Neonatal pain management

Tarun Bhalla[1,2], Ed Shepherd[3,4], Joseph D. Tobias[1,2,4]

[1]Departments of Anesthesiology and Pain Medicine and [3]Pediatrics, Nationwide Children's Hospital, [2]Departments of Anesthesiology and [4]Pediatrics, Ohio State University, Columbus, Ohio, U.S.

Address for correspondence:
Dr. Joseph D. Tobias,
Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205, USA.
E-mail: Joseph.Tobias@Nationwidechildrens.org

ABSTRACT

The past 2-3 decades have seen dramatic changes in the approach to pain management in the neonate. These practices started with refuting previously held misconceptions regarding nociception in preterm infants. Although neonates were initially thought to have limited response to painful stimuli, it was demonstrated that the developmental immaturity of the central nervous system makes the neonate more likely to feel pain. It was further demonstrated that untreated pain can have long-lasting physiologic and neurodevelopmental consequences. These concerns have resulted in a significant emphasis on improving and optimizing the techniques of analgesia for neonates and infants. The following article will review techniques for pain assessment, prevention, and treatment in this population with a specific focus on acute pain related to medical and surgical conditions.

Key words: *Neonatal anesthesia, neonatal pain management, opioids, pain scores*

INTRODUCTION

Several factors may be responsible for pain in the neonatal population, including mechanical ventilation, invasive procedures, repeated heel sticks for blood draws, postoperative issues, and acute medical illnesses, including necrotizing enterocolitis. The past 2-3 decades have seen many changes in the management of acute pain in the neonatal population. These changes began with the rejection of previously held misconceptions that neonates, infants, and children do not feel, experience, or react to pain such as adults because of the immaturity of their peripheral and central nervous system (CNS). These tenets, compounded by fears of addiction, concerns regarding the potential adverse effects of opioids, and the lack of effective pharmacokinetic data led to the under-treatment of pain in the operating room and during the perioperative period. However, such practices began to change after the publication of studies demonstrating that infants, children and adults experience similar levels of postoperative pain.[1-5] These studies showed that measurable alterations in physiologic and biochemical markers of stress existed following painful stimuli even in preterm infants.[1-5] In fact, when compared with the adult population, the changes in stress markers such as endogenous catecholamines and adrenocortical hormones were several-fold higher in neonates compared to their adult counterparts.[6,7]

Until recently, it was incorrectly thought that nociception was diminished in preterm infants due to the immaturity of their CNS. In fact, it now clear that skin receptors and sensory nerves around the mouth appear as early as the 7th week of gestation. Further, the immaturity of the CNS preferentially affects descending inhibitory pathways which modulate synapses in the dorsal horn of the spinal cord, which do not appear until the 32nd week of gestation. Thus, the developmental immaturity of the CNS potentially makes the preterm neonate more, rather than less, likely to feel pain. Aside from humanitarian and ethical concerns, the inadequate treatment of pain during infancy may have long-lasting physiologic and neurodevelopmental consequences, including increased susceptibility to chronic pain syndromes, and a heightened sensitivity to subsequent painful stimuli which may persist throughout childhood. During major surgical procedures including surgery for congenital heart disease, for instance, uncontrolled sympathetic stress responses can have significant deleterious effects on physiologic function and may impact outcome.[7-9] Data from the adult populations also suggest that inadequate analgesia may result in decreased tissue oxygenation due

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to vasoconstriction, leading to an increased incidence of wound infections.[10] Together, these concerns have resulted in a significant emphasis on improving and optimizing the techniques of analgesia for neonates and infants. The following article will review techniques for pain assessment, prevention, and treatment in this population with a specific focus on acute pain related to medical and surgical conditions.

