Analgesia and Local Anesthesia During Invasive Procedures in the Neonate

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ABSTRACT

Background: Preterm and full-term neonates admitted to the neonatal intensive care unit or elsewhere in the hospital are routinely subjected to invasive procedures that can cause acute pain. Despite published data on the complex behavioral, physiologic, and biochemical responses of these neonates and the detrimental short- and long-term clinical outcomes of exposure to repetitive pain, clinical use of pain-control measures in neonates undergoing invasive procedures remains sporadic and suboptimal. As part of the Newborn Drug Development Initiative, the US Food and Drug Administration and the National Institute of Child Health and Human Development invited a group of international experts to form the Neonatal Pain Control Group to review the therapeutic options for pain management associated with the most commonly performed invasive procedures in neonates and to identify research priorities in this area.

Objective: The goal of this article was to review and synthesize the published clinical evidence for the management of pain caused by invasive procedures in preterm and full-term neonates.

Methods: Clinical studies examining various therapies for procedural pain in neonates were identified by searches of MEDLINE (1980–2004), the Cochrane Controlled Trials Register (*The Cochrane Library*, Issue 1, 2004), the reference lists of review articles, and personal files. The search terms included specific drug names, *infant–newborn*, *infant–preterm*, and *pain*, using the explode function for each key word. The English-language literature was reviewed, and case reports and small case series were discarded.

Results: The most commonly performed invasive procedures in neonates included heel lancing, venipuncture, IV or arterial cannulation, chest tube placement, tracheal intubation or suctioning, lumbar puncture, circumcision, and SC or IM injection. Various drug classes were examined critically, including opioid analgesics, sedative/hypnotic drugs, nonsteroidal anti-inflammatory drugs and acetaminophen, injectable and topical local anesthetics, and sucrose. Research considerations related to each drug category were identified, potential obstacles to the systematic study of these drugs were discussed, and current gaps in knowledge were enumerated to define future research needs. Discussions relating to the optimal design for and ethical constraints on the study of neonatal pain will be published separately. Well-designed clinical trials investigating currently available and new therapies for acute pain in neonates will provide the scientific framework for effective pain management in neonates

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undergoing invasive procedures. (*Clin Ther.* 2005;27: 844–876)

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INTRODUCTION

Recent advances in neonatal intensive care have led to the increased survival of critically ill preterm and full-term neonates worldwide. Because these infants manifest extreme physiologic instability and various perinatal conditions, their medical care requires multiple invasive procedures, including tracheal intubation, capillary blood sampling, insertion of venous or arterial catheters, and oral, nasal, pharyngeal, tracheal, or gastric suctioning. Various studies have reported that invasive procedures are frequently performed without analgesia in the neonatal intensive care unit (NICU).[1–7] Benis et al[7] reported a mean of 6 procedures daily during the NICU stay of 15 neonates; Barker and Rutter[1] reported 61 procedures for each infant, as well as noting that 74% of all procedures were performed in preterm infants (<31 weeks' gestation); Porter and Anand[5] documented a mean of 53 procedures per patient; and Simons et al[6] found that neonates were exposed to a mean (SD) of 14 (4) procedures daily, with the highest frequency on the day of NICU admission. Many routine neonatal procedures are still performed without pharmacologic or nonpharmacologic analgesia,[2–4,6] despite specific recommendations from professional bodies for the management of procedural pain in neonates.[8–10]

The repeated pain occurring in the NICU is developmentally unexpected,[1–7,11,12] because it occurs at a time when the infant's natural milieu would still be the protective uterine environment.[13–15] Thus, painful stimulation elicits clear physiologic stress responses that have short- and long-term consequences. Perhaps secondary to their severity of illness, preterm infants are exposed to an increased frequency of procedures in the first week after birth compared with full-term infants.[1,5,6] The magnitude of change in the immediate response to painful procedures is reflected in an increase in heart rate (HR) of up to 40 beats/min and a decrease in O_2 saturation of up to 10%.[16] Multiple lines of evidence indicate the long-term effects of repeated procedural pain in the NICU.[13–15,17] Several studies have reported that repetitive procedural pain leads to a dampened behavioral response to pain,[18–21] which is an indicator of interrupted development or heightened peripheral sensitivity.[22–24] Mechanisms underlying the deleterious effects of repeated or prolonged inflammatory pain resulting from invasive procedures remain under active investigation in animal studies,[15,25–29] but the clinical implications of these mechanisms are poorly understood.

METHODS

As part of the Newborn Drug Development Initiative (NDDI), the US Food and Drug Administration (FDA) and the National Institute of Child Health and Human Development (NICHD) invited a group of international experts to form the Neonatal Pain Control Group to review the therapeutic options for pain management associated with the most commonly performed invasive procedures in neonates and to identify research priorities in this area. Based on the epidemiologic data reviewed, commonly performed procedures in neonates include heel lancing, venous or arterial cannulation, circumcision, tracheal intubation or suctioning, venipuncture, chest tube placement, lumbar puncture, and SC or IM injection (**Table I**).

Clinical studies examining various therapies for procedural pain in neonates were identified by searches of MEDLINE (1980–2004), the Cochrane Controlled Trials Register (*The Cochrane Library*, Issue 1, 2004), the reference lists of review articles, and personal files. The search terms included specific drug names, *infant–newborn*, *infant–preterm*, and *pain*, using the explode function for each key word. The English-language literature was reviewed; case reports and small case series (<5 patients) were discarded; and study findings were abstracted using a standard format. The findings were reviewed critically by at least 2 authors and compiled in summary or tabular form. Members of the Neonatal Pain Control Group discussed and evaluated these summaries to classify the studies based on the validity and reliability of their reported evidence. An independent reviewer (Bonnie Stevens, RN, PhD, University of Toronto, Toronto, Canada) was invited to assess the data synthesis and proposed recommendations at the NDDI Workshop in March 2004. Wider discussion of the data occurred at this workshop, which included participants from many academic institutions and disciplines, government agencies, and the pharmaceutical industry. These discussions were recorded and transcribed, and the final recommendations were shaped based on the views and new data presented at the workshop.

Table I. Commonly performed invasive procedures in neonates.

Invasiveness	Validated Procedures[6,11,12]	Other Procedures[8]
Mild	Insertion of gavage tube	Bladder catheterization
	Physical examination	Eye culture
	Umbilical arterial or venous catheter placement	Auditory evoked potential
	Nose culture	
	Tracheal suctioning	
Moderate	Arterial puncture	Central venous catheter removal
	Venous puncture	Thoracentesis
	Venous catheterization	Surfactant administration
	Heel lance	Suture removal
	Tracheal intubation	Tracheal extubation
	IM injection	Ventricular tap (percutaneous)
Severe	Arterial/venous cut-down	Bronchoscopy or endoscopy
	Arterial catheterization	Suprapubic bladder tap
	Circumcision	Central venous catheter placement
	Lumbar puncture	Chest tube placement
	Eye examination for retinopathy	Venous catheterization (>3 attempts)

COMMON PROCEDURES IN NEONATES

Heel Lance

Multiple epidemiologic studies have noted that the heel lance for capillary blood sampling is the most commonly performed invasive procedure in the NICU. For example, heel lances constituted 56% of 3283 procedures performed in 54 neonates in the study by Barker and Rutter[1] and 87% of 7672 invasive procedures performed in 144 neonates in the study by Porter and Anand.[5] Multiple incisions on the neonatal heel may lead to sensory hyperinnervation of this cutaneous area,[30] potentially causing impaired weight-bearing on the heel in ex-preterm children.[31]

Possible interventions to reduce pain include using a mechanical spring-loaded lance or venipuncture instead of manual heel lance, inserting a pacifier with or without 12% to 24% sucrose 2 minutes before the procedure, and employing other techniques such as flexed positioning and swaddling. Furthermore, primary prevention would be aided by careful evaluation of the necessity for heel lancing, particularly for routine blood monitoring (eg, levels of blood gases, glucose, bilirubin).

