Pain management is increasingly recognized as an integral part of effective management of vulnerable babies in the neonatal intensive care unit (NICU). Traditionally, neonates have not been accorded the same respect for pain as have their older counterparts because pain, as defined by the International Association for the Study of Pain, is “always subjective.” Babies requiring intensive care are unable to express discomfort. Furthermore, preterm neonates in particular do not have the strength to protest like older children or even term neonates. The parents, who would advocate for their babies, are often asked to wait outside the NICU while painful procedures are being performed (despite evidence that pain can be mitigated by parental involvement1). Furthermore, neonates do not fill out satisfaction surveys or express displeasure as a result of being exposed to painful stimuli, making them at risk for inadequate pain treatment.

Before 1980, pain in the newborn period was infrequently recognized or treated.2 Because the gold standard of pain assessment is self-reporting, which is clearly not possible in the newborn period, clinicians can only measure pain indirectly. Animal and human studies have documented that neonatal pain is associated with short- and long-term adverse consequences.3,4 Furthermore, the enhanced survival of extremely low-birth-weight babies makes them more susceptible to the effects of pain and stress because of increased exposure. Indeed, one study documented that neonates less than 32 weeks’ gestation were exposed to 10 to 15 painful procedures per day, up to 22 procedures per day in the first 2 weeks of life,5 and most of these procedures were untreated.6 Clinicians advocating pain relief continue to struggle. A recent study by Carbajol and colleagues7 has documented the increased occurrence and lack of treatment of neonatal pain in almost 80% of newborns in intensive care.

Analgesia and sedation in the NICU has been fraught with controversy because of concern about the safety of these drugs in the neonatal population, lack of adequate
pharmacokinetic and pharmacodynamic data in this population, difficulty in pain assessment, and lack of long-term neurodevelopmental assessment of survivors for the pain experienced in the neonatal period.8–11 Legitimate concern about safety has led to more governance for moderate sedation privileges for clinicians caring for neonates and more emphasis on obtaining consent for sedation,12 leading to roadblocks to giving sedation to neonates undergoing painful procedures. Furthermore, individual differences and decreased morphine metabolism in younger gestational age neonates may lead to the rapid development of tolerance and accumulation of the drug in extremely preterm neonates.13 Thus, the use of sedation and analgesia in the neonatal population although extremely important, must be done safely and effectively (Table 1).

In a practical sense, every NICU should have a program to reduce pain for the NICU patient. This program should include a comprehensive approach, as shown in Fig. 1. A stepwise approach should begin with avoidance of painful procedures as much as possible, followed by nonpharmacologic and then pharmacologic methods for pain relief. Because the projected pain is expected to become more severe, increasingly potent drugs (with increasing complications) should be used. An effective pain relief program also provides education for all healthcare providers.27,28

### NEONATAL PAIN ASSESSMENT

Pain assessment has been termed the “fifth vital sign” by the Joint Commission for the Accreditation of Hospitals. However, the gold standard is self-reporting, obviously not possible in neonates. Therefore, several pain assessment tools (>40 and still counting) have been developed for this purpose.10 Pain assessment is based on physiologic (heart rate, blood pressure, respiratory rate, and oxygen saturation) and behavioral (facial action, body movements, and cry) measures. Behavioral measures are more pain specific,29 whereas physiologic measures are more indicative of stress and not as specific for pain.30 Unfortunately, there is poor correlation between these two measurements,31 and neonatal pain assessment remains controversial. Furthermore, preterm neonates exhibit differential responses to pain as evidenced by the different pain scores in the Premature Infant Pain Profile, one of the pain assessment tools commonly used in NICUs.32 Clearly, the metabolic cost of mounting a robust response to pain for an extremely preterm neonate is not worth the energy expenditure given the limited energy reserves.33

