Journal of Perinatology (2007) 27, S4–S11

www.nature.com/jp

ORIGINAL ARTICLE

Pharmacological approaches to the management of pain in the neonatal intensive care unit

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Effective and consistent management of neonatal pain remains a controversial issue.

Premature infants are repeatedly subjected to painful tests and procedures or suffer painful conditions when they are most vulnerable. With different mechanisms transducing various types of pain the practice of 'one-drug fits all' becomes questionable.

Clinicians must use the latest non-pharmacologic and pharmacologic therapies for effective management of neonatal pain, distress, or agitation. Pharmacologic strategies for dealing with neonatal pain in the neonatal intensive care unit are described. Opioid therapy, once considered the mainstay for neonatal analgesia, may not be as effective as previously thought. Morphine infusions do not alter the neurological outcomes of preterm neonates and may not be effective against acute pain. Alternative approaches with methadone, ketamine, or local anesthetics should be considered. Clinicians must understand the contextual circumstances underlying pain in individual neonates and tailor therapy accordingly, using the most current evidence related to neonatal pain assessment and management.

Journal of Perinatology (2007) **27,** S4–S11. doi:10.1038/sj.jp.7211712

Keywords: infant-newborn; infant-premature; pain; agitation; stress; analgesia

Introduction

The International Association for the Study of Pain defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'[1] They further promulgate that pain is always subjective and takes on meaning based on each person's experiences, especially in early life. Thus, the definition of pain heavily weighs on the patient's ability to verbalize their experience of pain.

The ability to assess a patient's pain and respond to it effectively depends on his or her ability to describe the pain, specifically the location and intensity. Unfortunately, a vast number of patients lack the ability to describe their pain. These include adults with dementia, children with handicaps and infants, as well as anyone who is incapable of verbal self-report. On average, adult patients capable of verbal self-expression receive much more pain medication than those who are incapable of verbal expression.[2] Similar studies in children undergoing spinal surgery demonstrated that children with cognitive impairment received significantly less pain medication compared to children without cognitive impairment on post-operative days 1 to 3.[3]

To understand the physiologic outcomes of pain, it is helpful to understand how the body interprets painful stimuli. The identification, quantification and evaluation of pain, as well as the utilization of these data in treatment protocols, are of paramount concern to clinicians. Different types of pain are perceived and registered by many different mechanisms, although with some degree of overlap. Thus, the physiological pain caused by tissue injury is only one type of pain, although most commonly coupled with the term pain. In addition, there is inflammatory pain associated with inflammation, neuropathic pain resulting from nerve damage or inflammation, or visceral pain caused by distention, contraction, or inflammation of hollow or solid viscera. With the many different pain mechanisms, the practice of 'one-drug fits all' becomes less viable as a standard approach.

What are the sources of infant pain?

This article examines pain control in the neonatal intensive care unit (NICU) setting, focusing mainly on the pharmacologic management strategies when dealing with acute, established or prolonged pain. Acute pain may be caused by various diagnostic and therapeutic procedures, minor surgery, or placement of invasive monitoring devices; established pain is commonly associated with post-operative pain, inflammatory pain, thermal or chemical burns; whereas prolonged or disease-related pain results from contractures, nerve injury, or conditions such as necrotizing enterocolitis, thrombophlebitis, or osteomyelitis (Table 1).

Pain is a multilayered phenomenon often described as producing either primary or secondary hyperalgesia. Primary hyperalgesia is located in the area of specific tissue injury, whereas, secondary hyperalgesia occurs away from the site of injury or inflammation. In addition, if pain is caused by non-noxious

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Table 1 Sources of infant pain