PAIN ASSESSMENT

For patients able to communicate, self-report scales are the most commonly used and accepted method for pain assessment. Given that neonates are by nature unable to communicate, such techniques are not feasible, and clinicians must rely on alternative means of assessment. These assessments typically include a combination of subjective observations and objective signs that are then scored or scaled. Reliably determining levels of pain in neonates is remarkably difficult; indeed complexity of such assessment in this population are clearly demonstrated by the fact that there are more than 50 currently used pain scales.[11,12] These neonatal pain scores rely on a combination of behavioral observations (facial expression, body posture, tone, etc.) and physiologic parameters including heart rate, blood pressure, and oxygen saturation. Some data suggest that behavioral measures reflect pain specifically, while physiologic measures reflect generalized physiologic stress.[12-14] This lack of correlation between physiologic and behavioral responses to pain may be especially true in pre-term neonates.[15,16]

Some of the most commonly used pain assessment scales for neonates include premature infant pain profile, Children's Hospital of Eastern Ontario Pain Scale, children's and infants' postoperative pain scale, and crying, requires increased oxygen administration, increased vital signs, expression, and sleeplessness (CRIES). The reader is referred to references 17-21 for a more in-depth review of the various pain scales available for use in neonates and infants, as well as the advantages and disadvantages of the various techniques.,[17-21] One example of a simple, validated tool that can be applied during the bedside nursing routine is the CRIES scale which was first reported in 1995.[22] The tool is a 10-point scale, which the authors initially likened to the APGAR score. It is an acronym of five physiological and behavioral variables previously shown to be associated with neonatal pain.. As with pain assessment in other age groups, it is not the scale that matters, but , rather one's familiarity with it and the willingness to use it routinely. Our practice is to consider pain assessment as one of the vital signs and we require pain assessment whenever vital signs are otherwise obtained.

MEDICATIONS FOR ANALGESIA

Although generally well-studied in specific adult populations, there are limited studies evaluating the pharmacokinetics and pharmacodynamic properties of analgesic agents in critically ill-patients in general, and in neonates and infants in particular. The majority of pharmacokinetic studies are performed on healthy adult volunteers or postoperative patients and then extrapolated to the critical care population. In critically ill or unstable patients, there are likely be significant alterations in end-organ function, cardiorespiratory stability, volume of distribution, and metabolic processes; any of which can affect drug delivery, distribution, and elimination. The variability in the Neonatal Intensive Care Unit (NICU) patient can also include drug-drug interactions, end-organ (hepatic, renal) failure, malnutrition, low-plasma proteins with altered drug binding, as well as changes in uptake (of particular concern when using the nonintravenous [IV] route), distribution (due to alterations in cardiac output), total body water, and volume of distribution. While there are no clear guidelines to identify each of these problems and their eventual effects on the specific analgesic agent used, all should be considered when selecting a specific drug, choosing a dose, and the route of administration.

Acetaminophen and nonsteroidal antiinflammatory drug agents

As they have a limited adverse effect profile in regards to respiratory depression, there is great interest in the use of agents whose mechanism of action includes inhibition of prostaglandin formation. For moderate or severe pain, these agents are not used as the sole agent, but rather used as adjuncts to opioid analgesia. By doing so, the dose of opioid required is decreased thereby limiting opioid-related adverse effects. With acetaminophen, recent data suggest that previously used dosing regimens (10-15 mg/kg) administered per rectum result in inadequate plasma concentrations.[23,24] Based on these studies, Birmingham *et al*. showed that an initial loading dose of acetaminophen of 40 mg/kg, followed by 20 mg/kg every 6 h resulted in rapid attainment of analgesic plasma concentrations of 10-20 μg/ml; however, they also noted significant inter-patient variability.[23,24] Subsequently, a comprehensive review of the pharmacokinetics of acetaminophen based on six studies in neonates and infants was compiled by Anderson *et al*., with recommendations pertaining to the loading dose, maintenance and interval based on the route of administration (oral vs. rectal) and the available preparation.[25] Subsequently, IV acetaminophen was made available in the United States. It has been demonstrated that plasma concentrations within the

presumed analgesic threshold of 10-20 μg/ml at steady state can be achieved with dosing of 15 mg/kg every 6 h in term neonates.[26] Of note, the presence of unconjugated hyperbilirubinemia, was associated with a 40% reduction in acetaminophen clearance. The authors ultimately concluded that IV acetaminophen was an attractive agent for analgesia in neonates and that dosing should be based on gestational age. However, strict attention to dosing is required to prevent toxicity. With the introduction of a new IV preparation, there have already been reports of inadvertent overdosing of the 10 mg/ml solution resulting in 10-20-fold overdoses.[27] Our practice is to administer acetaminophen at scheduled intervals, not as needed, to patients with moderate to severe acute pain requiring opioid analgesia. As noted above, the purpose of this practice is to reduce opioid exposure and thereby opioid-related adverse effects.

