Clinicians balance the immediate risks and benefits of analgesia in infancy, but they also consider the long-term effects of repetitive acute pain against those of prolonged analgesic therapy on brain development. This issue of *Pain: Clinical Updates* summarizes the current evidence regarding acute pain management in newborns. In 2006, the American Academy of Pediatrics and the Canadian Pediatric Society published new guidelines recommending that each health care facility that treats neonates establish a neonatal pain control program. The responsibilities of this program include:

- Providing routine assessments to detect neonatal pain
- Reducing the number of painful procedures
- Preventing or treating acute pain from bedside invasive procedures
- Anticipating and treating postoperative pain following surgery
- Avoiding prolonged or repetitive pain and stress during neonatal intensive care

Despite these recommendations, acute neonatal pain results from 8.5 million untreated painful procedures annually in neonatal intensive care units in Europe, which extrapolates to 120 million painful procedures performed annually in newborns worldwide. Effective pharmacological and nonpharmacological therapies are available for acute neonatal pain, which can be used alone or in combination to treat medically induced acute pain in newborns (see Fig. 1).

### Nonpharmacological Approaches

#### Prevention

Acute procedural pain can be minimized by using indwelling catheters for blood sampling, by planning procedures with an analgesic approach, or by using mechanical devices such as spring-loaded lancets for heel sticks. Procedures must be limited to those absolutely necessary for the diagnostic or therapeutic management of neonates.

#### Swaddling, Positioning, and Touch

Swaddling consists of wrapping infants to restrict movements, with modest effects on pain-elicited distress during and after heel sticks in neonates. In preterm infants at 32 weeks, prone positioning was not a sufficient intervention for comfort during heel sticks, although gentle massage appeared to have analgesic effects.

#### Non-nutritive Sucking

The pacifying effects of non-nutritive sucking were clearly shown in multiple studies that reported decreased crying, lower heart rates and increased oxygenation in term...
and preterm neonates during painful procedures like heel sticks and venipuncture.\textsuperscript{9,10}

Sweet Solutions

The analgesic effect of sucrose was first reported by Blass et al. in 1991.\textsuperscript{11} A systematic Cochrane review in 2010 including 44 studies and 3496 infants concluded that sucrose is safe and effective for reducing procedural pain in neonates,\textsuperscript{12} although doses ranged widely, from 0.012 g to 0.12 g. In another meta-analysis, doses of 0.24 g sucrose given 2 minutes before painful stimuli were effective for term neonates,\textsuperscript{13} providing analgesia for 5–7 minutes. Repeated doses may be required if the procedure exceeds this duration. For painful procedures that involve breaking the skin, 24% sucrose can be placed directly on the infant’s tongue, using the following doses:

- 24–26 weeks gestation: 0.1 mL
- 27–31 weeks gestation: 0.25 mL
- 32–36 weeks gestation: 0.5 mL
- >37 weeks gestation: 1 mL

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Oral glucose or other sweet solutions also reduce acute pain in neonates during minor procedures; 30% glucose was effective in term neonates during heel sticks and venipunctures, and in preterm neonates during subcutaneous injections.\textsuperscript{14} Administration of a sweet solution with a pacifier was synergistic,\textsuperscript{15,16} providing stronger analgesic effects than either intervention alone. Only five of the 12 studies included in a Cochrane Review\textsuperscript{12} observed minor side effects. In the study most carefully designed to detect adverse events, only six infants (3%) experienced minor side effects, all of which resolved spontaneously without intervention.\textsuperscript{12}

Skin-to-Skin Contact (Kangaroo Care)

Gray et al. found that 10–15 minutes of kangaroo care between mothers and their term newborns reduced crying, grimacing, and heart rate during heel-stick procedures.\textsuperscript{17} Johnston et al. showed that kangaroo care significantly reduced the acute pain responses of preterm neonates at 32–36 weeks’ and 28–32 weeks’ gestation.\textsuperscript{18,19}

Breastfeeding Analgesia

Breastfeeding maintained throughout a procedure relieved heel-stick pain in term neonates more effectively than swaddling.\textsuperscript{20} In another study, Carbajal et al. found that breastfeeding effectively reduced venipuncture-associated pain in term neonates.\textsuperscript{21}