Venous Cannulation

Intravenous access is considered a priority in the management of critically ill neonates.[1-7,11,12] Although heel lance is the most commonly performed invasive procedure, the pain and stress associated with placement of peripheral IV catheters is likely to be grossly underestimated, as placement of each IV catheter may be associated with multiple attempts, repeated needle sticks, and prolonged holding, squeezing, and/or immobilization.[2,5,6,24] In addition, use of a tourniquet may result in noxious stimulation, and the tip of the transilluminator may cause skin burns. The sicker or more immature the neonate, the greater the difficulties in obtaining and maintaining IV access and the greater the tissue injury that occurs.[1] Potential analgesic treatments include the use a pacifier with or without 12% to 24% sucrose and application of topical anesthesia (eg, lidocaine 2.5%–prilocaine 2.5% cream*) to the site.[8,24]

Central Venous Catheterization

Central venous catheters are commonly used in neonates who require long-term venous access for delivery of total parenteral nutrition (TPN) and/or medications. Insertion of percutaneous central venous catheters (PCVC) or peripherally inserted central catheters (PICC) is standard practice in many NICUs.[32] The placement of central venous catheters can cause significant distress in neonates due to the combined effects of pain

*Trademark: EMLA® (eutectic mixture of local anesthetics) (AstraZeneca LP, Wilmington, Delaware).

from puncturing the skin and distress from prolonged handling and manipulation during the procedure. Recent surveys indicate that analgesics are being used increasingly during this procedure.[3,6,12,33] Various pharmacologic agents have been tried in the management of the pain of central venous catheter insertion, including opioids, topical anesthetics, benzodiazepines, and sucrose (Table II).[33,34]

Circumcision

Although circumcision is the most commonly performed surgical procedure in newborn infants (1.4 million infants annually[37]), it remains the most controversial one as well.[10,38,39] The putative benefits of newborn circumcision include prevention of cancer of the penis, balanoposthitis, phimosis, and poor hygiene leading to urinary tract infection and sexually transmitted diseases, including HIV.[37] These benefits seem to be balanced by the incidence of surgical complications and the availability of other methods for preventing these diseases.[10,40–42] While the practice of neonatal circumcision remains a matter of debate,[43] there is widespread consensus that effective pain relief should be provided for infants undergoing this procedure,[44–47] with increasing acceptance of analgesia among pediatricians,[10] family practitioners,[48] and obstetricians.[39] Potential analgesic interventions during circumcision include use of dorsal penile nerve block or ring block, topical anesthetics (eg, lidocaine–prilocaine cream, liposomal lidocaine 4% cream*), a less painful clamp (eg, Mogen clamp),

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Table II. Studies of analgesia for pain associated with insertion of a central venous catheter in neonates.

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Cordero et al[34]	RCT Broviac catheter N = 29	GA: mean, 27–28 wk BW: 600–1350 g PNA: 5–30 d Wt at time of study: 620–1320 g	Lidocaine 1% 5 mg/kg SC + fentanyl 2 μg/kg IV (F) OR lidocaine 1% 5 mg/kg SC + secobarbital 1 mg/kg IV (S)	↓ O_2 satn, FiO_2, and blood glucose, S vs F; no difference in HR, BP, epinephrine or norepinephrine levels	23 Infants ventilated; no. of successful attempts NR; blinding and AEs NR
Garcia et al[35]	DB RCT PCVC N = 13	GA: 25–33 wk BW: 740–1415 g PNA: 27–34 wk Wt at time of study: NR	Lidocaine–prilocaine cream 1–1.25 g × 1 h (L) OR zinc oxide placebo (P)	↓ Percent change in HR and RR, L vs P; no difference in BP, O_2 satn, or metHb after 4 h	All attempts successful; transient skin erythema/ blanching in all infants in L group
Moustogiannis et al[36]	Nonrandomized CT PCVC N = 19	GA: mean, 28.5–30 wk BW: mean, 1007–1054 g PNA: mean, 5–7.8 d Wt at time of study: mean, 1070–1365 g	Morphine 0.05 or 0.1 mg/kg IV (bolus?) (M) OR no treatment (NT)	↓ HR and skin blood flow, M vs NT; no difference in BP, RR, O_2 satn, or number of successful attempts	12 Infants ventilated, most in M group; AEs NR

RCT = randomized controlled trial; GA = gestational age; BW = birthweight; PNA = postnatal age; wt = body weight; satn = saturation; FiO_2 = fraction of inspired oxygen; HR = heart rate; BP = blood pressure; NR = not reported; AEs = adverse events; DB = double-blind; PCVC = percutaneous central venous catheter; RR = respiration rate; metHb = methemoglobin; CT = controlled trial.

a pacifier, 24% sucrose, and swaddling, preferably in combination.[46]

Tracheal Intubation

Tracheal intubation for mechanical ventilation or airway protection may not be preceded by analgesia/sedation in some neonates or infants. Awake intubation occurs more frequently in neonates than in older children,[4,49,50] despite the fact that an evidence-based consensus statement has recommended consideration of awake intubation only for delivery-room resuscitation or in other life-threatening situations.[8] In any age group, awake intubation is associated with severe pain and stress, with acute changes in vital signs (tachycardia/bradycardia, hypertension, oxygen desaturation, increased intracranial pressure), prolongation of the first attempt, need for multiple attempts, and potential supraglottic or tracheal damage.[51] In some clinical situations, however, clinicians may want to avoid the delays associated with obtaining IV access and preparing drugs, as well as to avoid the hemodynamic and respiratory effects of analgesia/sedation or loss of airway-protective reflexes, before performing an emergency intubation.

A recent survey from France found that analgesia and/or sedation was used before intubation in 37% of neonates, 67% of infants, and 92% of children, with minimal use among preterm neonates.[52] Multiple studies have reported that the use of premedication with thiopental,[53,54] alfentanil,[55] morphine,[56] or fentanyl[57] can reduce hemodynamic responses, intracranial pressure, or physiologic instability during intubation, as well as upper airway injury and the time required for intubation.[58–61] Despite this evidence, elective intubations are not routinely performed with analgesia/sedation in all neonates or infants.[49,50,52,62] There is a need for randomized controlled trials (RCTs) that investigate the optimal analgesia/sedation techniques for neonatal intubation using validated pain measures and assessing short- and long-term clinical outcomes.[63]

OPTIONS FOR DRUG THERAPY

Therapeutic options for procedural pain in neonates include the commonly used opioid analgesics, sedative drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, topical local anesthetics, and sucrose or other sweeteners. Because procedural pain occurs repeatedly, clinicians must consider the effects of repeated administration of these agents. Therefore, studies of the prevention and management of procedural pain in neonates should include assessments of efficacy and safety with repeated dosing of analgesic, anesthetic, or sedative drugs. In this regard, dose-ranging studies are needed to identify the minimum effective dose of the therapies described in the following sections so that cumulative or repetitive exposures can be minimized. In addition, there is a need for studies of specific combinations of pharmacologic agents and nonpharmacologic interventions to improve efficacy and minimize adverse effects.

Opioids

Although opioids are considered the mainstay of the treatment of moderate to severe pain, they may not be appropriate for the acute pain associated with a single brief procedure. If neonates are to be subjected to repeated invasive procedures (eg, blood sampling, venous cannulation, repeated suctioning with ongoing tracheal intubation), use of low-dose continuous opioids, or intermittent boluses for specific procedures may be considered. Fentanyl, morphine, alfentanil, and methadone appear to be the most commonly used opioids in neonates.[2,3,64] Therefore, opioid analgesic preparations that require further study in neonates are listed in order of priority in **Table III.** Some of the high-priority opioids are discussed in more detail in the following sections, whereas others are not indicated for procedural pain or there is little or no information regarding their use in neonates.

Fentanyl

A synthetic opioid with activity on μ_1- and δ-opioid receptors, fentanyl is frequently used in neonates because of its ability to provide rapid analgesia,[65] maintain hemodynamic stability, block endocrine stress responses,[66,67] and prevent pain-induced increases in pulmonary vascular resistance.[68] Studies in adults suggest that fentanyl is 80 to 100 times more potent than morphine, but most pediatric studies have estimated a potency ratio of 13 to 20.[69] Fentanyl is highly lipophilic, crosses the blood–brain barrier rapidly, accumulates in fatty tissues, and causes less histamine release compared with morphine. Tolerance develops more rapidly with fentanyl than with morphine,[70] requiring dose escalation during prolonged administration.[71,72] Analgesia for procedural pain is provided by administering fentanyl 0.5 to 2 μg/kg IV every 2 to 5 minutes until

Table III. Opioids to be studied further in neonates, by priority.

High Priority	Intermediate Priority	Low Priority
Fentanyl (IV)	Buprenorphine (IV/IM)	Tramadol
Morphine (IV/IM/PO)	Nalbuphine (IV/IM)	Hydrocodone/acetaminophen (PO)
Alfentanil (IV)	Butorphanol (IV/IM)	Oxycodone/acetaminophen (PO)
Methadone (IV/PO)	Meperidine (IV/IM/PO)	Tramadol/acetaminophen (PO)
Remifentanil (IV)		Levorphanol (IV/PO)
Codeine/acetaminophen (PO)		Oxymorphone (IV)
Oxycodone (PO)		
Hydromorphone (IV/IM)		
Fentanyl patch (transcutaneous)		

the desired clinical effect is obtained.[34,57,68,73] The chest-wall rigidity that may follow rapid IV administration of doses >1 μg/kg can be managed by administering a neuromuscular relaxant and/or naloxone.[66–69,73]

The literature search found no published RCTs examining the use of fentanyl for procedural pain in neonates, although 1 blinded RCT investigated the responses of 22 ventilated preterm neonates (<32 weeks' gestation) to a single dose of fentanyl.[73] Behavioral measures (Neonatal Facial Coding System [NFCS] and Modified Postoperative Comfort Score), vital signs, blood gases, and hormonal–metabolic stress responses were assessed before and at 30 and 60 minutes after the fentanyl dose. Fentanyl reduced changes in HR ($P = 0.01$) and increased growth hormone levels ($P = 0.036$), corresponding to significantly reduced pain behaviors after analgesia ($P < 0.05$).