The primary mechanism of action of non-steroidal antiinflammatory drugs (NSAIDs) resides in their ability to inhibit cyclooxygenase, the enzyme responsible for the production of prostaglandins. This occurs both in the CNS and the periphery. Since neonates and infants have immature hepatic enzyme systems and decreased glomerular filtration rates (GFRs), NSAIDs typically have a prolonged half-life. There are currently three NSAIDs available for IV administration in the United States: Indomethacin, ibuprofen, and ketorolac. The pharmacokinetics of ibuprofen and indomethacin have been well-studied in this population in the context of patent ductus arteriosus (PDA) closure,[28-32] but there are limited data investigating the analgesic effects of such therapies. In preterm infants with a PDA, the incidence of necrotizing enterocolitis and renal insufficiency may be less with ibuprofen than indomethacin, but prophylactic administration of indomethacin in high-risk infants is associated with a lower rate of severe intraventricular hemorrhage than ibuprofen.[28] Neither medication is associated with improvements in long-term outcomes when used to close the PDA.

Ketorolac is the most commonly used IV NSAID for analgesia in neonates and infants, but data regarding safety and efficacy is mostly anecdotal or retrospective. In one retrospective analysis including infants <6 months of age, ketorolac in doses ranging from 1 to 1.5 mg/kg/day, for up to 48 h, decreased morphine requirements following abdominal surgery (0.03 ± 0.03 vs. 0.14 ± 0.07 mg/kg/day, $P = 0.01$).[33] Despite its recognized effect on platelet and renal function, two groups of investigators reported no adverse outcomes when using ketorolac following surgery for congenital heart disease.[34,35] These studies included a slightly older population (age <6 months and median age of 10 months, respectively) and cohort sizes of 53 and 70, respectively. However, other studies have shown conflicting and perhaps more concerning results. In a retrospective review of 57 postsurgical neonates between 0 and 3 months of age, there was an increased risk of bleeding in those receiving ketorolac.[36] Of the 57 patients, 10 (17.2%) had a bleeding event. These patients received ketorolac at a mean age of 20.7 days with 70% receiving the drug at <14 days of age, whereas those without a bleeding event received ketorolac at a mean age of 31.9 days ($P = 0.04$). The authors concluded that infants younger than 21 days of life and <37 weeks gestation were at significantly increased risk for bleeding events and should not be candidates for ketorolac therapy. Given the paucity of trials of NSAID's in neonates and the potential for adverse effects (alterations in cerebral blood flow, intraventricular hemorrhage, platelet dysfunction, decreased GFR), the practitioner must carefully weigh the risks and benefits on a case-by-case basis. We would caution against their use in preterm infants and during the first few weeks of life. If such therapy is provided, there should be close observation for clinical signs of bleeding or deterioration of renal function. Future clinical trials are needed to define the role, efficacy and adverse effect profile of the NSAID's in general and the cyclooxygenase II specific inhibitors in particular in the control of acute pain in the neonatal population.

Opioid analgesia

Choice of opioid

The pharmacokinetics of opioids are significantly altered in the neonatal population, and there is significant inter-patient variability. In general, neonates have a lower plasma clearance, a higher volume of distribution, decreased protein binding resulting in a greater free fraction, and decreased renal clearance due to decreased GFR. These factors, compounded by alterations related to acute illnesses and prematurity and further changes in renal or hepatic clearance, will lead to altered opioid pharmacokinetics.[37-39] The immaturity of the blood-brain barrier also alters the potential of the more water soluble opioids (morphine) to cause respiratory depression.