Acute pain	Diagnostic and therapeutic procedures
	Minor surgery
	Suctioning oral/nasal/tracheal
Established pain	Postoperative pain
	Inflammatory pain
	Thermal/chemical burn
Prolonged pain	Meningitis
	Necrotizing enterocolitis
	Phlebitis
	Osteomyelitis from repeated heelsticks

stimuli, it is labeled as allodynia. For example, tactile stimuli applied to an inflamed joint are converted into painful stimuli because of the hyperexcitability of nociceptors in the tissue (peripheral sensitization) and neurons in the spinal cord or supraspinal areas (central sensitization). Repeated noxious stimuli causing increasing amounts of activation in the pain pathways is termed as windup or temporal summation.[4,5]

There are specialized nociceptors and nerve fibers in the periphery and specialized neurons in the dorsal root ganglia responsible for pain transmission.[6] The different sensory systems, such as visual, auditory, or tactile systems, are designed to develop normally with incident stimulation that occurs during early life. In contrast, the pain system is the only sensory system that develops normally without any incident stimulation during early life.[7] For the neonate, early developmental periods can easily modify pain systems, especially from the exposure to frequent and multiple painful stimuli. The repetitive stimulation of the pain system may attenuate peripheral sensitivity or decrease behavioral responses resulting in altered development.[8–10]

The three categories of pain (acute, established, or prolonged) based on their duration will result in different clinical manifestations. Most pain studies in neonates have studied models of acute pain, heel sticks or circumcision, two of the most common invasive procedures performed in neonates. Acute pain results in a psychophysiological activation, with increased heart rate, respiratory rate, blood pressure, changes in skin blood flow and oxygen saturation, vagal tone and palmer sweating. Behavioral changes can also be seen with increases in crying activity, body movements and facial expressions. When pain becomes established or prolonged, however, there is a dampening of normal behavior and physiological responses. Heart rate and blood pressure may even be below resting rates, also associated with the elimination of normal physiological variability, like sinus arrhythmia.[11,12] Clinicians at the bedside need to be keenly aware of the different types of pain to be better able to evaluate and treat infants and neonates.

Multiple lines of evidence suggest that infants are more sensitive to pain. In evaluating the dorsal cutaneous flexor withdrawal reflex, preterm infants have a third to 50% of the threshold for the dorsal cutaneous flexor reflex reaction to pain as compared to term infants.[13] The afferent limb of the withdrawal reflex is conducted by C-fibers, which are pain-conducting fibers. Term infants have a lower threshold for this reflex compared to older children or adults because there is a delayed maturation of descending inhibitory fibers.[14–16] In practice, if an intravenous line were to be inserted in the hand of a 30-week-old baby, there would be less physiological response as opposed to inserting that same intravenous line in the baby's foot. The reasoning behind this is that the descending inhibitory fibers are growing from the supraspinal brainstem nuclei, only reaching the cervical section of the spinal cord by 30–32 weeks. As they have not reached the lumbar section of the spine by 30 weeks, the pain threshold is higher in the upper extremities and lower in the lower extremities, resulting in increased sensitivity to pain in the lower extremities.[17–19] A phenomenon known as wind-up occurs when an infant is subjected to prolonged pain, resulting in a temporal summation and hyperalgesia, which can last for up to 30–60 minutes in preterm infants.[14,15,16,19]

Despite being unable to express pain, the premature infant reacts to painful stimuli with activation of the highest level of sensory function in the brain. Bartocci *et al*.[20] evaluated the cortical activation responses following tactile and painful stimuli. Infrared spectroscopy probes were placed on both sides of the somatosensory cortex and measured for a baseline period. Tactile stimulation produced by an alcohol swab caused an increase in blood flow to the somatosensory cortex. A venepuncture resulted in several-fold increases in blood flow to the somatosensory cortex, but no changes occurred in blood flow to the occipital cortex, demonstrating that this was not caused by global increases in cerebral blood flow but a functionally specific response (Figure 1). In contrast, hemodynamic responses in older preterm infants were associated with changes in the contralateral somatosensory cortex after painful stimuli from a heelstick (Figure 2). Thus, the repeated exposure to painful stimulation may lead to a maturation of the cortical responses to pain in preterm neonates.