Fentanyl Patch

When IV access is limited, transdermal administration of fentanyl may provide an alternative approach to pain management. Fentanyl transdermal systems (TDS), which are available with absorption rates of 25, 50, and 100 μg/h, maintain constant serum levels after 12 to 24 hours of application, eliminating the peaks and troughs associated with IV dosing. These TDS have limited utility in neonates because of the relatively high fentanyl doses delivered (a system delivering 12.5 μg/h is under investigation) and the high permeability of the skin in preterm neonates due to the thin epidermis.[74,75] Other concerns with fentanyl TDS include a slow increase in plasma concentrations to therapeutic levels (8–10 h), alterations in the rate of absorption related to changes in skin perfusion, and a gradual "tail off" after removal of the TDS due to residual absorption from the subcutaneous adipose tissue at the site of application. These considerations preclude use of fentanyl TDS for procedural pain in neonates, although there may be a limited role in the management of chronically ventilated preterm neonates, particularly if they are opioid tolerant.

Morphine

Morphine produces analgesia through activity on μ_1- and μ_2-opioid receptors, thus reducing behavioral and hormonal responses,[76,77] improving ventilator synchrony,[78] alleviating postoperative pain,[76,79–81] and sedating ventilated preterm neonates[82,83]; however, its effect on the acute pain caused by invasive procedures remains unclear. Initial studies using laser Doppler flowmetry found that capillary blood flow to the skin increased by 27% to 134% during invasive procedures such as heel lances, physical handling, tracheal suctioning, or chest physiotherapy, and that skin blood flow decreased significantly at 20 minutes after administration of IV morphine (*P* value not reported).[84] In infants undergoing PCVC placement, skin blood flow increased significantly in infants who did not receive analgesia (97%; *P* value not reported), whereas it remained unchanged in neonates given IV morphine before the procedure.[36] In a study in 48 neonates receiving continuous morphine infusions during heel sticks,[85] the pain response (measured using the NFCS) was reduced during morphine administration compared with before and after morphine infusion ($P < 0.01$). Similarly, in a pilot RCT,[86] pain responses (measured using the Premature Infant Pain Profile [PIPP]) elicited by endotracheal tube suctioning were significantly reduced in ventilated preterm neonates receiving infusions of morphine ($P < 0.001$) or mid-

azolam (P = 0.002) compared with those receiving placebo.

More recent evidence, however, seems to refute the effectiveness of morphine for acute pain in neonates. A descriptive study in full-term neonates showed no significant differences in plasma norepinephrine levels, vagal tone index, or flexor withdrawal reflexes before and at 20 and 60 minutes after administration of the first postoperative dose of morphine 0.1 mg/kg.[87] More recently, a blinded RCT comparing the effects of morphine and placebo infusions in ventilated preterm neonates showed no analgesic effects of morphine, based on similar pain scores after endotracheal tube suctioning in both groups (PIPP, Neonatal Infant Pain Scale, and global pain assessment by the bedside nurse using a visual analog scale).[88] In the Neurologic Outcomes and Pre-emptive Analgesia in Neonates (NEOPAIN) trial,[89] heel lances were performed in ventilated preterm neonates before the loading dose and at 2 to 3 hours and 20 to 28 hours after receipt of morphine or placebo. There were no differences in pain responses before or after therapy with morphine or placebo, as measured on the DAN (Douleur Aiguë du Nouveau-né) behavioral pain scale or the PIPP, and there was no correlation between plasma morphine levels and pain scores. These accumulating data raise questions about the effectiveness of morphine analgesia for acute procedural pain in the neonate, possibly related to the uncoupling of opioid receptors in the forebrain.[90]

Alfentanil

Alfentanil's short duration of action supports a role in procedural analgesia in neonates, and numerous studies have examined its pharmacokinetics,[91–94] protein binding,[95] adverse effects,[96,97] and physiologic effects[98,99] in preterm and full-term neonates. Two RCTs have examined the efficacy of alfentanil for procedural pain in neonates.[98,100] Physiologic and hormonal (β-endorphin and cortisol) responses to nasotracheal intubation were studied in 20 neonates (age range, 0.1–23 d) randomized to receive meperidine 1 mg/kg or alfentanil 20 μg/kg before intubation.[98] Oxygen desaturation occurred in all 10 infants in the meperidine group and 7 of 10 infants in the alfentanil group, with a significantly longer duration in the meperidine group. Hormonal responses and other physiologic responses were not significantly different between groups. In a crossover RCT,[100] 10 preterm neonates (age range, 29–36 wk) received IV infusions of alfentanil 10 or 20 μ/kg or placebo in random order 2 minutes before tracheal suctioning. Alfentanil was found to prevent HR responses, normalize pain scores, and decrease plasma epinephrine values. The higher alfentanil dose was associated with an increased incidence of chest-wall rigidity but had no additional clinical effects. Despite these promising reports, alfentanil has not been tested in a large RCT with sufficient power to determine efficacy and safety for procedural pain in preterm or full-term neonates. Also, there are currently no published studies comparing alfentanil with other opioids (eg, fentanyl) or other analgesics.

Methadone

The analgesic efficacy of methadone can be explained by its μ-opioid–agonist activity (L-methadone only) and its noncompetitive blockade of L-methyl-D-aspartate (NMDA) receptors (both enantiomers, D- and L-methadone).[101,102] Methadone causes desensitization of δ-opioid receptors by uncoupling the receptor from its G-protein,[103,104] thus reducing the development of morphine tolerance.[104,105] A scientific rationale for the use of methadone analgesia in neonates may include its specific μ-opioid effects, desensitization of δ-opioid receptors, NMDA-receptor blockade, prolonged duration of action, and oral bioavailability.[106]

When oral methadone was used for the treatment of severe pain in 70 hospitalized children,[107] it was reported to provide potent analgesia, a rapid onset of action, prolonged clinical effects, high enteral bioavailability, and minimal adverse effects at a low cost. Methadone is often used in patients with opioid tolerance and withdrawal because of its safety and prolonged duration of action,[108–110] although there are limited data on its safety, efficacy, or pharmacokinetics in neonates. In a pharmacokinetic study in children (age range, 1–18 years), reported only in abstract form, methadone had a prolonged but variable half-life (mean [SD], 19.2 [13.6] h; range, 3.8–62.0 h).[111] In another study,[112] methadone provided prolonged postoperative analgesia in children aged 3 to 7 years and produced no major adverse effects compared with morphine. Although an RCT found that methadone produced greater ventilatory depression than morphine or pethidine, the risk of clinically significant hypoventilation was small, and the incidence of other adverse effects (ie, nausea, vomiting, and urinary retention) was similar in all 3 treatment groups.[113] However, the results of studies on the pharmacokinet-

ics, analgesic potency, and adverse effects of methadone in older children cannot be extrapolated to neonates.

The half-life of methadone in neonates (34–43 weeks' gestation) born to methadone-dependent mothers was ranged from 16 to 25 hours. Neonates with plasma methadone levels >0.06 μg/mL showed no signs of opioid withdrawal.[114] In the study by Mack et al,[115] the mean (SD) elimination half-life of methadone was 41 (22) hours, indicating slower plasma clearance of methadone in these infants. Both studies, however, were complicated by unreported maternal ingestion of methadone, exposure to other drugs of abuse, and variable intervals between the last dose of methadone and delivery.

Research Considerations

The clinical role of opioids for the pain of manipulation and tissue injury during invasive procedures may be limited in neonates because of their prolonged duration of action and concerns about their analgesic effectiveness for acute pain in these patients. The ideal opioid drug would have a rapid onset of action, short duration of action, proven efficacy against acute pain, and minimal adverse effects (eg, hypotension, respiratory depression, chest-wall rigidity). Long-acting drugs such as morphine and methadone may not be appropriate, whereas short-acting drugs such as fentanyl, alfentanil, and remifentanil deserve further investigation in procedural pain. With the exception of fentanyl, very little is known about the pharmacology of these drugs at different gestational ages or among neonates with different diagnoses and various degrees of critical illness. In addition, studies of repeated administration are needed to evaluate safety and efficacy over short periods (eg, 24 hours) as well as cumulative exposure over the entire NICU stay.