The majority of clinical experience in the neonatal population is with either morphine or fentanyl. Morphine is dependent on hepatic metabolism for elimination resulting in the production of its primary metabolite, morphine-6-glucoronide (M6G). M6G has substantially greater analgesic and respiratory-depressant effects than morphine; these effects are typically blunted by its limited lipid solubility, except in the setting of decreased renal function where significant amounts of M6G can accumulate.

Following a single IV dose of morphine (0.1 mg/kg) to 20 neonates with a gestational age of 26-40 weeks, the

free fraction was 80% compared to 65-70% in adults and clearance was lower so that dosing at a 4-6 h interval was feasible.[37,38] Similar data were noted by Lynn and Slatery using continuous infusions of morphine ranging from 20 to 100 μg/kg/min.[39] Infants (birth weight >1500 g) who were 1-4 days of age had a longer elimination half-life (6.8 vs. 3.9 h) and decreased clearance (6.3 vs. 23.8 ml/min/kg) when compared to infants more than a week of age. As a follow-up, Lynn *et al.* evaluated the respiratory effects of morphine infusions in 30 patients ranging in age from 2 to 570 days.[40] Using CO_2 response curves, they noted respiratory depression with morphine levels >20 ng/ml. Within the ages studied, they noted no differences in morphine's effects on respiratory function. Given the decreased clearance and increased free fraction, longer dosing intervals (4-6 h) or decreased infusion rates (10-20 μg/kg/h) are recommended in neonates and young infants. The latter regimen allows for effective analgesia without impeding weaning from mechanical ventilation. In addition to providing adequate analgesia, morphine has been shown to effectively blunt the sympathetic response to pain, reducing stress hormone surges in neonates requiring endotracheal intubation and mechanical ventilation for hyaline membrane disease.[41]

Similar developmental alterations in pharmacokinetics have been reported for the synthetic opioids alfentanil and fentanyl.[42-44] One study of the pharmacokinetics of alfentanil in six-preterm infants versus nine older infants and children demonstrated a larger volume of distribution, decreased clearance, and a prolonged elimination half-life (525 ± 305 vs. 60 ± 11 min) in the preterm infants. Changes in pharmacokinetics related to immature hepatic enzyme systems are further compounded by alterations in hepatic blood flow related to surgical procedures. After major abdominal procedures associated with high intra-abdominal pressures (repair of gastroschisis or omphalocele), plasma fentanyl levels persisted with markedly prolonged clearance.[44,45] Given these concerns, close monitoring of respiratory function is mandatory whenever opioid analgesia is provided for neonates.

Remifentanil is a novel opioid with properties that make it a potentially attractive option for neonates and infants. Remifentanil is eliminated by nonspecific esterases and is not dependent on hepatic metabolism. This unique metabolism also means that elimination is not context-sensitive so that its duration of action is not affected by the duration of the infusion. These properties make it particularly useful agent for major surgical procedures when rapid awakening and tracheal extubation are desired; however, may limit its utility as a postoperative analgesic agent. The lack of residual postoperative effects have been clearly demonstrated in patients <8 weeks of age undergoing pyloromyotomy.[46,47] Following anesthetic induction and endotracheal intubation, a remifentanil infusion was started at 0.4 μg/kg/min along with 60% nitrous oxide in oxygen and adjusted as needed. When compared with patients receiving halothane for intraoperative anesthesia, there was no difference in intraoperative hemodynamic variables, time to tracheal extubation, post-anesthesia care unit discharge time, pain medication use, and adverse effects. Further, in those having a normal preoperative pneumogram, the postoperative study was normal in all patients who received remifentanil and abnormal in three patients who were anesthetized with halothane ($P = 0.04$). Remifentanil is also the only opioid with clinically similar clearance in all age ranges. Ross *et al.* evaluated remifentanil pharmacokinetics following a bolus dose of 5 μg/kg in patients ranging in age from 0 to 18 years.[48] The volume of distribution of remifentanil, like other opioids, was largest in the infants <2 months of age, but no difference was noted in half-life between the groups.