Where do we go from here?

The scientific proof that neonates feel and react to painful stimuli is evident. Pain, unfortunately, is a common occurrence in the NICU setting. The complexity of their inability to verbalize pain and inherent variability of pain dependent on its source and duration adds layers of intricacy to appropriate identification (Table 1). A proposed clinical approach (Figure 3) assesses potential sources considering both continuous and episodic pain, prevents unnecessary tests and procedures and develops specific protocols for pain management. There are myriad pain measurement tools to choose from the Premature Infant Pain Profile (PIPP), the CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness) tool and the Neonatal Infant Pain

Scale are most commonly used. Of these three pain assessment tools, only the PIPP adjusts for gestational age. Evidence-based pain assessment recommends standardized and validated methods that are specific for acute versus prolonged pain. For example, a universal scale of 0 to 10 would be beneficial among the different assessment methods. In addition, clinicians must evaluate contextual factors, behavioral and physiological indicators.

Numerous studies have documented the poor compliance in administering analgesia to neonates before painful procedures. Barker and Rutter[21] demonstrated that neonates less than 30 weeks are more likely to have invasive procedures (Figure 4). Porter followed 144 neonates who underwent 7672 pain-inducing procedures, of which 87% were heel sticks and only 3% were preceded by analgesia.[22] More recently, Simons *et al*.,[23] followed 151 neonates for the first 14 days of their NICU admission and

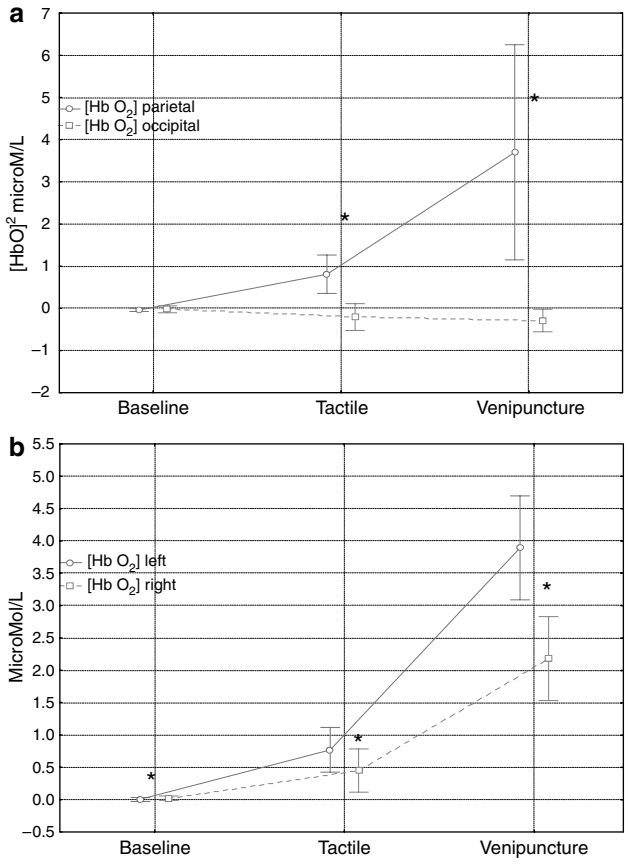

Figure 1 Acute pain is associated with increased blood flow (representing neuronal activation) to the bilateral somatosensory cortex (lower panel). This is functionally specific because pain activates the contralateral somatosensory cortex but not the occipital cortex. Bartocci M *et al*. *PAIN* 2006; **122:** 109–117. Used with permission.