Many invasive procedures may not cause sufficiently severe pain (eg, heel sticks, peripheral venous cannulation) to warrant use of powerful opioid agents, particularly if repeated dosing is required and the infant is not ventilated. There may be >10-fold differences between individuals in the doses required to produce opioid analgesia. In neonates, individual differences in drug responsiveness are accentuated because currently available methods for the assessment of pain intensity involve behavioral observation and combinations of indicators that may not be highly correlated with each other.[116] Genetic differences caused by single nucleotide polymorphisms (SNPs) may explain some interindividual differences in the analgesic requirement among critically ill children.[117,118]

In the μ-opioid–receptor (MOR) gene in humans, a nucleotide substitution at position 118 (A118G) predicts an amino acid change at codon 40, from asparagine to aspartate (*asp*), with 3-fold increases in β-endorphin binding affinity[119] and reduced potency of morphine-6-glucuronide.[120,121] Another abundant SNP of the cathechol O-methyltransferase (COMT) gene encodes the substitution of valine (*val*) by methionine (*met*) at codon 158, reducing COMT enzyme activity by 3- to 4-fold, with diminished activation of the endogenous μ-opioid system in response to pain ($met^{158}met < val^{158}met < val^{158}val$) and higher sensory/affective pain ratings.[122] Pilot data suggest that both these SNPs may reduce the need for postoperative morphine analgesia in infants, but only the COMT mutation was found to be statistically significant ($P = 0.034$), because only 6 patients were homozygous for the $asp^{40}asp$ MOR in this sample.[123] Further research on opioid analgesia in neonates should include assessment of these and other genetic variations.

Sedative–Hypnotics

Midazolam

Midazolam, like other benzodiazepines, activates the γ-aminobutyric acid subtype A ($GABA_A$)/benzodiazepine–receptor complex to inhibit neuronal activity, producing sedation, hypnosis, anxiolysis, muscle relaxation, and antiepileptic effects.[124–127] Despite numerous articles on the pharmacokinetics of midazolam in neonates,[128–135] use of continuous midazolam infusions for sedation in ventilated neonates,[86,131,136–141] and use of continuous midazolam infusions for invasive procedures or seizures in older children,[125,126,142–152] there have been few studies of the use of midazolam for procedural sedation in preterm or full-term neonates. Apart from a case series on the use of nasal ketamine and midazolam for cryotherapy in neonates with retinopathy of prematurity[153] and a placebo-controlled RCT of midazolam sedation for tracheal intubation in preterm neonates,[154] other studies have included small numbers of neonates among children undergoing cardiac catheterization,[142] oncologic diagnostic procedures,[144] urodynamic studies,[148] and esophageal manometry.[151]

Attardi et al[154] performed a double-blind, placebo-controlled RCT comparing atropine and placebo (n = 6), atropine and midazolam (n = 7), and placebo (n = 3)

in preterm neonates undergoing tracheal intubation. The study had to be terminated early because of an increased incidence of oxygen desaturation at intubation (86%) and a need for cardiopulmonary resuscitation (29%) in neonates receiving midazolam compared with the other groups. Although the study was underpowered because of early termination, its results indicate a need for caution in the use of midazolam as routine premedication for tracheal intubation in premature infants. Hypotension has also been reported with the use of midazolam in other studies in preterm neonates.[133,137,139,155] Combining midazolam with opioids is a common practice in many NICUs, despite limited data to support this practice and an increased incidence of adverse effects.[155,156]

Lorazepam

Lorazepam is a long-acting benzodiazepine that has been used to provide long-term sedation in patients requiring mechanical ventilation.[157] Like midazolam, it can be used for the treatment of seizures, but it does not exhibit any analgesic effects in patients undergoing invasive procedures. Not infrequently, lorazepam is used for sedation in preterm and full-term neonates requiring mechanical ventilation,[64,127] but its use for sedation during invasive procedures has not been reported.

Thiopental

A short-acting oxybarbiturate, thiopental is frequently used for anesthetic induction in neonates and older children. It has been reported to have efficacy in suppressing phenobarbital-resistant seizures in neonates.[158] A significantly greater proportion of thiopental has been found to remain unbound in neonatal serum compared with adult serum at all levels of pH studied (pH 7.2, 7.4, and 7.6) ($P < 0.005$).[159] One placebo-controlled, unblinded RCT in full-term neonates undergoing nasotracheal intubation found that HR increased to a greater degree ($P < 0.03$) and blood pressure increased to a lesser degree ($P < 0.002$) in neonates receiving thiopental 6 mg/kg compared with those receiving placebo, whereas blood pressure was significantly lower in the thiopental group after intubation ($P < 0.001$).[54] The time required for intubation was reduced in the thiopental group ($P < 0.04$), but there were no significant between-group differences in oxygen saturation during or after intubation. Clinical concerns about myocardial depression and hemodynamic changes associated with thiopental may be accentuated when this agent is used in preterm neonates, although no RCTs have been reported.

Ketamine

Ketamine is a unique anesthetic agent in that it produces sedation, analgesia, and amnesia. It has mild effects on respiratory drive, increases blood pressure, produces bronchodilatation, and can be used via the IV, IM, or enteral route.[160] There are relatively few reports on the use of ketamine in newborn infants, despite studies reporting its use in pediatric patients undergoing cardiac catheterization[142,161,162]; interventional radiology procedures[163]; or invasive procedures in the pediatric intensive care unit,[164,165] emergency department,[166] or oncology ward[144]; and for postoperative analgesia,[167] with or without combination with midazolam.

Forty-four preterm neonates requiring tracheal intubation for anesthetic induction were randomized to receive isoflurane 0.75%, halothane 0.5%, fentanyl 20 μg/kg, or ketamine 2 mg/kg.[168,169] Anterior fontanel pressure decreased 9% to 11% during receipt of each of these anesthetics (statistically significant but clinically mild changes), whereas the incidence of clinically significant decreases in arterial blood pressure was significantly reduced in neonates receiving ketamine (*P* values not reported). A crossover RCT of increasing doses of ketamine 0.5, 1, and 2 mg/kg or placebo in preterm neonates before tracheal suction found that plasma ketamine concentrations increased linearly with the dose (mean [SD], 103 [49], 189 [75], and 379 [97] ng/mL after 0.5, 1, and 2 mg/kg, respectively), HR decreased after the 2-mg/kg dose, and the increase in pain score in response to tracheal suction was attenuated by the 1-mg/kg dose but not by the 0.5- or 2-mg/kg doses.[170] A case series involving 10 preterm neonates (body weight range, 670–1885 g; gestational age range, 26–33 wk) receiving a single dose of ketamine 5 mg/kg before venous cannulation showed no changes in HR, cardiac output, transcutaneous pressures of oxygen ($TcPO_2$) or carbon dioxide ($TcPCO_2$), end-diastolic velocity, peak systolic velocity, mean arterial velocity, or Pourcelot's resistance index (measured in the anterior cerebral artery by pulsed-wave Doppler ultrasound before and after ketamine injection).[171] Although ketamine is frequently used for anesthesia during surgical procedures in neonates, further studies are needed to examine its physiologic and behavioral effects when used to treat procedural pain in preterm and full-term neonates.

Propofol

Propofol is a popular agent for anesthetic induction in neonates and infants,[172,173] and has been used in critically ill children undergoing invasive[164,174] or radiologic procedures.[175,176] Despite available data on the pharmacokinetics, physiologic effects, and adverse effects of propofol,[175,177–180] no studies have assessed its efficacy and safety for procedure-related analgesia/sedation in neonates. Adverse effects, which may be accentuated in neonates, are a major concern, including systemic hypotension, respiratory depression, upper airway obstruction, and bradycardia. Close monitoring and specialized expertise are necessary if propofol is to be used for procedural sedation in neonates. As noted in older pediatric patients, repeated or prolonged use of propofol may lead to metabolic acidosis, myocardial failure, hepatic dysfunction, and death as a result of mechanisms that are currently unknown.[177]

Chloral Hydrate

Chloral hydrate is an orally administered sedative–hypnotic that has limited usefulness for invasive procedures because of its delayed onset of action, prolonged elimination, lack of analgesic effects, multiple adverse effects, and risk of accumulation with repeated dosing.[127,181,182] For noninvasive procedures, a single dose of chloral hydrate 20 to 100 mg/kg PO/PR produces short-term sedation with minimal respiratory depression,[160] and one RCT in older children found that a chloral hydrate–promethazine combination was more efficacious for sedation than a midazolam infusion.[147] Further studies in preterm and full-term neonates are warranted, given the relatively frequent use of chloral hydrate for sedation in the NICU.[64]

Research Considerations

The role of sedative–hypnotics for invasive procedures in neonates may include adjuvant use in invasive procedures associated with tissue injury and primary use in procedures not associated with tissue injury. Drugs with potent analgesic effects such as ketamine, however, may play a primary role in both types of procedures. Future investigations should examine the role of these drugs as primary agents and in combination with opioids or other agents. The pharmacology of these drugs in preterm neonates remains unclear, as does the effect of differences in gestational age and severity of illness. The potential neurotoxic effects of sedatives, general anesthetics, and antiepileptic drugs in preterm neonates and older infants need to be investigated in models that closely approximate the doses and duration of exposure in the neonate undergoing surgery.[183] Genetic and developmental differences that center on the $GABA_A$/benzodiazepine receptor may explain some of the variability in drug effects noted with these drugs. The effects of these agents in infants who are neurologically compromised and other considerations in the use of systemic opioids should also be studied.