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Balance between treatment for pain and concerns regarding treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reasons to Treat for Pain</strong></td>
<td><strong>Concerns Regarding Treatment</strong></td>
</tr>
<tr>
<td>Beneficial short-term effects (less ventilator asynchrony, splinting, faster intubation, decreased morbidity especially after surgery)14</td>
<td>Adverse short-term effects (hypotension, respiratory depression, prolonged ventilator dependence, intraventricular hemorrhage)16,17</td>
</tr>
<tr>
<td>Beneficial long-term effects (improved response to pain, downregulation of the hypopituitary-adrenal axis)19</td>
<td>Prolonged metabolism of opioids and benzodiazepines21</td>
</tr>
<tr>
<td>Less stress associated with pain22</td>
<td>Hyperalgesia23</td>
</tr>
<tr>
<td>Decreased neuronal cell death in the presence of pain24</td>
<td>Enhanced neuronal cell death25</td>
</tr>
<tr>
<td>Compassion26</td>
<td>Unknown effects of commonly used drugs</td>
</tr>
</tbody>
</table>
Almost all pain assessment scores have been developed for acute pain in neonates, but chronic pain is common and important for neonatal assessment. Assisted ventilation, necrotizing enterocolitis, and postsurgical trauma are all chronic painful conditions in need of treatment. To date, only two pain assessment tools have been validated for chronic neonatal pain: the Neonatal Pain and Discomfort Scale and the Echelle Douleur Inconfort Nouveau-Ne Scale. Although there are advocates for each of these pain scales, it is more important for providers to become familiar with at least one scale that can be used to assess acute and chronic pain and assess neonates of different gestational ages.

**NONPHARMACOLOGIC METHODS**

Nonpharmacologic pain treatment in neonates has been clearly demonstrated to relieve mild to moderate pain. The best studied techniques include nonnutritive sucking (with and without sucrose); breastfeeding; swaddling; kangaroo care (skin-to-skin contact); and massage therapy. Nonnutritive sucking and sucrose work by increasing endogenous endorphins. Although sucrose has been shown to enhance effectiveness, they have both been shown to decrease crying time and improve pain scores after acute mild pain, such as heel-stick pain. Sucrose is efficacious in reducing the pain from single events, such as retinopathy of prematurity screening, oral gastric tube insertion, and heel lance. However, sucrose is controversial when given repeatedly, possibly leading to adverse long-term outcomes. Kangaroo care, which was first used in developing countries to decrease neonatal mortality, has also been shown to relieve neonatal pain. Kangaroo care decreases the pain associated with single procedures, such as heel lance, but the magnitude of the effect is unknown. Swaddling decreases acute mild-to-moderate pain, such as the pain associated with heel-lance procedures. Massage therapy has been inadequately studied; however, it has shown promise in ameliorating heel-stick pain and it is effective in multisensorial stimulation. Nonpharmacologic techniques are safe and have
demonstrated effectiveness in relieving mild-to-moderate neonatal pain associated with single procedures. These methods generally require parental involvement; thus, family centered care in the NICU should be encouraged to ameliorate neonatal pain.

**PHARMACOLOGIC METHODS**

**Opioids**

Opioids are commonly used in modern NICUs. They provide procedural pain relief, such as for intubation premedication; relief from chronic pain, such as necrotizing enterocolitis; and ventilation. Several studies and reviews have pointed to the conclusion that they should be used selectively. A recent Cochrane review found insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. The Cochrane review looked at pain scales, and overall found that a significant effect on pain was found in the treatment group. No significant effect was found in favor of the treatment group with respect to neonatal mortality; duration of ventilation; neurodevelopmental outcome, short-term and long-term; incidence of severe intraventricular hemorrhage (IVH); any IVH; and periventricular leukomalacia (PVL). Given the likely long-term adverse consequences associated with the chronic pain and stress of mechanical ventilation, it is reassuring that short-term adverse effects are not more common in the opioid-treated groups.

**Morphine**

Morphine is the most frequently used opioid analgesic in all ages, and is the most commonly used drug for analgesia in ventilated neonates. Morphine has a slow onset of analgesia. Its mean onset of action is 5 minutes and the peak effect is at 15 minutes. It is metabolized in the liver into two active compounds: morphine-3-glucuronide and morphine-6-glucuronide. The former is an opioid antagonist, and the latter is a potent analgesic. Preterm infants mostly produce morphine-3-glucuronide, which explains why after 3 to 4 days of morphine therapy, the infant develops tolerance. Side-effects of morphine include hypotension in neonates with pre-existing hypotension and gestational age less than 26 weeks, prolonged need for assisted ventilation, and increased time to reach full feeds. Others have suggested that morphine may have a specific effect on pulmonary mechanics, possibly caused by undefined direct toxicity, such as histamine release or bronchospasm. Although commonly used, there is controversy as to whether morphine is effective in the treatment of acute pain.