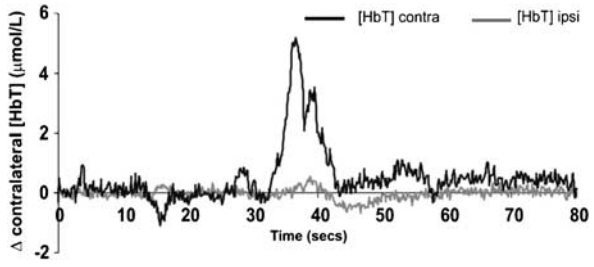

Figure 2 Hemodynamic responses in the somatosensory cortex of a ventilated 25 week premature infant, demonstrating the evoked changes in total hemoglobin in the contralateral (black) and ipsilateral (grey) cortex following a heelstick at $t = 20$ s. Slater R, Cantarella A, Gallella S, *et al*. Cortical Pain Responses in Human Infants. *J Neuroscience* 2006; **26**(14): 3662–3666. Used with permission.

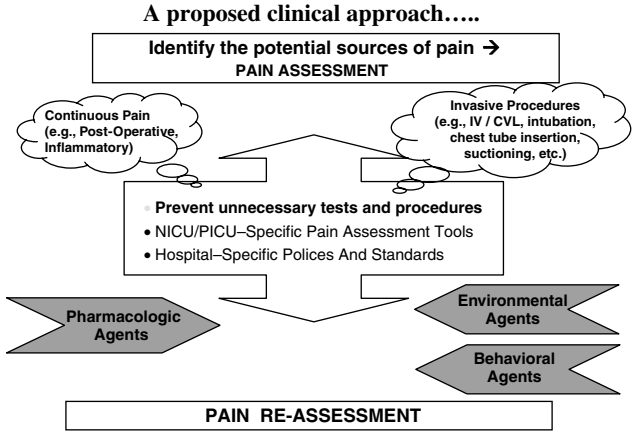

Figure 3 A proposed clinical approach for assessment and management of pain in neonates.

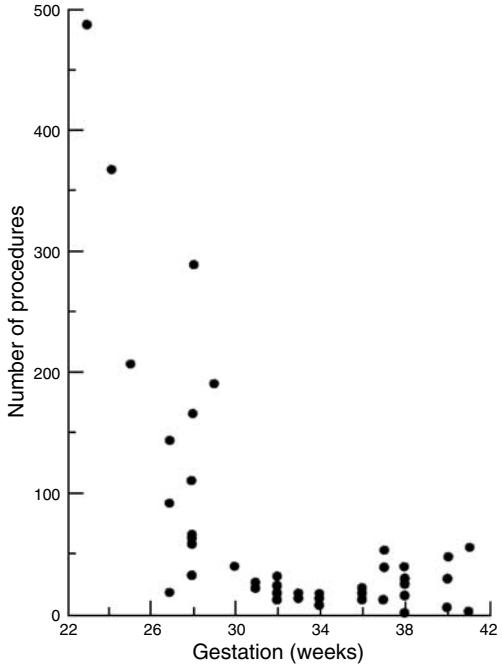

Figure 4 Total number of invasive procedures experienced by preterm neonates during their stay in the Neonatal ICU. Archives of Disease in Childhood, 1995, vol. 72, pp. F47–F48, reproduced with permission for the BMJ Publishing Group.

documented almost 20,000 pain-producing procedures, of which 31% were repeat attempts when the first procedure was not successful. This averaged 196 procedures per neonate, or between 12 and 15 procedures per day. Although physicians and nurses rated these procedures in the range of moderate to severe pain using a visual analog scale, less than 35% of these procedures were associated with some form of analgesia.

Quality improvement projects have evaluated pain management in several NICUs. One such study found that if pain was assessed by clinicians with prescriptive authority, such as physicians or nurse practitioners, neonates had a fourfold increase in the odds ratio for post-operative analgesia, as opposed to pain assessment by nurses.[24] A collaborative approach by all clinicians in the NICU to manage pain may better serve these patients. For physicians and nurse practitioners, pain assessment should be part of their routine physical exam.[24] Incorporating parental assessment including baseline behavior may be especially valuable. Parents know their infants and children on a patterned and intuitive level, this knowledge should be utilized when assessing pain in these patients.[25]