NSAIDs and Acetaminophen

NSAIDs have antipyretic and analgesic properties. They inhibit the enzyme cyclooxygenase (COX), and the COX-1 and COX-2 isoforms are responsible for the conversion of arachidonic acid to prostaglandins. Prostaglandins are mediators of pain signaling that are expressed peripherally or centrally in a variety of painful conditions; thus, their inhibition leads to a reduction in pain. Structural differences between NSAIDs confer differing capabilities to inhibit COX-1 and COX-2. NSAID-induced adverse effects are primarily the result of inhibition of the physiologic functions mediated by COX-1, including protection of the gastric mucosa, platelet aggregation, and glomerular filtration. Acetaminophen, unlike other NSAIDs, acts primarily on central nervous system COX enzymes and therefore lacks the adverse-effect profile of other NSAIDs.[184] The efficacy of acetaminophen and other NSAIDs for neonatal pain has not been well investigated, although these drugs may have a limited role in the treatment of acute pain caused by invasive procedures.

Acetaminophen/Propacetamol

Three double-blind RCTs evaluating the efficacy of acetaminophen in neonates demonstrated no benefits in the treatment of procedural pain. Acetaminophen given for circumcision[185] or heel lance[186] pain had no significant effects on behavioral measures of pain or vital signs, although it appeared to reduce pain-related clinical symptoms after delivery by vacuum extraction or circumcision in full-term neonates (Table IV).[187] The pharmacokinetics of acetaminophen after oral or rectal administration in preterm and full-term neonates has been described by several investigators[188–194] and reviewed recently.[184] In general, bioavailability is lower by the rectal route than the oral route, requiring administration of higher doses (30–45 mg/kg) than have been prescribed previously (10–15 mg/kg).[195,196]

Table IV. Studies comparing acetaminophen (A) with placebo (P) for procedural pain in neonates.

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Howard et al[185]	DB RCT Circumcision N = 44	GA: 37–42 wk BW: NR PNA: >24 h Wt at time of study: NR	A 20 mg/kg PO 2 h before circumcision, then q6h x 4 doses OR P	↓ Attia Postoperative Comfort Score 6 h after circumcision, A vs P; no difference in HR, RR, duration of crying during circumcision, or deterioration in feeding behavior after circumcision	Infants studied in newborn nursery rather than NICU; AEs NR
Shah et al[186]	DB RCT Heel lance for newborn screening N = 75	GA: mean, 39.5 wk BW: mean, 3.5 kg PNA: mean, 35 h Wt at time of study: NR	A 20 mg/kg PO OR P	No difference in facial action or crying time	Infants studied in newborn nursery rather than NICU; 11 infants vomited dose
Van Lingen et al[187]	DB RCT Vacuum extraction delivery N = 112	GA: mean, 40 wk BW: mean, 3.6 kg PNA: 1st d of life Wt at time of study: NR	A 20 mg/kg PR after delivery, then at 6, 12, and 18 h OR P	↓ Clinical symptoms* after 1st dose, A vs P; no difference in pain,† clinical symptoms	Infants studied in newborn nursery rather than NICU; no mention of AEs

DB = double-blind; RCT = randomized controlled trial; GA = gestational age; BW = birthweight; NR = not reported; PNA = postnatal age; wt = body weight; HR = heart rate; RR = respiration rate; NICU = neonatal intensive care unit; AEs = adverse events.
*Irritability, crying, pain on handling, vomiting, grunting, poor feeding, and/or abdominal distension.
†Assessed at 1, 7, 13, and 19 hours using 5-point faces scale (range, 0–4) for increasing pain.

IV administration of the prodrug, propacetamol, is preferable in many neonates, improving the probability of achieving adequate and timely therapeutic concentrations[197,198]; however, this preparation is not currently available in the United States. The dose–response relationship requires further study to optimize use of acetaminophen in this population.[199,200]

Ketorolac Tromethamine

IV ketorolac tromethamine has shown efficacy and tolerability in a variety of conditions in infants and children.[201–204] Few neonates were included in these studies, and no studies have investigated the analgesic effects of ketorolac for procedural pain. One retrospective study reported a decrease in the postoperative opioid requirement with the use of ketorolac after abdominal surgery in infants aged <6 months.[203] Increased postoperative bleeding has not been a problem, except after tonsillectomy.[205] No pharmacokinetic studies of ketorolac in preterm and full-term neonates have been reported.

Ibuprofen

Multiple studies have examined the use of orally or rectally administered ibuprofen for antipyresis in infants and children.[196,206,207] An IV preparation, ibuprofen lysine, has been effective for closure of patent ductus arteriosus[208–210] and has not been associated with any significant neurologic, intestinal, renal, hepatic, or hematologic complications, or changes in cerebral perfusion or cerebral oxygenation (compared with indomethacin).[209,211] Protein binding was slight-

ly lower in preterm neonates compared with older children and adults, and ibuprofen pharmacokinetics showed large interindividual variability, with a prolonged half-life in preterm neonates, although drug elimination was not affected by gestational age and birthweight.[208] At clinically appropriate concentrations, ibuprofen caused 4-fold increases in free bilirubin, which may increase the risk for kernicterus in preterm infants.[212] No information is available on the analgesic efficacy of ibuprofen in the setting of procedural pain in preterm or full-term neonates.

Research Considerations

Apart from the studies reviewed here, there is limited information on the use of NSAIDs in neonates.[213,214] Drugs such as sulindac or mefenamic acid have been used for closure of patent ductus arteriosus in preterm neonates,[215,216] but information on analgesic efficacy and safety is not available. NSAIDs may be associated with potentially serious adverse effects in various organ systems (eg, kidney, gastrointestinal tract) due to prostaglandin inhibition, as well as with drug interactions (eg, increased plasma concentrations of aminoglycosides or digoxin). Therefore, without proof of efficacy, their routine use for neonatal analgesia cannot be recommended until further studies regarding dose–response characteristics and risk–benefit ratios have been performed.[184,213,217] Acetaminophen and other NSAIDs have opioid-sparing properties when used for postoperative pain in children,[213] and it is likely that they may have similar benefits in neonates. Areas for further research include the effect of acetaminophen and other NSAIDs on the inflammation that may be associated with procedural pain (eg, repeated heel lances, circumcision, chest tube insertion), the comparable efficacy of acetaminophen and other NSAIDs, and the combined effects of acetaminophen and other NSAIDs (as has been studied in fever-management trials in children[214]).

Local Anesthetics

Injectable Lidocaine

Lidocaine is a member of the aminoacyl amide class of local anesthetics and exerts its pharmacologic effects by reversibly inhibiting the transmission of nerve signals. Infiltration of lidocaine is an effective analgesic for cutaneous procedures, with a relatively quick onset of action (~1–2 minutes) and prolonged duration of action (30–90 minutes). Lidocaine infiltration does not entail any special monitoring requirements, although it does cause intense burning pain when injected subcutaneously. This was thought to result from the acidic pH of lidocaine solutions; although buffering in a ratio of 9 parts lidocaine (1%) to 1 part sodium bicarbonate (1 mEq/mL) does not diminish the injection pain when used for circumcision in neonates or laceration repair in older children.[44,218,219]

Studies of the efficacy and safety of SC lidocaine injection for procedures in neonates have been limited to circumcision and lumbar puncture (Table V). Infiltration of local anesthetic drugs is the most effective single method of analgesia for circumcision.[223,224] The usual method of administration is the dorsal penile nerve block, which involves administering 2 injections of lidocaine 1% (0.2–0.4 mL each) subcutaneously at the base of the penis. Other less commonly used methods include injection of lidocaine into the foreskin or subpubic space. Pain is not prevented in all infants receiving local anesthesia, partly due to technical failures.

There has been much concern about the potential for serious adverse effects from the systemic lidocaine toxicity that may occur after inadvertent intravascular injection of the drug. However, systemic toxicity is easily prevented by applying negative pressure to check for the absence of blood during injection. To date, systemic lidocaine toxicity has not been reported after injection of lidocaine during circumcision. Injection-related adverse effects include bruising and/or hematoma.[223] When used for lumbar puncture, lidocaine has not been demonstrated to interfere with the ease of the procedure, but neither has it been consistently demonstrated to decrease pain. Perhaps the complexity of the procedure, coupled with the severity of illness and insensitive pain markers, explains the lack of observed effects in this procedure.

Topical Local Anesthetics

The availability of topical local anesthetics that can penetrate intact skin and produce reliable and safe anesthesia has advanced the prevention of procedural pain in children. The first product to be marketed was lidocaine–prilocaine cream, an oil-in-water emulsion. Since its introduction in the 1980s, many other topical local anesthetic agents have become commercially available, including tetracaine 4% gel,* liposo-

*Trademark: Ametop® (Smith & Nephew plc, London, United Kingdom).

