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Neonatal pain management

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ABSTRACT

Pain management in the neonatal ICU remains challenging for many clinicians and in many complex care circumstances. The authors review general pain management principles and address the use of pain scales, non-pharmacologic management, and various agents that may be useful in general neonatal practice, procedurally, or at the end of life. Chronic pain and neonatal abstinence are also noted.

Introduction

We will do everything we can to keep him comfortable.

This sentiment is often articulated by clinicians in an attempt to provide families with a sense of reassurance to patients and families at the end of life (EOL). However, a neonatal patient can pose unique challenges that may diminish the clinician's confidence in achieving this goal. The non-verbal nature of the neonate forces reliance on any of a multitude of semi-objective pain scales to interpret the degree of discomfort and provides no means for assessing other common EOL symptoms, such as air hunger or agitation. Even though today the majority of neonatal deaths occur after the withdrawal of life support[1] evidence-based literature regarding neonatal pain management at the EOL remains sparse.[2] Nonetheless, both provider and parental perception of pain control is a crucial component in their overall EOL experience.[3]

Pain management is certainly not reserved only for the dying neonate and many of the goals and principles of palliative care—including pain control—are universally applicable in the neonatal intensive care unit (NICU). We will broadly review neonatal pain management options and strategies for the NICU population as a whole, with discussion of assessment of pain, acute versus chronic pain, neonatal abstinence syndrome, and EOL care.

Pain assessment

Frequent, accurate, objective assessment of pain is the first fundamental step in achieving adequate pain control in any patient population. Since the Joint Commission on Accreditation of Healthcare Organizations released their 2000–2001 pain management standards,[4] great attention has been paid to pain assessment with many entities adopting pain as the fifth vital sign. The NICU was not exempt from this movement and a myriad of pain assessment tools have since been developed. Reliance on a quality pain assessment tool is desirable in caring for the uniformly non-verbal neonatal population. Multimodal assessments appear to be most informative. In these tools, facial expressions (grimace), physiologic measurements (vital signs such as heart rate and blood pressure, respiratory rate, and pulse-oximetry readings/oxygen requirement), and behavioral components (crying/consolability or motor activity), are often combined to develop a pain score. Commonly used pain assessment tools include as follows:

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- CHIPS: children's and infants' post-operative pain scale.
- COMFORT: alertness, calmness/agitation, respirations, physical movement, heart rate, blood pressure, muscle tone, and facial tension.
- CRIES: cry, requirement for more oxygen, increased vital signs, expression, and sleeplessness.
- FLACC: face, legs, activity, cry, and consolability.
- MAPS: multidimensional assessment of pain scale.
- N-PASS: neonatal pain, agitation, and sedation scale.
- NIPS: neonatal infant pain scale.
- PIPP: premature infant pain profile.
- VAS: visual analog scale.

A recent review of these neonatal pain scale from a palliative care perspective states that current evidence is insufficient to recommend one pain scale over another. All cited studies were able to demonstrate a statistically significant decline in pain scores following the administration of pain medication, likely indicating that all scales are valid for pain evaluation.[5] There may be added benefit to a scale that assesses not only pain/discomfort, but also the level of sedation (i.e., N-PASS). Ultimately, when choosing a pain assessment tool, buy-in from all disciplines as well as the clinician's comfort level and familiarity with scoring, is vital to ensuring standardized assessment and discussion of pain across all neonatal health care providers.

Importantly, assessment of pain, and decisions to act upon such assessment, are interactive phenomena laced with the potential for individual behavioral and social nuances (knowledge about pain and its expression, sensitivities to the patient, and attitudes or biases regarding pain and its validity), that may facilitate excellent pain assessment and management—or not. Such factors variably impact each context and episode of pain and a caregiver's predisposition to treat it by reducing environmental stressors and noxious stimuli, providing a supportive environment or employing the use of pharmacologic agents. Furthermore, an initial assessment of pain and provision of treatment must be met with a follow-up assessment that the pain has been sufficiently reduced.[6] Beliefs about pain at the EOL or upon the withdrawal of life-support technologies may be facilitators or barriers to the provision of comfort, the reduction of agitation, and the relief of pain.