Pharmacologic management

Both non-pharmacological and pharmacological approaches play a role in the management of pain in the neonate and infant. The use of swaddling, sucrose, pacifiers and decreased environmental stimuli have shown limited therapeutic efficacy in treating mild to moderate painful stimuli. Local and systemic analgesia are often the treatment of choice for invasive procedures. Local analgesia, such as various topical agents or lidocaine infiltration, can be effective in managing procedural pain, although not as effective as opioid therapy.[26] Most topical agents also need to be applied 30 min before a procedure and are not effective against heel-stick blood draws. However, the following discussion will focus only on the pharmacological management with systemic analgesics, most notably treatment with opioids and other options including ketamine and midazolam (Table 2).[27,28]

Opioids

The mainstay of systemic analgesia for moderate to severe pain is the use of opioid therapy. Opioids provide both sedation and analgesia, have a wide therapeutic window, and decrease hemodynamic and metabolic stress responses, but they do not provide amnesia. Benzodiazepines are a better choice when amnesia is required.[29] Morphine and fentanyl are the most commonly used opioids in the NICU population.[30]

Morphine

Morphine is the most commonly used opiate used for analgesia, but wide variability occurs in dosing and clinical usage.[31] Some studies suggest that babies require higher plasma concentrations than older children or adults to receive pain relief,[32] although other studies disagree.[33–36] In the past, morphine was thought to be a pure opioid agonist, but this theory was disproven long ago.[37] Morphine has a ceiling effect; after a certain therapeutic level has been reached, higher doses will produce more adverse effects rather than increased analgesia. Clinical experience suggests that a ceiling effect may be reached by using doses up to 0.5 mg/kg. Morphine has a slow onset of analgesia owing to lower lipid solubility, especially in premature infants.[29] Its mean onset of action is 5 min and the peak effect is at 15 min. Morphine is metabolized in the liver into two active compounds, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G is an opioid antagonist, which at high levels can cause seizures; whereas M6G is a potent analgesic with a half-life greater than morphine. In the maturation of hepatic glucuronidation,

Table 2 Analgesic medications.[27,28]

Agent	*Class*	*Neonatal dosing*
Morphine	Opioid	IM, IV, SQ – initial dose 0.05-mg/kg every 4–6 h; maximum 0.1 mg/kg/dose
		IV continuous infusion – 0.001–0.03 mg/kg/h
Fentanyl	Opioid	IV slow push – 0.3–2 mcg/kg/dose
		IV continuous infusion – 0.3–5 mcg/kg/h
Methadone	Opioid	IV–0.05–0.2 mg/kg/dose every 12–24 h (for neonatal abstinence syndrome)
Ketamine	NMDA antagonist	IV slow push – 0.5–2 mg/kg/dose
		IV continuous infusion – 0.5–1 mg/kg/h
		IM, SQ – 1–2 mg/kg/dose
		Oral – 5–8 mg/kg/dose
Midazolam	Benzodiazepine	IV continuous infusion – (<32 weeks): 0.03 mg/kg/h or 0.5 mcg/kg/min; (>32 weeks): 0.06 mg/kg/h or 1 mcg/kg/min
		IV – 0.05 – 0.15 mg/kg over at least 5 min, repeat Q2–4 h as needed
		Intranasal or Sublingual–0.2 mg/kg/dose (use injectable form)

IV, intravenous; IM, intramuscular; SQ, Subcutaneous; mg, milligrams; kg, kilograms; mcg, micrograms; Q, every; h, hour; min, minutes.