Table V. Studies comparing lidocaine 1% (L) injection with no treatment (NT) for lumbar puncture (LP) pain in neonates.

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Carraccio et al[220]	RCT Emergency department N = 100	Age range, 0.3–35 mo	L injected SC (dose NR) OR NT	No difference in no. of attempts or no. of traumatic LP*	AEs NR
Pinheiro et al[221]	RCT N = 116	GA: NR BW: mean, 1.8 kg PNA: mean, 10.8–17.2 d Wt at time of study: 563–4100 g	L 0.1–0.4 mL SC (L) OR NT	↓ Struggling scores,† L vs NT during LP; no difference in no. of attempts,‡ failure rate, or no. of traumatic LP*	27 Infants on IMV/CPAP ventilation; 1 infant in L group had apnea; 6 infants in NT group had bradycardia/O_2 desaturation
Porter et al[222]	RCT N = 81	GA: mean, 31.5–32.4 wk BW: mean, 1814–2047 g PNA: mean, 7.2–7.8 d Wt at time of study: mean, 1920–2041 g	L 0.1 mL/kg SC OR NT	↑ Procedure duration, L vs NT; no difference in HR, RR, transcutaneous O_2 and CO_2 tension, or no. of attempts‡	47 Infants ventilated; no AEs attributable to L

RCT = randomized controlled trial; NR = not reported; AEs = adverse events; CT = clinical trial; GA = gestational age; BW = birth weight; PNA = postnatal age; wt = body weight; IMV = intermittent mandatory ventilation; CPAP = continuous positive airway pressure; HR = heart rate; RR = respiration rate.

*Defined as a red blood cell count >10,000 x 10^6/L. (If this definition were to be applied to Carracio et al, there would be an increase in the number of traumatic attempts, L vs NT.)

†Scale: 0 = no struggling, 1 = mild struggling, 2 = moderate struggling, 3 = severe struggling.

‡A meta-analysis of the mean number of attempts with L and NT in these studies is pending.

mal lidocaine cream, and lidocaine 70 mg–tetracaine 70 mg gel.*

Lidocaine–prilocaine cream (**Table VI**) and tetracaine gel (**Table VII**) have been relatively well investigated in neonates, children, and adults. A systematic review concluded that these 2 preparations have similar efficacy in children.[244] Both were evaluated for decreasing the pain of heel sticks and venipuncture in neonates, and neither preparation was effective for heel-stick pain. It has been postulated that the higher skin blood perfusion in the heel compared with other dermal regions leads to rapid clearance of drug from that site.[245] In addition, heel lancing is a more invasive procedure that involves extensive manipulation and tissue damage, whereas topical agents merely inhibit pain receptors located in the dermis. Efficacy data suggest that both topical anesthetics may decrease pain during venipuncture,[8,226–229] although there are insufficient data on their efficacy in other procedures. Lidocaine–prilocaine cream has been repeatedly shown to decrease the pain of circumcision, as assessed by multiple measures of pain, including behavioral and physiologic measures.[8,10,46–48,223,224,234–237] A recent study by Ballantyne et al[243] found tetracaine gel safe but ineffective for PICC line insertion in neonates.

*Trademark: S-Caine® (Zars, Inc., Salt Lake City, Utah).

Table VI. Studies of lidocaine–prilocaine 5% cream (L-P) for procedural pain in neonates.

Venipuncture pain (L-P vs placebo [P])

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Acharya et al[225]	DB CO RCT N = 19	GA: 26–33 wk BW: 0.916–2.246 kg PNA: 3–65 d Wt at time of study: NR	L-P 0.5 mL × 60 min OR P 0.5 mL × 60 min to dorsum of hand or foot	No difference in HR, BP, O_2 satn, facial action, cry duration, or ease of venipuncture; no difference in metHb at 1 h, but ↑ metHb at 8 h, L-P vs P	No supplemental oxygen; pallor in several infants in both groups (no./group NR)
Larsson et al[226]	DB RCT N = 120	GA: 37–43 wk BW: 2.33–4.94 kg PNA: 3–8 d Wt at time of study: NR	L-P 0.5 mL × 60 min OR P 0.5 mL × 60 min to dorsum of hand	↓ Facial action, L-P vs P; ↑ time to collect sample, L-P vs P; no difference in cry duration or no. of attempts to obtain sample	PKU test in FT infants AEs NR
Lindh et al[227]	DB RCT N = 60	GA: 37–42 wk BW: mean, 3.7 kg PNA: 72–120 h Wt at time of study: NR	L-P 1 g × 60 min OR P 1 g × 60 min to dorsum of hand	↓ HR, ↑ HR variability and low-frequency power, L-P vs P; no difference in incidence of cry and high-frequency power	PKU test in FT infants AEs NR
Abad et al[228]	DB RCT Venipuncture at antecubital fossa N = 51	GA: 37–42 wk BW: mean, 3.2–3.4 kg PNA: <4 d Wt at time of study: NR	L-P 1 g × 45–60 min OR L-P + sucrose (L-P/S) OR 24% sucrose 2 mL PO (S) OR P water 2 mL PO	↓ HR and cry duration, L-P/S and S vs P; no difference in RR or O_2 satn	Pacifier put in infant's mouth until needle insertion; no AEs with L-P

(continued)

Table VI. (Continued)

Venipuncture pain (L-P vs active control)

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Gradin et al[229]	DB RCT N = 201	GA: 32–43 wk BW: 1168–5510 g PNA: 1–30 d Wt at time of study: NR	L-P 0.5 g × 60 min + P water OR 30% glucose 1 mL PO + P L-P (G) to dorsum of hand	↓ PIPP and cry duration, G vs L-P; no difference in HR, no. of successful attempts, or duration of procedure	More infants sucking, G vs L-P; 1 skin "blush" in L-P group

Heel lance pain (L-P vs P)

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
McIntosh et al[230]	Nonrandomized CO CT N = 35	GA: 26–34 wk BW: NR PNA: 7–35 d Wt at time of study: NR	Sham heel lance (Sh) followed by L-P (dose NR) OR spring-loaded lancet OR nurse comfort during heel lance	↑ HR, HR variability, and transcutaneous O_2 tension, L-P vs Sh; no difference in RR or transcutaneous $C0_2$ tension	16 Infants ventilated; AEs NR
Larsson et al[231]	DB RCT N = 112	GA: 36.8–42.6 wk BW: 2.6–4.9 kg PNA: 3 d Wt at time of study: NR	L-P 0.5 mL × 10, 20, 30, 40, 50, 60, 90, or 120 min (7/group) OR P at same time points	No difference in incidence of cry or response to von Frey hair stimulation	Pallor in 39 infants and redness in 3 infants with L-P; pallor in 35 infants in P group
Stevens et al[232]	DB, RCT N = 106	GA: mean, 230 d BW: mean, 1.8 kg PNA: 1–5 d Wt at time of study: NR	Phase I: L-P 0.5 g × 30 min OR P Phase II: L-P 0.5 g × 60 min OR P	No difference in PIPP or MetHb after 8 h in either phase	Minor skin reactions (redness, swelling, blanching) in 33 infants

(continued)

Table VI. (Continued)

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Fitzgerald et al[24]	DB RCT Flexion reflex threshold (not heel lance pain) N = 17	GA: 27–32 wk BW: NR PNA: NR Wt at time of study: NR	L-P rubbed onto 1 heel q4h x 4 wk (dose NR, not occluded) OR P OR NT	↑ Flexor reflex threshold after 4 wk, L-P vs P and NT	AEs NR

Circumcision pain (L-P vs P)

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Benini et al[233]	RCT Gomco clamp N = 27	GA: mean, 39.3 wk BW: mean, 3.6 kg PNA: 1st 7 d of life Wt at time of study: NR	L-P 0.5 g x 45–65 min OR P	↓ Facial action, cry duration, HR, and O_2 satn, L-P vs P	No AEs reported with L-P
Taddio et al[234]	DB RCT Gomco clamp N = 68	GA: mean, 277 d BW: mean, 3.6 kg PNA: 1st 5 d of life Wt at time of study: NR	L-P 1 g x 60–80 min OR P	↓ Facial action, crying time, and HR, L-P vs P; no difference in BP or metHb after 1–18 h	Pallor in 16 infants
Lander et al[235]	RCT Gomco clamp N = 52	GA: >37 wk BW: 2.23–4.805 kg PNA: 1st 3 d of life Wt at time of study: NR	L-P 2 g x 90 min OR L nerve block OR L ring block OR P	↓ HR and cry duration, L-P vs P; (block groups superior to L-P); ↑ metHb after 6 h, L-P vs other groups	Skin AEs NR

(continued)

Table VI. (Continued)

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Woodman et al[236]*	DB RCT Gomco clamp N = 61	GA: 37–42 wk BW: mean, 3.4–3.6 kg PNA: 6–72 h Wt at time of study: NR	L-P 1 g × 60 min OR L 30% 1 g × 60 min OR P	↓ HR and cry duration, L-P vs other groups; no difference in O_2 satn or BP	Skin AEs NR
Joyce et al[47]*	RCT Instrument NR N = 23	GA: 37–42 wk BW: >2.5 kg PNA: mean, 11 h Wt at time of study: NR	L-P × 60 min (dose NR) OR L-P P combined with music OR music P	No difference in RIPS, HR, O_2 satn, or salivary cortisol level	No skin reactions observed

DB = double-blind; CO = crossover; RCT = randomized controlled trial; GA = gestational age; BW = birth weight; PNA = postnatal age; wt = body weight; NR = not reported; HR = heart rate; BP = blood pressure; satn = saturation; metHb = methemoglobin; PKU = phenylketonuria; FT = full-term; AEs = adverse events; RR = respiration rate; PIPP = Premature Infant Pain Profile; CT = clinical trial; NT = no treatment; RIPS = Riley Infant Pain Scale.