Sensorial Saturation

Concomitant use of various nonpharmacological techniques achieves greater clinical effectiveness than any one of these
Concomitant use of various nonpharmacological techniques achieves greater clinical effectiveness than any one of these techniques used alone

Local Anesthetics

Cutaneous infiltration of lidocaine or other local anesthetics treats pain from skin-breaking procedures and lasts for 30–90 minutes, although the efficacy and safety of this intervention have been studied only for circumcision and lumbar puncture. Local anesthetics, via the dorsal penile nerve block or ring block, provide the most effective analgesia for circumcision, but their efficacy for lumbar puncture remains unproven. Systemic toxicity can be easily prevented by avoiding intravascular injection.

Several topical anesthetics, including lidocaine-prilocaine cream,4% tetracaine gel, liposomal lidocaine, and lidocaine-tetracaine gel, are now available. Efficacy data suggest that lidocaine-prilocaine cream and tetracaine gel are ineffective for heel sticks, but decrease pain during venipunctures. Lidocaine-prilocaine cream decreases circumcision pain; tetracaine gel is safe but ineffective for venous catheterization in neonates. When applied to intact skin, lidocaine-prilocaine cream requires 60 minutes and tetracaine gel requires 30–45 minutes to produce local anesthesia. Both preparations are safe for single use in preterm and term neonates. The safety and efficacy of topical anesthetics reported in children need to be verified in neonates.

Opioid Analgesics

Morphine

Morphine is commonly used for moderate to severe acute pain, for preoperative sedation, and during anesthesia. Morphine and other opioids must be used cautiously for persistent or chronic pain because of concerns about tolerance, dependence, and other adaptations that reduce their efficacy and utility over time. Morphine is mainly metabolized by the enzyme UDP-glucuronosyl transferase 2B7 (UGT2B7) into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G antagonizes the antinociceptive effects of morphine and M6G, whereas M6G has greater analgesic potency than morphine, but also causes respiratory depression. Sulfation is a minor pathway in adults, although more important in neonates. The metabolites are cleared by the kidneys and partly by biliary excretion. Although morphine can be administered by different routes, its use in newborns is limited to the intravenous route.

Intravenous morphine with continuous infusions of 10–30 μg/kg/hour decreases pain in ventilated preterm neonates.

Plasma concentrations of 15–20 ng/mL are generally required for adequate analgesia, although clinical titration using small incremental doses (5–20 μg/kg) may be required because of wide variability in the pharmacokinetics and pharmacodynamics of morphine. Newborns, especially preterm neonates, are more sensitive to opioids and are at risk for respiratory depression, apnea, hypotension, and urinary retention. The hypotensive effects of morphine are more likely to occur in preterm neonates born at 23–26 weeks’ postmenstrual age (PMA), or in neonates with a prior history of hypotension, but can occur in all neonates when high dosages are used (100–200 μg/kg).

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Fentanyl

Fentanyl is a synthetic opioid that is 50–100 times more potent than morphine, with faster onset and shorter duration of action. It is mostly eliminated by the kidneys, although a significant fraction undergoes hepatic metabolism to norfentanyl. Plasma clearance in infancy may be significantly impaired by decreased hepatic blood flow. Intravenous doses should be injected slowly to avoid side effects such as apnea, bradycardia, or chest wall rigidity.

In ventilated preterm neonates, fentanyl infusions decrease pain responses, stress hormone levels, and episodes of hypoxia. Fentanyl also reduces postoperative pain in term neonates. Fentanyl and other synthetic opioids improve conditions for tracheal intubation and reduce the pain associated with central venous catheterization and other procedures.

Compared to morphine, fentanyl analgesia is associated with less severe sedative or hypotensive effects, reduced effects on gastrointestinal motility, and less urinary retention, but greater opioid tolerance and withdrawal. We do not routinely use fentanyl infusions in ventilated preterm neonates, but reserve its use for invasive procedures in a controlled setting, for postoperative pain (e.g., post-cardiac surgery), or for infants with pulmonary hypertension.