Two large randomized studies have compared morphine with placebo in neonates. A randomized controlled trial conducted in the Netherlands compared the analgesic effect of morphine with placebo infusions for the duration of 7 days in 150 newborns who received mechanical ventilation. The findings of this study suggested that routine morphine infusion in preterm newborns who received ventilatory support neither improved pain relief nor protected against poor neurologic outcome, defined as severe IVH, PVL, or death within 28 days. The Neurologic Outcomes and Preemptive Analgesia in Neonates trial included ventilated preterm neonates from 16 centers in the United States and Europe. It compared the effect of morphine with placebo infusions, after a loading dose, on the neurologic outcomes of the ventilated neonates. The results suggested that continuous morphine infusion did not reduce early neurologic injury in ventilated preterm neonates, defined as severe IVH, PVL, or death. Hypotension did occur more frequently in the morphine versus the placebo group.

One study assessed the long-term outcome at 5 to 6 years of prematurely born children (<34 weeks of gestation) who by randomization received morphine in the
neonatal period to facilitate mechanical ventilation. This study looked at children from two trials. The first one included 95 infants who were randomly assigned to receive morphine alone, pancuronium alone, or morphine and pancuronium. The second trial included 21 infants who received morphine and 20 infants who received placebo. Each child was assessed using three scales: the full scale Weschler Preschool and Primary Scale of Intelligence, the Movement Assessment Battery for Children, and the Child Behavior Checklist. There were no adverse effects found on intelligence, motor function, or behavior.61

**Fentanyl**
Fentanyl is an opioid analgesic that is 50 to 100 times more potent than morphine.62 It is used frequently because of its ability to provide rapid analgesia.63 It may be used as a slow intravenous push every 2 to 4 hours or as a continuous infusion. Tolerance may develop and withdrawal symptoms may occur after 5 days or more of continuous infusions.62 In a masked randomized controlled trial, a single dose of fentanyl given to ventilated preterm newborns significantly reduced pain behaviors and changes in heart rate. It also increased growth hormone levels.64 In another study, fentanyl provided the same pain relief as morphine but with fewer side effects.65 In other studies, fentanyl use resulted in lower heart rates, behavioral stress scores, and pain scores compared with placebo; however, the infants receiving fentanyl required higher ventilator rates and peak inspiratory pressures at 24 hours.66 Fentanyl may also be used transdermally in patients with limited intravenous access. Side effects of fentanyl include bradycardia, chest wall rigidity, and opioid tolerance after prolonged therapy.

**Methadone**
Methadone is a potent analgesic with a rapid onset of action and prolonged effect.63 It has minimal side effects, high enteral bioavailability, and a low cost.

**Other opiates**
Other opiates include the short-acting drugs sufentanil, alfentanil, and remifentanil. All are useful for short procedures, such as intubation. Sufentanil and alfentanil are metabolized by the liver, which is immature in preterm neonates resulting in increased levels with repeated infusions, especially in preterm neonates.67 Remifentanil, however, is rapidly cleared by plasma esterases and is unaffected by the maturity of the liver enzyme system, making it attractive for short neonatal surgery or other procedures when rapid recovery is anticipated (Table 2).67

**Benzodiazepines**
The benzodiazepines are anxiolytic drugs that have limited analgesic effect but are commonly used in NICUs to produce sedation, muscle relaxation, and provide amnesia (in older patients), but they provide little analgesia. This class of drugs inhibits γ-aminobutyric acid A receptors.68 The main complications include myoclonic jerking, excessive sedation, respiratory depression, and occasional hypotension.