Table VII. Studies comparing tetracaine 4% gel (T) with placebo (P) for procedural pain in neonates.

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Jain et al[238]	DB RCT Heel lance N = 60	GA: 28–42 wk BW: 1.0–3.94 kg PNA: 1–16 d Wt at time of study: NR	T 1.5 g × 60 min OR P 1.5 g × 60 min	No difference in cry or facial action	No infants ventilated; no local skin reactions with either treatment
Jain and Rutter[239]	DB RCT Venipuncture N = 40	GA: 27–41 wk BW: 0.85–3.35 kg PNA: 2–17 d Wt at time of study: NR	T 1.5 g × 60 min OR P 1.5 g × 60 min	↓ Cry and facial action, T vs P; no difference in no. of attempts to obtain sample	No infants ventilated; no local skin reactions with either treatment
Moore[240]	DB RCT IV cannulation N = 40	GA: 32–40 wk BW: 1.25–4 kg PNA: NR Wt at time of study: NR	T × 30 min (dose NR) OR P × 30 min	↓ Pain (composite measure of facial action, cry, HR, ease of cannulation), T vs P; no difference in ease of cannulation	1 Infant in T group with erythematous rash
Jain and Rutter[241]	DB RCT Experimental pain, von Frey hair stimulation on foot N = 72	GA: 27–42 wk BW: 0.79–4.1 kg PNA: 1st 2 wk of life Wt at time of study: NR	T 1.5 g to 1 foot and P 1.5 g to other × 30 min OR T 1.5 g to 1 foot and P 1.5 g to other × 60 min	Using cutaneous withdrawal reflex, ↑ in responders in 30- and 60-min groups, T vs P; duration of action longer for 60 min vs 30 min; no difference in strength of response	No infants ventilated; no local skin reactions with either treatment
Jain and Rutter[242]	DB RCT Experimental pain, von Frey hair stimulation on foot N = 60	GA: 29–42 wk BW: 1.03–4.62 kg PNA: 1st wk of life Wt at time of study: NR	T 1.5 g × 60 min OR P 1.5 g × 60 min	Using cutaneous withdrawal reflex, ↑ in responders and strength of response, T vs P	No infants ventilated; 2 infants in T group with erythema disappearing after <20 min

(continued)

Table VII. (Continued)

Study	Design/ No. of Patients	Patient Characteristics	Drug Regimens	Outcomes	Comments
Ballantyne et al[243]	DB RCT PICC line insertion N = 49	GA: 27–41 wk (mean [SD], 33 [4.2] wk) BW: 0.97–1.0 kg PNA: 2–85 d (mean [SD], 18 [23] d) Wt at time of study: 1.98–2.39 kg	T 1.0 g × 30 min OR P 1.0 g × 30 min	No difference in PIPP scores	Transient erythema noted with T (incidence NR)

DB = double-blind; RCT = randomized controlled trial; GA = gestational age; BW = birth weight; PNA = postnatal age; wt = body weight; NR = not reported; HR = heart rate; PICC = peripherally inserted central catheter; PIPP = Premature Infant Pain Profile.

Administration of lidocaine–prilocaine cream or tetracaine gel involves application of the cream or gel, at a usual dose of 0.5 to 1 g, to intact skin under an occlusive dressing. Lidocaine–prilocaine cream requires 45 to 60 minutes to penetrate the skin and produce local anesthesia, whereas tetracaine gel requires 30 to 45 minutes. Single doses of lidocaine–prilocaine cream were reported to be safe in preterm and full-term neonates.[246] There may be cumulative absorption from higher and/or multiple doses and a risk of methemoglobinemia due to the oxidative properties of the prilocaine in lidocaine–prilocaine cream. Multiple-dose safety data are limited. Only 1 multidose study has been reported, involving 12 preterm neonates (30–36 weeks' gestation); in this study, 4 doses of lidocaine–prilocaine cream (0.5 g × 30 min) over 24 hours were well tolerated.[247] No systemic adverse effects have been reported with tetracaine gel.[248]

Lidocaine–prilocaine cream is not an ideal topical anaesthetic for use in neonates because of its long onset of action and risk of methemoglobinemia, particularly when it is used outside the recommended dosing guidelines (ie, overdose) and after repeated administration. Tetracaine gel, although having a shorter onset of action and no risk of methemoglobinemia, may be more likely to cause sensitization with repeated use through a delayed type IV hypersensitivity reaction mediated by T-lymphocytes, whereby re-exposure to the same antigen leads to a contact dermatitis.

Liposomal lidocaine cream has some advantages over lidocaine–prilocaine cream and tetracaine gel and is being used increasingly in pediatric patients. It has an onset of action of 20 to 30 minutes and can be applied without an occlusive dressing (lower cost, less discomfort from removal of the dressing). In addition, its use entails no risk of methemoglobinemia, and it may have fewer vasoactive effects compared with lidocaine–prilocaine cream and tetracaine gel. In 2 published trials in children undergoing venipuncture and venous cannulation,[249,250] liposomal lidocaine cream had similar efficacy to lidocaine–prilocaine cream. An open-label RCT compared the tolerability and efficacy of liposomal lidocaine cream with those of lidocaine–prilocaine cream and dorsal penile nerve block for topical anesthesia in newborns undergoing circumcision and found no significant between-group differences.[251]

Lidocaine–tetracaine gel employs a unique delivery system combining a eutectic mixture of the 2 local anesthetics in a 1:1 ratio with a controlled heating system that enhances the rate of delivery into the dermis. It has shown efficacy after 30-minute application and is currently under investigation in children.[252]

Research Considerations

Acceptable extrapolations of data on the efficacy of local anesthetics from other populations and what needs to be investigated in neonates remain unclear. For example, studies in children have shown that lidocaine–prilocaine cream decreases pain from venipuncture, IV cannulation, lumbar puncture, IM injection, and other cutaneous procedures.[253] Given this information, is it reasonable to test these preparations under each condition in neonates as well, or would it be reasonable to suggest that local anesthesia can be used for similar procedures in neonates without proof of benefit? The burning pain caused by lidocaine infiltration may be counteracted by coadministration of topical anesthetics or systemic analgesia; however, these measures have not been shown to decrease pain in neonates. Other examples of procedures for which evidence is lacking in neonates are lumbar puncture, venous cutdown, and IM injection. Perhaps trials with flexible-randomization designs can address some of these research topics.

Important outcomes for future research may include longer-term measures of the cumulative effects of regular analgesic use, including the potential to decrease pain hypersensitivity (hyperalgesia). The possibility of such a potential is supported by results of a previous study in which regular pretreatment of heel-lance pain with lidocaine–prilocaine cream mitigated the development of cutaneous hyperalgesia.[24] The conduct of studies investigating combination therapy with other analgesic strategies (eg, opioid + local anesthetic + sucrose + environmental intervention) in various procedures is also warranted.[224] With respect to topical local anesthetics, newer formulations such as lidocaine–tetracaine gel appear to offer the best risk–benefit profile in neonates, and future investigations should focus on these preparations.

Sucrose

Oral administration of sucrose solutions has been studied widely as a pharmacologic intervention for the management of pain in preterm and full-term infants. Sucrose is a disaccharide composed of fructose and glucose that has been shown to promote calming be-

haviors and reduce distress associated with acute painful events in animal models and humans. This calming effect is thought to be mediated via endogenous opioid mechanisms.[254] Gustatory inputs from the taste buds presumably lead to cholecystokinin release in the brain stem, thus activating descending inhibitory opioid mechanisms.[254] The efficacy of sucrose for the management of procedural pain has been addressed in successive systematic reviews.[255]

Abundant evidence supports the use of sucrose for procedural pain in preterm and full-term neonates.[255] The analgesic effect is present at a 24% sucrose dose as low as 0.1 mL.[256] Other sweet-tasting liquids, such as glucose, mother's milk, and saccharin, have been reported to be equally effective.[8,44,233,257,258] Administration of sucrose via a pacifier, which stimulates nonnutritive sucking, marginally increases its effectiveness. Six immature preterm infants in one study showed immediate adverse effects such as gagging or choking.[259] Another study reported no differences between groups of preterm neonates who received repeated sucrose doses during the first week after birth and those who did not; subsequent within-group analyses suggested poorer neurobehavioral outcomes in infants of <31 weeks' gestational age who had received multiple doses of sucrose.[256] This finding requires further investigation.