One major caveat in regard to all of the synthetic opioids is the rare, idiosyncratic effect of chest wall rigidity.[49-51] Chest wall rigidity occurs more commonly with large doses and rapid administration; however, our clinical experience suggests that this may be more common in neonates and infants and may occur even with small, analgesic doses (1-2 μg/kg).[49] Chest wall rigidity is thought to be mediated in part through gamma-amino butyric acid pathways at the spinal cord and basal ganglia levels via fentanyl binding to μ_1 and κ opioid receptors or cerulospinal noradrenergic pathways within the CNS. Clinical manifestations include rigidity of the respiratory musculature with associated decreased thoracic compliance and resultant hypoventilation, oxygen desaturation, hypercarbia, decreased tidal volume, and the need for sometimes substantially increased peak inflating pressures to achieve adequate mechanical ventilation.[50-52] Failure to intervene in severe cases can lead to profound hypoxemia, bradycardia, and eventual asystole. Other manifestations may include laryngospasm with inability to perform effective bag-mask ventilation and/or achieve endotracheal intubation. Although adherence to dosing guidelines recommending that the synthetic opioids be administered slowly and in small increments, while titrating to effect likely minimizes the risk, chest wall rigidity may still occur. Chest wall rigidity can often be treated with naloxone; however, rapid administration of a neuromuscular blocking agent and endotracheal intubation may be required. Therefore, naloxone, airway management equipment, and neuromuscular blocking agents should be immediately available anytime synthetic opioids are administered to neonates.

There is limited evidence-based medicine comparing the various opioids in the neonatal population. Given the safety profile, pharmacokinetic data and abundance of clinical experience with fentanyl and morphine in the neonatal population, these two agents remain the most commonly used opioids for acute pain management in neonates. In a patient with compromised cardiovascular status or at risk for pulmonary hypertension such as an infant with a large preoperative systemic to pulmonary shunt or a diaphragmatic hernia, the synthetic opioids (fentanyl, sufentanil) provide cardiovascular stability, beneficial effects on pulmonary vascular resistance, and blunting of the sympathetic stress. These agents may alter postoperative morbidity and mortality in high-risk patients following surgery for congenital heart disease.[8,9] None of the synthetic opioids (fentanyl, sufentanil, alfentanil), appear to have distinct, inherent advantages. Remifentanil, as discussed previously, is metabolized differently, with a resultant clinical half-life of 5-10 min, even in the neonatal population. An increasing body of literature with remifentanil shows it to be a promising agent in this age group for intraoperative surgical anesthesia as a means of limiting postoperative respiratory compromise. However, in such scenarios, alternative means of postoperative analgesia are needed. One additional use for remifentanil is to provide sedation for brief periods of time during endotracheal intubation while still allowing rapid awakening for tracheal extubation in patients who require 48-72 h of airway control following airway surgery.[53]

Opioid requirements are highly variable among NICU patients and, therefore, dosing recommendations for all opioids should be viewed as suggested starting doses. The practitioner must carefully titrate dosing to achieve the desired level of sedation or analgesia while avoiding adverse effects. Katz and Kelly, for instance, demonstrated significant inter-patient variability regarding opioid requirements of the ICU population[54] with adequate doses varying between 0.47 and 10.3 μg/kg/h. Given the potential for significant respiratory depression regardless of the clinical scenario, close monitoring of respiratory status with continuous cardiac monitoring and pulse oximetry is mandatory whenever opioids are administered to neonates and infants.