Remifentanil and Alfentanil

Remifentanil has a chemical structure similar to that of fentanyl and has twice its potency, but with an ultra-short duration of action (3–15 minutes). Metabolized by plasma esterases in tissue and erythrocytes, it is independent of liver and renal function. It is used for brief procedures such as central line placement or tracheal intubation. Alfentanil is more potent than morphine but less potent than fentanyl and has a short duration of action (20–30 min). These drugs have been used successfully for tracheal intubation and other brief invasive procedures.
procedures in neonates, but detailed safety and efficacy data are lacking.52

Nonopioid Analgesics

Acetaminophen

Acetaminophen (paracetamol) can be used to manage mild to moderate procedural or postoperative pain, but it is not effective by itself for circumcision53 or heel sticks.54 Data showing good efficacy are available for infants 3–6 months and older, while efficacy data in newborns have been generally negative, except for marginal effects during neonatal circumcision.53,55 Plasma clearance of acetaminophen is slower in preterm and term infants than in older children, so dosing is required less frequently.56,57 Recommended doses are 10–15 mg/kg orally or 20–25 mg/kg rectally, administered every 6–8 hours. Recommendations for intravenous acetaminophen, based on population pharmacokinetics in 158 infants at 27–45 weeks PMA, are a loading dose of 20 mg/kg, followed by 10 mg/kg every 6–8 hours.58 Maximum doses should not exceed 40 mg/kg/day for infants at 26–32 weeks PMA and 60 mg/kg/day for infants at 32–42 weeks PMA because of immature hepatic enzymes. Enteral and intravenous formulations of acetaminophen are associated with minimal adverse effects in infants, in contrast to older children or adults.58–60 Hepatic or renal toxicity58,59 or hypothermia occur rarely, if ever, following routine acetaminophen use in neonates.61

Nonsteroidal Anti-inflammatory Agents

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively in older children and adults, but infrequently in neonates because of their well-known adverse effects.62,63 The use of indomethacin or ibuprofen for patent ductus arteriosus (PDA) closure in preterm infants is associated with gastrointestinal bleeding, platelet dysfunction, and renal toxicity.62,63 NSAIDs are generally not used for neonatal analgesia because safer and more effective agents are available. NSAIDs taken during pregnancy may cause prenatal PDA closure, leading to severe pulmonary hypertension in the newborn.64

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Ketamine

Ketamine is a dissociative anesthetic that provides analgesia, amnesia, and sedation. Ketamine has been studied and used extensively in older children,65 but relatively few studies have been conducted in newborns. Ketamine transiently increases blood pressure and heart rate, decreases respiratory drive, induces bronchodilation,66 and does not alter cerebral blood flow.67 Because of these effects it is used for cardiac catheterization of neonates with certain types of congenital heart disease and persistent pulmonary hypertension.68 Effective analgesic doses for tracheal suctioning in ventilated neonates are 1–2 mg/kg.69 Ketamine decreased neuronal cell death following repetitive stimulation to induce inflammatory pain in immature rats, which would also make it attractive for preterm neonates, although this possibility has not been confirmed in human studies.70 In spite of these theoretical advantages, ketamine is a potent anesthetic that has received minimal study in neonates. As such, it should only be used for surgery or highly invasive procedures.

Summary and Conclusions

Over the past 25 years, significant advances have occurred in the recognition, reduction, and management of acute neonatal pain. Evidence-based management includes reducing the numbers of painful procedures, using sucrose, kangaroo care, sensorial saturation, or other nonpharmacological approaches, coupled with the judicious use of opioids (morphine or fentanyl) and nonopioid analgesics (acetaminophen, ketamine, or other agents). Clinicians must weigh the short-term and long-term consequences of acute neonatal pain against the adverse effects of using analgesia.

Clinicians must weigh the short-term and long-term consequences of acute neonatal pain against the adverse effects of using analgesia

References


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International Association for the Study of Pain • 111 Queen Anne Avenue North, Suite 501, Seattle, WA 98109-4955 USA
Tel: +1-206-283-0311 • Fax: +1-206-283-9403 • Email: iaspdesk@iasp-pain.org • www.iasp-pain.org
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