**Midazolam**
The most commonly used benzodiazepine in the NICU is midazolam. When administered with morphine, it has been shown to provide better sedation than morphine alone in ventilated patients, without adverse effects.69 The minimal effective dose for most neonates is 200 μg/kg with a maintenance dose of 100 μg/kg/h.70 Although it can be given orally, the bioavailability is only half that of intravenous midazolam in neonates.71 Intranasal midazolam has been shown to be effective for fundoscopic
examinations in older children, but this mode of delivery has not been tested in neonates. One recent review found no apparent clinical benefit of midazolam compared with opiates in mechanically ventilated neonates. Furthermore, midazolam was associated with worse short-term adverse effects (death, severe IVH, or PVL) in the NOPAIN trial compared with morphine alone. Midazolam seems to provide sedative effects in mechanically ventilated neonates, but it should be used with caution because of reported adverse effects, particularly when used alone. The decreased number of γ-aminobutyric acid A receptors in neonates compared with adults may contribute to the neonate’s risk of neuroexcitability and clonic activity that resembles and, in some cases may be, seizure activity. Finally, metabolism for these drugs occurs through glucuronidation (hydroxymidazolam) in the liver, and there is potential for decreased bilirubin metabolism, especially in asphyxiated or preterm newborns. Its half-life is only 30 to 60 minutes, but it may be prolonged in preterm and sick neonates. Thus, pharmacokinetic and pharmacodynamic data are unreliable in sick neonates and drug levels correlate poorly with sedative effects, so it should be titrated using a validated pain scale. Although there are relatively few studies to support the use of midazolam in neonates, it is common practice to use this drug as a sedative for ventilated neonates and for procedural pain. A Cochrane report described only three trials using this drug, which could not be combined for analysis because of different tools used to assess sedation. There are some concerns regarding the use of midazolam in neonates. One study reported an increased incidence of adverse short-term effects (IVH, PVL, or death) and a longer hospital stay associated with midazolam. Finally, midazolam has been associated with benzyl alcohol exposure. There have been no long-term studies describing benefit or harm with midazolam. It has been shown (along with morphine) to adhere to the tubing in patients on extracorporeal membrane oxygenation, increasing dosing requirements by 50% in those patients.

Lorazepam
Lorazepam has also been used in the intensive care nursery. Because it is a longer-acting drug than midazolam with a duration of action of 8 to 12 hours, it does not

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>Potent pain relief</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Better ventilator synchrony</td>
<td>Arterial hypotension</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>Constipation, nausea</td>
</tr>
<tr>
<td></td>
<td>Hypnosis</td>
<td>Urinary retention</td>
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<tr>
<td></td>
<td>Muscle relaxation</td>
<td>Central nervous system depression</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>Tolerance and dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term outcomes not studied</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged ventilator use</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Fast acting</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Less hypotension</td>
<td>Short half-life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quick tolerance and dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chest wall rigidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inadequately studied</td>
</tr>
<tr>
<td>Remifentanyl</td>
<td>Fast acting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Degraded in the plasma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unaffected by liver metabolism</td>
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</table>
have to be given as a drip or as frequently. It has been used successfully for seizure control in neonates who are refractory to phenobarbital and phenytoin despite its potential neuronal toxicity.\(^81\) It has been associated with propylene glycol exposure (Table 3).\(^79\)

**Barbiturates**

**Phenobarbital**

Phenobarbital is usually considered the drug of choice for seizure control. Despite animal evidence for antinociception, it is often used for analgesia.\(^82\) It is also used in conjunction with opioids for sedation,\(^16\) although there is little recent evidence that it is effective. Classically, it has been used for neonatal abstinence syndrome, but recent work by Ebner and coworkers\(^83\) demonstrates that opiates shorten the time required for treatment. However, because of its anticonvulsant effects, phenobarbital is an attractive adjunct for patients with seizures.

**Chloral Hydrate**

Chloral hydrate is commonly used in neonatal intensive care when sedation, particularly sleep, is required without analgesia. It is commonly used for radiologic procedures, electroencephalography, echocardiography, and dental procedures in older patients. It is converted to trichloroethanol, which is also metabolically active.\(^84\) A recent retrospective review found an increased incidence of apnea and desaturation in term neonates less than 1 month and in preterm neonates less than 60 weeks post-conceptual age who underwent magnetic resonance imaging.\(^85\) Thus, this drug should be used with caution in preterm and young term neonates.

**Propofol**

Propofol has become popular as an anesthetic agent for young children, but it has not been studied extensively in neonates.\(^86\)–\(^88\) One study compared propofol with morphine, atropine, and suxamethonium for intubation and found that propofol led

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Benzodiazepines</th>
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</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Better ventilator synchrony</td>
</tr>
<tr>
<td></td>
<td>Antianxiety</td>
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<tr>
<td></td>
<td>Sedation</td>
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<td>Hypnosis</td>
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<td></td>
<td>Muscle relaxation</td>
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<td></td>
<td>Amnesia</td>
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<td></td>
<td>Anticonvulsant</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Most studied benzodiazepine</td>
</tr>
<tr>
<td></td>
<td>Quickly metabolized</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Longer acting</td>
</tr>
<tr>
<td></td>
<td>Better anticonvulsant</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Not recommended in the neonate</td>
</tr>
</tbody>
</table>
to shorter intubation times, higher oxygen saturations, and less trauma than the combination regimen in neonates. However, propofol should be used with caution in young infants because clearance is inversely related to neonatal and postmenstrual age. There is significant interindividual variability in the pharmacokinetics of propofol in that population and its use has led to transient decreases in heart rate and oxygen saturation and more prolonged (60 minutes) hypotension.