The IV route is optimal for most patients; however, in rare clinical situations non-IV routes may be necessary for the treatment of acute pain in the NICU setting. Drug incompatibilities may preclude IV administration in patients with limited IV access, for instance. In these scenarios, alternative routes of delivery such as subcutaneous administration may be employed for the delivery of morphine and fentanyl.[55]

REGIONAL ANESTHETIC TECHNIQUES

As in the adult population, there are several potential applications of regional anesthesia for intraoperative and postoperative care of the neonate, with the goal of minimizing exposure to the risks of general anesthesia and opioids. Interest in such practices started more than 50 years ago as spinal anesthesia provided a safer alternative to the potentially difficult task of providing general anesthesia to neonates.[56] This practice decreased as general anesthesia subsequently became safer in neonates, but regional anesthesia resurfaced in the 1980's as a means of avoiding general anesthesia and the risk of postoperative apnea in former preterm infants. More recently, data suggest that general anesthesia may be associated with accelerated neuronal apoptosis and adverse effects on eventual neurocognitive outcome in neonates has led to a renewed interest in regional anesthesia.[57,58]

Regional anesthesia for neonates generally consists of three of peripheral nerve blockade or neuraxial techniques (intrathecal opioids and epidural analgesia). These techniques can be used to replace general anesthesia, as an adjunct to decrease the intraoperative requirements for general anesthetic agents and thereby allow earlier tracheal extubation, for postoperative analgesia, and/or for the management of nonsurgical, acute pain. Several recent advances in equipment and ultrasound guidance have markedly improved the success rates of peripheral nerve blockade for infants.[59] Indeed, peripheral blockade may offer better safety profiles even than central techniques (caudal and epidural blockade).[60] However, given the limited number of peripheral procedures and a general lack of experience, the use of such techniques is limited in neonates.[61,62]

The caudal epidural block remains the most commonly used regional anesthetic technique in all pediatric age groups. This technique can be used to replace general anesthesia, as an adjunct to general anesthesia or for postoperative analgesia. This technique involves the placement of a needle into the epidural space through the sacrococcygeal ligament at the base of the sacrum (between the two sacral cornu). For postoperative analgesia, a single-shot technique is generally chosen using concentrations of ropivacaine or bupivacaine varying from 0.125% to 0.25%. Depending on the height of the block required, the volumes can be varied from 0.75 to 1.5 ml/kg. Lower volumes are used for penoscrotal surgery while higher volumes are needed for upper abdominal and umbilical procedures. Regardless of the volume and dose used, the total dose of bupivacaine or ropivacaine is generally limited to <3 mg/kg to limit

the risk of toxicity. Alternatively, when higher doses and concentrations are required (if caudal anesthesia is used instead of general anesthesia, for instance), chloroprocaine may be used.[63] This technique may also be used with general anesthesia for major abdominal procedures as a means of avoiding the use IV fentanyl and allowing for early tracheal extubation. Since chloroprocaine is metabolized by nonspecific esterase's, its metabolism is rapid even in the neonatal population thereby limiting the risk of toxicity with continuous infusions or repeated bolus dosing.

While caudal blockade provides effective anesthesia, use of a single-shot technique with will provide only 6-12 h of postoperative analgesia. Several options exist to prolong the duration of anesthesia, including the use of hydrophilic opioids like morphine or catheter techniques with continuous infusions. Despite the potential for late respiratory depression, clinical experience with epidural opioids in neonates and infants suggests that, with appropriate monitoring, these techniques can be used safely and effectively in our youngest patients. The dosing variations in the literature are significant with epidural morphine doses varying from 30 to 120 μg/kg. Our preference and the recent literature demonstrate effective analgesia and a limited adverse effect profile with the use of lower doses (30 μg/kg). When epidural opioids are administered in any age group, inpatient monitoring of respiratory function with continuous cardiac monitoring and pulse oximetry for 24 h is required. For neonates, this should occur in the NICU. Anecdotal experience also suggests the efficacy of intrathecal morphine in doses ranging from 10 to 20 μg/kg. Given its hydrophilic nature and the eventual cephalad spread that occurs, lumbar intrathecal morphine can be used to provide analgesia following upper abdominal and thoracic procedures.[64,65] With intrathecal morphine, the caveats for respiratory monitoring are the same as those for epidural opioids.