Research Considerations

Some major questions remain underinvestigated or unexplored in regard to the dosing of sucrose in neonates. How much should be given during a single procedure? Is there a dose–response curve or threshold effect? Do more intensely painful procedures require higher doses than less painful procedures? How much sucrose can be given over a 24-hour period without negative long-term effects? Which are the neonatal populations most at risk for developing long-term adverse neurobehavioral effects? What is the dose–response relationship in such adverse metabolic effects as hyperglycemia and metabolic acidosis? Is opioid responsiveness altered in children who are exposed to sucrose in the neonatal period? What is the upper limit of age or development at which sucrose analgesia remains effective? Are dose–response relationships altered in different age groups? Does sucrose have an interactive effect with other analgesics? What are the most appropriate outcome measures at the extremes of prematurity, when gestational age and severity of illness might confound the sucrose response? What are optimal outcome measures when sucrose is used as an analgesic (eg, behavioral responses may show significant differences, whereas cardiac/physiologic measures may not)? What are the interactions between sucrose therapy and additional nonpharmacologic measures, such as nonnutritive sucking and rocking? What do we know about sucrose metabolism and efficacy at the extremes of illness and prematurity (ie, with intraventricular hemorrhage) and pharmacologic interactions with other medications? For how many days is the consistent management of pain with sucrose safe and effective? What are the long-term consequences of sucrose therapy in relation to clinical, behavioral, and neurodevelopmental outcomes?

OBSTACLES TO DRUG STUDIES IN NEONATES

There are numerous obstacles to the implementation of drug studies in neonates. Among the barriers to studies of procedural pain in neonates are lack of neonatal expertise on local institutional review boards; rigidity or variability in the interpretation of guidelines; limited numbers of eligible patients; and neonatal discharge to outlying hospitals before completion of study procedures for collection of longer-term outcomes. In addition, sharing of the population with competing studies leads to difficulties in recruitment and enrollment. Low staffing levels of NICU nurses increases the burden on bedside staff to follow study protocols and collect data. Further difficulties involve parents' inability to understand the need for randomization in analgesia-related studies and their emotional response to the thought of a baby suffering pain. Finally, blood sampling is limited in these patients, as few have indwelling catheters to allow painless collection of blood samples.

GAPS IN KNOWLEDGE

Analgesic Formulations

Gut sensitivity, fragility, bioavailability, disposition, metabolism, and elimination of drugs are influenced by rapid developmental changes in preterm and full-term neonates. In general, there are limited data on the effects of prematurity on these processes. Analgesics are available in a variety of dosage forms (including enteral, parenteral, transcutaneous, transmu-

cosal, and intrapulmonary). There is a need to identify and develop age-appropriate analgesic formulations.

Oral Formulations

There have been few bioavailability studies in neonates regarding the rate of absorption and extent to which absorption is affected by high intragastric pH (>4) and developmental changes in intraluminal pH.[260] Data are required on the influence of immature biliary function on the solubility of lipophilic agents, and the effects of low cytochrome P450 (CYP) 1A1 activity on drug metabolism.[261,262] Oral formulations must be tested for stability and must allow accurate dosing without the need for multiple dilutions or compounding procedures, giving due consideration to volume restrictions in the preterm neonate.

Topical Formulations

Immature development of the epidermis in preterm neonates is associated with high skin permeability to lipophilic drugs (eg, diamorphine[75]) but low permeability to other less lipophilic drugs (eg, lidocaine[263]). Skin permeability does not appear to alter the clinical toxicity of lidocaine–prilocaine cream.[232,264] The full potential of topical formulations has yet to be explored in preterm and full-term neonates.[24,74,245,265,266]

Intravenous Formulations

Immature drug metabolism (delayed glucuronidation or oxidation via the CYP pathway) and decreased renal function (low glomerular filtration rate) may lead to cumulative increases in plasma concentrations, poor drug elimination, and increased drug toxicity.[267–269] In addition, the effects and stability of agents in the vehicle for IV drugs (eg, propylene glycol, alcohol, sodium benzoate) need to be considered. The concentration of the formulation must allow individualized dosing for very preterm neonates, as the dilution of higher-strength formulations may result in loss of stability, dosage errors, or volume overload.

Intramuscular and Subcutaneous Formulations

The administration of IM and SC formulations is associated with acute pain and is limited by the decreased muscle mass and delicate skin of preterm neonates. The IM and SC routes of administration should be avoided except in extreme circumstances (eg, IM administration of ketamine for intubation in neonates without IV access).

Rectal Formulations

Decreased and variable absorption of rectally administered acetaminophen in preterm, full-term, and older infants has been noted in numerous studies.[189,190,192,194,195,270] Rectal formulations of lipophobic drugs are unlikely to provide therapeutic drug levels for procedural pain in neonates; however, limited information is available on lipophilic drugs.

Intrapulmonary Formulations

Morphine has been administered via the intrapulmonary route for the relief of dyspnea in children.[271] The systemic bioavailability of nebulized morphine is poor. However, more efficient methods of delivery that use a smaller particle size may increase delivery of the opioid to the alveoli, resulting in analgesia through systemic absorption.[272,273] As evidence accumulates regarding the usefulness of this route of administration for analgesia, applicability to the preterm and full-term neonate must be investigated in terms of the effect of developing lung function on systemic absorption.

Comparative Studies

Most studies of procedural pain in neonates have compared one effective agent against a placebo control, although a few comparative studies have been published (morphine vs fentanyl,[69,70,274,275] morphine vs diamorphine,[83] and various interventions for circumcision[44,46,47,219,235,276–284] or heel sticks[285–287]). There is a need for comparative studies of systemic analgesics for procedural pain in neonates, including investigations of the comparative efficacy and safety of fentanyl and alfentanil, morphine and fentanyl, ketamine and morphine or fentanyl, remifentanil and alfentanil, and other drug combinations. Optimal dosing regimens for long-acting and short-acting opioids need to be developed, particularly for preterm neonates of different gestational ages. Comparisons of the safety and efficacy of topical preparations for procedural pain (eg, lidocaine–prilocaine cream vs amethocaine, liposomal lidocaine vs amethocaine, lidocaine–prilocaine cream vs lidocaine) in preterm and full-term neonates are also needed.

Regional analgesic approaches are used infrequently in neonates, despite their applicability in specific procedures (eg, intercostal nerve block for chest tube placement, ilioinguinal/iliohypogastric nerve block for hernia repair/reduction, femoral nerve block for clubfoot repair or manipulation of lower extremity frac-

tures, caudal epidural for hypospadias repair). Different regional analgesic drugs (lidocaine, bupivacaine, ropivacaine) or combinations of these drugs with drugs from other classes (eg, clonidine,[288,289] ketorolac,[201–205] fentanyl,[290] morphine,[288,291–298] naloxone[294]) need to be investigated in neonates. Finally, there is a need to study the safety and efficacy of combination approaches employing systemic analgesics, regional techniques, topical agents, and behavioral/environmental techniques appropriate to specific invasive procedures in neonates.

Pharmacogenetic Analyses

There is a need for studies of the developmental regulation of genetic polymorphisms encoding for receptors targeted by analgesic drugs, the enzymes responsible for the metabolism of analgesic drugs, and other genetic systems involved in pharmacokinetic/pharmacodynamic variability in preterm and full-term neonates.

Methods of Assessment

Despite the availability of multiple methods of assessing procedural pain in neonates, none have been validated for extremely premature infants or for mechanically ventilated or chemically paralyzed infants. Further research is needed to develop validated assessment tools for exceedingly preterm infants and those whose responses are mechanically, neurologically, or physically compromised.

Costs of Interventions

Few, if any, studies have addressed the costs of interventions for procedural pain in neonates. Little is known about the comparative costs (direct, indirect) involved in use of the various therapies for procedural pain. Further research is needed to investigate these costs and develop more elegant cost–benefit analyses for the evaluation of competing therapeutic options.

CONCLUSIONS

There are various options for managing the pain associated with invasive procedures in neonates, including systemic analgesic agents such as opioids, NSAIDs, acetaminophen, and sucrose; sedatives and anesthetic agents with or without analgesic effects; and injectable or topical local anesthetics. Different drug classes and/or modes of administration may be combined to optimize efficacy and minimize the occurrence of adverse effects. To ensure safe use of these therapeutic approaches, toxicity or drug overdose resulting from repetitive use of these agents must be taken into consideration, as well as the enhanced vulnerability of special populations (eg, extremely premature infants; neonates with sepsis, hypotension, or renal failure). Much research is necessary to provide drug-labeling information and a scientific framework for the management of procedural pain in preterm and full-term neonates.

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