UDP-glucuronyl transferase, preterm infants produce mostly M3G, which is why after three or four days of therapy the infant develops a degree of tolerance as a result of continued treatment.[38,39]

Morphine causes some histamine release and may lead to several side effects as a result.[29] For those infants on fluid restriction for patent ductus arteriosus (PDA) and those on diuretics, morphine will produce some degree of hypotension. Caution should be used when prescribing morphine in patients with asthma or bronchopulmonary dysplasia, because of the risk of histamine-induced bronchospasm. Compared to fentanyl, morphine has decreased risks of causing dependence or withdrawal[40] and greater effects on gastrointestinal (GI) motility and biliary spasm.[29]

There is accumulating evidence that morphine may not be effective in the treatment of acute pain. Franck *et al*.[41] revealed that in the post-operative period for preterm infants, a dose of morphine did not produce any change in plasma norepinephrine, vagal tone, or flexor withdrawal. Simons demonstrated that morphine did not have any analgesic effects associated with tracheal suctioning.[42] More recently, in a blinded study of morphine versus placebo, there was no change in the response to heel sticks before and after a loading dose (100 mcg/kg followed by an infusion of 10 to 30 mcg/kg/h) of morphine on two different pain scales (PIPP and DAN scales).[38] There are some data suggesting that acute pain leads to an uncoupling of opiate receptors in the forebrain.[43] In the case of preterm infants, immaturity of opiate receptors could be a reason for the lack of response. Some studies suggest that infants have a decreased production of M6G and an increased production of M3G, thereby resulting in a decrease in the potent analgesia effect and an increase in the opioid antagonist effect.[44]

However, there are also recent studies that support the use of morphine for acute pain. Taddio *et al*.[26] demonstrated that intravenous morphine was more effective than topical tetracaine for the management of pain associated with central line placement in neonates. Angeles *et al*.[45] showed that opioid use in asphyxiated term neonates had a positive effect on the neuroimaging outcomes and clinical outcomes at 18 months.

Overall, the routine use of morphine for the management of pain in preterm neonates is controversial. In addition to analgesia, a question arises if morphine therapy may have beneficial effects on the neurological outcomes of preterm neonates. The NEOPAIN trial investigated this issue.

The (Neurologic Outcomes & Pre-emptive Analgesia In Neonates) Trial

The Neurologic Outcomes & Pre-emptive Analgesia In Neonates (NEOPAIN) trial is the largest randomized, placebo-controlled trial for any analgesic in the neonatal age group. The trial was designed to evaluate poor neurological outcomes of ventilated preterm neonates treated with a morphine infusion compared to a placebo control group. Of the original 4254 neonates screened, a total of 898 neonates were enrolled in the trial. Poor neurologic outcomes were defined as death at less than 28 days before NICU discharge, severe intraventricular hemorrhage (IVH, grade III or IV), or periventricular leukomalacia (PVL). At the end of the study, the incidence of the primary outcome was similar between the two groups (morphine, 27%; placebo, 26%; $P = 0.58$). In sub-group analyses, there was no change in the stratified gestational age groups of 23 to 26 weeks (morphine, 40%; placebo, 42%; $P = 0.70$) or 30 to 32 weeks (morphine, 10%; placebo 15%; $P = 0.31$). There was, however, a trend towards increases in poor neurologic outcomes in the 27 to 29 week neonates receiving morphine (23 versus 15%; $P = 0.053$). Morphine was administered as a loading dose (100 mcg/kg) followed by continuous infusions based on gestation age (23 to 26 weeks, 10 mcg/kg/h; 27 to 29 weeks, 20 mcg/kg/h; 30 to 32 weeks, 30 mcg/kg/h). These dosages were based on single-dose pharmacokinetics, and were not based on the infusion pharmacokinetics of morphine. These were large doses of morphine, infusions of 3–5 mcg/kg/h may be effective, particularly in the younger gestational age groups.[46]

The most prevalent side effects of morphine were hypotension and respiratory depression, which resulted in an increased duration of ventilation by one day ($P = 0.03$). Morphine's effects on GI motility increased the time required to reach full volume nasogastric feeds ($P = 0.04$). Logistic regression analyses revealed that neonatal death was related to lower gestation (OR 0.71, $P < 0.0001$) and greater severity of illness (OR 1.23, $P < 0.0001$), but not to treatment group (OR 1.16). Severe IVH was related to gestation (OR 0.74, $P < 0.0001$), severity of illness (OR 1.08, $P = 0.02$), lack of antenatal steroids (OR 0.29, $P < 0.0001$), and maternal race ($P = 0.04$), but not the treatment group ($P = 0.22$). PVL was not related to gestation or treatment group; it was only predicted by maternal chorioamnionitis (OR 2.05, $P = 0.03$) when all other clinical factors were controlled for in the logistic regression model.[46]

