continuous infusion of 0.1 – 0.2 mg kg−1 h−1 (max: 0.4 mg kg−1 h−1) is optional

	Dosage Suggestions
Intraoperative use of Co-analgesic Drugs	
Lidocaine	intravenous bolus: 1.5 mg kg−1, continuous infusion 1.5 mg/ kg−1 h−1 until the end of the procedure
Methylprednisolone	1 mg kg−1
Dexamethasone	0.15−0.25 mg kg−1 (max: 0.5 mg kg−1)
Clonidine	intravenous bolus: 1−3 micrograms kg−1
Dexmedetomidine	intravenous bolus: 0.5−1 micrograms kg−1, continuous infusion 0.2−0.7 micrograms kg−1 h−1 until the end of the procedure
Intraoperative/postoperative intravenous Metamizole	
Metamizole	10 to 15 mg kg−1every 8 h 2.5 mg kg−1 h−1 (continuous infusion following an intraoperative loading dose) (Due to the risk of agranulocytosis after long-term use metamizole is recommended for short term postoperative use in a hospital setting only)
Intravenous analgesics for breakthrough pain in PACU depending on age and procedure	
Fentanyl	0.5 to 1.0 micrograms kg−1, titrated to effect
Morphine	25 to 100 micrograms kg−1 depending on age, titrated to effect
Tramadol	1 to 1.5 mg kg−1, titrated to effect
Ketamine/S-Ketamine	0.5 mg kg−1, titrated to effect consider reduced dose (0.25−0.5 mg kg−1) when using S-ketamine,
Intravenous analgesics for breakthrough pain in the ward, including adequate monitoring	
Tramadol	1 to 1.5 mg kg−1, every 4−6 hours
Morphine	< 3 months 25−50 micrograms kg−1, every 4−6 hours 3−12 months 50−100 micrograms kg−1, every 4−6 hours 1−5 years 100−150 micrograms kg−1, every 4−6 hours 5−18 years 150−200 micrograms kg−1, every 4−6 hours single dose adjusted according to response
Metamizole	10 to 15 mg kg−1 every 8 h
Oral analgesics for breakthrough pain in the ward	
Tramadol	1−1.5 mg kg−1, every 4−6 hours
Metamizole	10 mg kg−1every 8 h
Morphine	When changing from intravenous to oral administration, the daily dose should be increased by 2−3 times due to lower bioavailability. <3 months 50−100 micrograms kg−1, every 4−6 hours 3−12 months 100−150 micrograms kg−1, every 4−6 hours 1−5 years 150−200 micrograms kg−1, every 4−6 hours 5−18 years 200−300 micrograms kg−1, (max10 mg) every 4−6 hours single dose adjusted according to response

	Dosage Suggestions antiemetic drugs	
Dexamethasone	0.15 mg kg−1 every 12 h	
Ondansetron	0.15 mg kg−1 every 8 h	not to be combined with tramadol
Metoclopramide	0.1 mg kg−1 every 8 h	not to be combined with tramadol; not if <1y old

Taken and modified from Vittinghoff M, Lönnqvist PA Postoperative Pain Management in children: guidance from the Pain Committee of the European Society for Paediatric Anaesthesiology (ESPA Pain Management Ladder Initiative) Part II. Anaesth Crit Care Pain Med. 2024

Conclusion

The management of pain in neonates, infants, and children is a complex but achievable goal. It requires a paradigm shift from reactive to proactive care. Clinicians must **understand** the unique neurophysiology of pain in development, **utilize** validated, age-appropriate pain assessment tools, **use a multimodal strategy** that combines non-pharmacological comfort measures with a stepped pharmacological approach, and **tailoring** every plan to the individual child, their specific context, and the type of pain anticipated.

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