**Ketamine**

Ketamine is a dissociative anesthetic that provides analgesia, amnesia, and sedation. Ketamine has been studied and used extensively in older children, but there have been few studies in newborns. Ketamine causes mild increases in blood pressure and heart rate, decreases in respiratory drive, and mild bronchodilation with minimal effects on cerebral blood flow, making it an attractive choice for some unstable hypotensive neonates requiring procedures, such as cannulation for extracorporeal membrane oxygenation. Doses for effective pain management of the pain caused by endotracheal suctioning in ventilated neonates were 2 mg/kg in one Finnish study. It has also been shown to decrease inflammatory cell death in the presence of pain in immature rodents in the author’s laboratory, which would also make it attractive for preterm neonates, although this has not been shown in human studies. Despite these theoretical advantages, ketamine is a potent anesthetic with minimal study in neonates. As such, it should only be used for highly invasive procedures.

**Acetaminophen**

Acetaminophen acts by inhibiting the cyclooxygenase (COX) enzymes in the brain, and it has been well studied in newborns. It is useful for mild pain, in conjunction with other pain relief, or after circumcision.

**Local Anesthetics**

**Lidocaine**

Lidocaine inhibits axonal transmission by blocking Na+ channels. Lidocaine is commonly used for penile blocks for circumcisions. In this circumstance, its use has demonstrated effectiveness in decreasing pain response to immunizations as long as 4 months after circumcision compared with neonates who received placebo. Compared with a dorsal penile root block or eutectic mixture of local anesthetics cream, the ring block has been shown to be the most effective means of pain relief for circumcision.

**Topical anesthetics**

Topical anesthetics have demonstrated effectiveness for certain types of procedural pain, such as venipuncture, lumbar puncture, or immunizations. Complications include methemoglobinemia and transient skin rashes. In preterm neonates with thin skin the concern for methemoglobinemia is accentuated. Unfortunately, topical anesthetics have not been effective in providing pain relief for the heel prick, one of the most common skin-breaking procedures, because of increased skin thickness. Newer topical anesthetics include 4% tetracaine and 4% liposomal lidocaine. Although the newer agents have a shorter onset of action, they are no more effective.