Overall, from the NEOPAIN trial, continuous morphine infusion did not alter the neurologic outcomes of preterm neonates. Gestational age differences may be related to either severity of illness or the effects of increasing morphine infusion rates. Intermittent boluses were required more frequently in neonates that had developed IVH or PVL before study enrollment.[46]

Fentanyl

Another commonly used opioid, fentanyl has a rapid onset of action (2 to 3 min), short duration of action (60 min with bolus doses) and minimal hemodynamic effects.[47] Prolonged elimination occurs with fentanyl infusions,[48] resulting from rebound plasma concentrations. Chest wall rigidity may occur with rapid fentanyl IV boluses. Fentanyl is metabolized in the liver to inactive compounds.[47] The potency ratio of fentanyl compared to morphine

is different in adults (80 to 100 times) as compared to infants (13 to 20 times).[38] Tolerance develops rapidly, especially with infusions compared to boluses. In addition, the risk of dependence and withdrawal is greater as compared to morphine.[40] Fentanyl is also available as a transdermal patch. The use of fentanyl patches is limited and should be considered only when IV access is not available. The problem arises because the lowest dose fentanyl patch provides 12.5 mcg/h, which is a huge dose for preterm infants. In addition, any vasodilation close to the infant's skin will increase the absorption rate of the drug. One advantage is that the gradual 'tail-off' effect after removing the patch does not occur because there is less subcutaneous fat in preterm infants.[11] Intravenous infusion is considered the safest way to administer fentanyl.

Methadone

Methadone is currently being studied as a viable drug to reduce pain in neonates. It is equipotent with morphine, but has additional mechanisms of action that may be advantageous in the preterm neonate population. In addition to activating specifically the μ-opiate receptors as morphine does, it also causes a desensitization of delta-opiate receptors and antagonism of the NMDA receptors. The action on the delta-opiate receptors reverses the tolerance that occurs with morphine.[49] As an NMDA antagonist, methadone blocks NMDA receptors, producing additive analgesic effects and delayed development of tolerance.[50] Methadone has a slow onset of action (20 min with IV, 30 to 60 min with oral),[47] good oral bioavailability (75 to 85%) and prolonged elimination half-life ($t_{1/2ß:}$ children 19 h; neonates 41 h).[22]

Critical issues with opioids

Tolerance and withdrawal

With the widespread use of opioids, critical issues of tolerance and withdrawal occur. Clinicians are ever vigilant of patients developing opioid tolerance, requiring higher doses to illicit the same analgesic effect. As higher doses of opioids are administered over longer periods of time, withdrawal becomes an even greater concern. Some procedural and therapeutic approaches may help prevent the development of tolerance. Methadone is commonly used owing to its long half-life. Novel combination therapies to prevent tolerance include morphine with low-dose ketamine, which will block NMDA receptors.[6] Morphine can also be combined with ultra-low dose naloxone. With the use of ultra low-dose naloxone, picomolar concentrations of naloxone at the receptor level only block the opioid receptors coupled with the stimulating G-protein and do not affect the receptors coupled to the inhibitory G-protein that are producing analgesia.[51] Randomized trials are now being designed to look at these novel therapies.

Beyond opioids: ketamine and midazolam

In addition to the usual opioids, other options should be evaluated. Consideration should also be given to short-term infusions of ketamine or midazolam, recognizing that midazolam is a sedative amnesic agent, and not an analgesic.