There is also increasing use of continuous catheter techniques in the neonatal population with placement at the level of surgical procedure and techniques that allow for threading of an epidural catheter from the caudal space to the desired level of the neuraxis.[66-68] These techniques allow the provision of analgesia beyond that provided by a single-shot caudal epidural (6-12 h) or neuraxial morphine (12-24 h). In the older pediatric population, epidural catheters are generally placed at the level of the surgical procedure; however, in the neonatal population, a catheter can be threaded from the caudal space to the lumbar or thoracic levels.[66-68] Given that there is some variability in the success of these techniques, a dye study should be considered postoperatively to verify placement. Alternatively, a radio-opaque catheter which can be identified on routine postoperative radiographs is also available or ultrasound guidance can be used as the catheter is threaded in a cephalad direction. Once placed, a continuous infusion of a dilute local anesthetic and a lipophilic opioid is generally used.

Any use of regional anesthesia in the neonatal population must take into consideration the potential for toxicity related to local anesthetic dosing whether by single shot or continuous infusion. As with most other drugs, the pharmacokinetics of local anesthetic agents can be quite variable in the neonatal population. The hepatic microsomal enzyme systems, although functional even in the preterm infant, do not attain adult levels until 1-3 months of age. In addition, decreases in binding proteins (α_1 acid glycoprotein) result in a greater free fraction and potentially increased risk of toxicity.[69,70] With single-shot techniques, attention to dosing is critical to ensure that the volume and concentrations result in a total dose of <3 mg/kg of either bupivacaine or ropivacaine. Furthermore, during administration, inadvertent systemic injection may occur. Early identification of such problems may be facilitated by the use of a test dose containing epinephrine.[71] Given the potential utility of intralipid in the treatment of local anesthetic toxicity, immediate access to intralipid is suggested whenever regional anesthetic techniques are employed.[72]

For continuous infusions, local anesthetic concerns include not only the initial bolus dose, but also the potential for accumulation following prolonged postoperative infusion. Given the potential for accumulation and local anesthetic toxicity, current recommendations suggest limiting the bupivacaine dose to 0.1-0.2 mg/kg/h with cessation of the infusion at 48 h.[73] More recent data suggest that the pharmacokinetics of ropivacaine in neonates and infants are more stable with limited risk of accumulation and thus it may be a better option.[74] Given concerns of toxicity, there has also been anecdotal clinical experience in the neonatal population with lidocaine as there is ready access to routine lidocaine plasma concentrations for monitoring. Alternatively, given its rapid metabolism by plasma esterases, chloroprocaine has also been used for continuous epidural analgesia in neonates.

CONCLUSIONS AND FUTURE PERSPECTIVES

Because of the diversity of patients and clinical scenarios presenting in the NICU, a cookbook approach to acute pain management and analgesia is impossible.

Provision of effective analgesia is best accomplished by a combination of nonpharmacologic and pharmacologic techniques, and dosing of analgesic agents should be guided by an age-appropriate pain assessment scale. Options for pharmacologic management include agents to inhibit prostaglandin production (acetaminophen and the NSAIDs), opioids and regional anesthetic techniques. Given the age and developmental variations, an understanding of the differences in the pharmacokinetics of these agents in the neonatal population is necessary. The pharmacokinetics and pharmacodynamics of these agents may be affected by the unique physiology of the neonate, gestational age, chronological age, the surgical procedure itself, associated co-morbid conditions, and drug-drug interactions. Given the limited data in the neonatal patient, further pharmacokinetic investigations are needed. Although opioids remain the primary analgesic regimen, there are several options for regional anesthesia in neonates. The safe use of regional anesthesia in the neonate requires appropriate experience and training, use of proper and age-appropriate equipment, and attention to local anesthetic doses to avoid adverse effects.

Future studies are needed to better quantify the adverse effects of untreated pain on neonates and infants to further emphasize the important role of analgesia in this population. Given the developmental aspects of organ development, clinical trials are needed todefine the pharmacokinetics of the various agents reviewed in this manuscript and their role in acute pain management in neonates. Clinical trials comparing various regimens are needed to define the optimal modality and techniques for acute pain management.

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