**COMMON PROCEDURES**

Common neonatal procedures and advantages and disadvantages of pain relief are summarized in Table 4.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Drugs</th>
<th>Advantages of Treatment</th>
<th>Disadvantages of Treatment</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation&lt;sup&gt;16,55,56,65&lt;/sup&gt;</td>
<td>Fentanyl (1–3 μg/kg), morphine (0.1 mg/kg), midazolam (0.1–0.2 mg/kg)</td>
<td>Improved ventilator synchrony, lower pain scores</td>
<td>Prolonged time on assisted ventilation, prolonged time to full feeds, increased bladder catheterization, hypotension</td>
<td>Use sedation as needed, not pre-emptively; Midazolam associated with adverse short-term effects in NOPAIN Trial</td>
</tr>
<tr>
<td>Circumcision&lt;sup&gt;98,102&lt;/sup&gt;</td>
<td>Lidocaine (1 mL), Eutectic mixture of local anesthetics</td>
<td>Less pain response up to 4 months postprocedure</td>
<td>Allergic reaction, bruising at injection site</td>
<td>Ring block is more effective than dorsal penile nerve root block</td>
</tr>
<tr>
<td>Heel lance&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Sucrose</td>
<td>Shorter crying, less changes in heart rate</td>
<td>None</td>
<td>Eutectic mixture of local anesthetics cream is not effective</td>
</tr>
<tr>
<td>Venipuncture, arterial puncture, lumbar puncture&lt;sup&gt;100,101&lt;/sup&gt;</td>
<td>Topical anesthetic (eutectic mixture of local anesthetics), sucrose</td>
<td>Lower premature infant pain profile scores, less crying</td>
<td>Local reaction, rare methemoglobinemia</td>
<td>Other nonpharmacologic treatments effective</td>
</tr>
<tr>
<td>Intubation&lt;sup&gt;52,53,89,104,105&lt;/sup&gt;</td>
<td>Morphine 0.1 mg/kg, fentanyl 1–3 μg/kg, remifentanil 1 mg/kg, midazolam 0.2 mg/kg, propofol 2–6 mg/kg, ketamine 1 mg/kg, suxamethonium 2 mg/kg</td>
<td>Shorter time to intubation, less trauma, less desaturation, better maintenance of vital signs</td>
<td>None</td>
<td>No accepted premedication Opiates most common class used</td>
</tr>
<tr>
<td>More invasive procedures, such as cannulation for extracorporeal membrane oxygenation&lt;sup&gt;106,107&lt;/sup&gt;</td>
<td>Propofol 2–6 mg/kg, ketamine 1 mg/kg, fentanyl 1–3 μg/kg</td>
<td>Maintenance of cardiovascular stability</td>
<td>Questionable neurotoxicity with ketamine</td>
<td>Ketamine may be neuroprotective</td>
</tr>
<tr>
<td>Postsurgical pain&lt;sup&gt;108&lt;/sup&gt;</td>
<td>Fentanyl 1–3 μg/kg, morphine 0.1 mg/kg, acetaminophen 15 mg/kg</td>
<td>Lowered neuroendocrine response, faster recovery</td>
<td>Respiratory depression, hypotension with opiates</td>
<td>Acetaminophen for mild pain only</td>
</tr>
<tr>
<td>Endotracheal suctioning&lt;sup&gt;70,109&lt;/sup&gt;</td>
<td>Midazolam 0.2 mg/kg, morphine 0.1 mg/kg, fentanyl 1–3 μg/kg</td>
<td>Anxiolytic</td>
<td>Respiratory depression, hypotension, dependence</td>
<td>Usually not treated</td>
</tr>
<tr>
<td>Imaging (magnetic resonance imaging)&lt;sup&gt;110&lt;/sup&gt;</td>
<td>Chloral hydrate 50–100 mg/kg</td>
<td>Sedation</td>
<td>Respiratory depression, hypotension</td>
<td>Chloral hydrate provides sedation only</td>
</tr>
</tbody>
</table>
FUTURE DIRECTIONS

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are used extensively for pain relief in children and adults but they are mainly used for patent ductus arteriosus closure in neonates. They act by inhibiting the COX enzymes (COX-1 and COX-2) responsible for converting arachidonic acid into prostaglandins, thus producing their analgesic, antipyretic, and anti-inflammatory effects. The analgesic effects of nonsteroidal anti-inflammatory drugs have not been studied in neonates, although ibuprofen and indomethacin have been studied for use in patent ductus arteriosus closure. Concern about side effects of renal dysfunction, platelet adhesiveness, and pulmonary hypertension has limited their study for this indication. However, ibuprofen has demonstrated beneficial effects on cerebral circulation in human studies and beneficial effects on the development of chronic lung disease in baboon experiments, making it an attractive analgesic in preterm neonates.

Nonpharmacologic Methods

Nonpharmacologic approaches, such as acupuncture and music, may be effective, but their use in acute pain relief needs further research. Music has beneficial effects on mothers, but it has not yet been shown to consistently relieve pain. Acupuncture has been studied extensively in older children and adults but it has not yet been studied in neonates. Acupuncture, especially electroacupuncture, has great potential to relieve neonatal pain, but it has also been inadequately studied.

Quality Improvement Approach

A suggested approach to evidence-based recommendations for the treatment of neonatal pain includes the following:

1. Recognition of neonatal pain as a valid concern
2. Recognition of acute procedural and chronic neonatal pain in need of treatment
3. Validated assessment tool for neonatal pain
4. Educational resources for caregivers and parents in the NICU
5. Protocolized stepwise treatment plan for the procedures and conditions encountered in the NICU using nonpharmacologic and pharmacologic approaches to treatment
6. Continued auditing to ascertain appropriate treatment for neonatal pain
7. A well-planned program of coordination, facilitation, and using local champions and project teams to elicit a beneficial change in practice.

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