Ketamine is commonly used for procedural pain. It produces a dissociative state by blocking *N*-methyl-D-aspartic acid (NMDA) receptors, resulting in sedation, analgesia and amnesia. It is the only drug that causes all three effects. It has been shown to be safe and effective for sedation in pediatric critical care procedures.[52] It increases muscle tone and blood pressure, thus maintaining hemodynamic stability. Ketamine does not cause respiratory depression and maintains respiratory drive. With regard to opioid tolerance and withdrawal, methadone and ketamine work in a similar way; these novel co-therapies are being investigated and may prove to be effective. Low-dose ketamine, 0.3 mg/kg/h with a morphine infusion, has been efficacious in blocking morphine tolerance by blocking NMDA receptors.[6] Although apoptosis occurs in the brain of newborn rats, this has been reported with doses that are 100 times of those used in clinical practice;[53] these data may not apply to human neonates receiving clinical doses.[54]

As previously mentioned, midazolam is a benzodiazepine drug that produces anxiolysis, sedation, amnesia, and muscle relaxation but no analgesia. It is often used before induction of anesthesia and for conscious sedation before diagnostic procedures. Midazolam is frequently used for infants <32 weeks during mechanical ventilation, with initial doses of 0.03 mg/kg/h (0.05 mcg/kg/min). It activates the inhibitory γ-amino butyric acid receptors in the brain, brainstem, and spinal cord. Onset of action ranges from 2 to 6 min, lasting 1 hour after a single IV dose. Although the combination of opioids with midazolam is common practice in many NICUs, extreme caution is suggested because of the many serious adverse events. Midazolam may cause respiratory depression, hypotension, and bradycardia.[47] In addition, midazolam has been known to cause a decrease in cerebral blood flow in preterm neonates.[55]

Conclusions

The multifaceted issues of pain management can be addressed in different ways rather than relying on the 'one-drug-fits-all' approach (Table 3). Exposure to repetitive pain occurs commonly in preterm and term neonates. Pain assessment methods are currently available specific for acute pain, but newer methods are currently being developed to evaluate prolonged pain. An appropriate approach to the management of pain needs to assess the type of pain the neonate is experiencing. For acute physiological pain, avoiding invasive procedures, utilizing sucrose pacifiers, and topical/local anesthetics can be useful. For post-operative pain, a short duration (24 to 48 h) of opioid therapy, positioning, removing drains, and considering adjuvant therapies would be appropriate. For inflammatory pain, caused by meningitis or phlebitis, anti-inflammatory agents should be considered. Opioids can be used in this setting if the pain is severe or extensive.

Table 3 Pain management approaches

Type of pain	*Pain management approaches*
Acute pain	Avoid invasive procedures Sucrose Pacifier Local/topical anesthesia
Postoperative pain	Short-term opioid infusion (24–48 h) Positioning Remove drains Consider adjuvant therapies
Inflammatory pain	Non-steroidal anti-inflammatory agents (non-specific, or specific Cox-1 or Cox-2 inhibitors) Consider opioids if severe or extensive
Visceral pain	Oxybutynin for bladder pain/spasms Metoclopramide for intestinal cramping Consider epidural analgesia Specific therapies for underlying condition
Neuropathic pain	Relieve nerve compression Steroids for reducing nerve inflammation Consider nerve blocks or epidurals or spinal anesthesia Specific agents: Mexiletine, memantine, gabapentin, phenytoin and other agents (not tested in neonates)

A comprehensive knowledge base and familiarity with current research related to pain assessment and management are paramount, to help the clinician treating neonates in the NICU. Future research must define efficacy of specific therapeutic approaches, applicability to specific neonatal populations, combination approaches, and comparative studies between analgesic drugs.

Acknowledgments

I gratefully acknowledge grant support from the NICHD (U10 HD500009), the help of Dr Evelyn R. Hermes-DeSantis (Ernest Mario School of Pharmacy) and Dr Sohini Sarkar (Robert Wood Johnson University Hospital) in preparing this paper.

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