Pain management

Infants born at less than 32-weeks' gestation are exposed to numerous painful procedures every day, especially in the first 2 weeks of life.[7] Unfortunately, in many of these painful procedure, pain is left untreated.[8,9] With the multitude of treatment options and modalities available, leaving pain untreated or under-treated is not clinically defensible and may be considered unethical.[10,11]

Opioids

Opioids can be used for a variety of pain management circumstances in the NICU, including procedural pain, operative and post-operative pain, chronic pain and during ventilation.[12] Choice of agent, dose, route of administration and continuous vs. intermittent dosing are all decisions facing the medical team when prescribing opioid analgesia and varying, limited degrees of evidence are available to guide them. Potential side effects must also be taken into account. Fentanyl and morphine, the two most commonly prescribed opiates in the NICU, have both similar and distinctive side effects. Compared to morphine, fentanyl is more potent and possesses a more rapid onset of action, but has a shorter half-life. Additionally, there is a recognized risk of chest wall rigidity with fentanyl that is not seen with morphine. Chest wall rigidity typically occurs in $<10\%$ of patients and tends to be seen with higher bolus doses.[13] Bolus fentanyl dosing may also be associated with an increase incidence of apnea compared to continuous infusions.[14] Intranasal fentanyl provides an additional route of administration for neonates that do not have established intravenous access. While empirical evidence is limited, intranasal administration appears to be an effective and safe means to provide palliative pain control.[15]

Respiratory depression is also a known side effect with morphine analgesia, but it has been reported far less frequently than with fentanyl. In a study by Bouwmeester,[16] only 11 episodes of respiratory insufficiency occurred in 204 patients receiving morphine. Continuous morphine infusions have not been shown to achieve better pain control than intermittent dosing in the neonatal population.[17,18] Nevertheless, when chosen for sedation in ventilated newborns, morphine is typically prescribed as a continuous IV infusion.[19] A small number of patients who have received continuous morphine infusion may develop hyperalgesia and even myoclonus, which can be treated with conversion to methadone and concomitant treatment with clonidine.[20]

In EOL care, both the clinical circumstance and logistics of administration must be taken into account when choosing a dosing regimen for particular patients. Morphine use is very common in the EOL care of newborns for whom life-support technologies are withdrawn[21–24] but is generally not felt to hasten death.[25,26] Its beneficial effects are both sedation and analgesia and among populations who are communicative—both children and adults—there is a reduction in apparent dyspnea.[27–29]

Sedatives/anxiolytics

Midazolam or lorazepam may be used as sedatives or as an adjunct to the analgesic effects of opiates both in everyday care and more specifically at the EOL in many newborns. Up to 10% of infant receiving midazolam, and potentially other benzodiazepines, may experience myoclonic jerking or pseudoseizures.[30] The myoclonic jerking seen with benzodiazepine use in neonates may be secondary to hypoxic injury or immaturity of the central nervous system.[30] Although benzodiazepines cannot be recommended as sole agents for routine sedation[31] in conjunction with opioids, they provide the added benefit of mitigating anxiety and agitation. While these symptoms are clearly reported in older patient populations, means to objectively assess anxiety in the neonate are often lacking. For this reason, the NICU clinician must first address

the patient's airway position and its patency; the patient's positioning; and the effectiveness of the particular mode of assisted ventilation before simply prescribing an anxiolytic for observed agitation. These agents can be given orally, intravenously, across the buccal mucosa, or by the intranasal route. Intranasal midazolam provides effective control of seizures, which might be of use in EOL care for a patient who has no intravenous access or who cannot take enteral anti-epileptics. A single French study reports that intranasal midazolam provides rapid and effective sedation when used as a premedication for tracheal intubation in the delivery room.[32]

Barbiturates may also be of use in treating anxiety and agitation, though they are not analgesics. While great familiarity with phenobarbital exists in the NICU, it has not been expressly studied as an EOL sedative and its half-life is very long. Shorter acting barbiturates such as pentobarbital may be given intravenously or orally and their effects are generally more profound than what is seen with phenobarbital except when the latter is used at very high doses. Pentobarbital can be safely administered and has a wide dosage range when given as an IV infusion. Phenobarbital or pentobarbital may be of help in chronically managed patients, but their impact on certain hepatic enzymes and the metabolic clearance of other drugs must be kept in mind. Tobias reported the use of pentobarbital as a primary mode of sedation in 50 children (aged 1 month to 14 years) after lengthy management on opioids and benzodiazepines proved ineffective, likely due to tolerance.[33] Finally, it is important that some persons may be uncomfortable with the use pentobarbital at EOL as it has been used in euthanasia protocols around the world. Great clarity in the rationale for its use, and understanding by caregivers and families alike, should be sought when it is used.

Acetaminophen and non-steroidal anti-inflammatory (NSAID) agents

Studies examining the effect of acetaminophen and NSAIDs on opioid analgesic needs have demonstrated somewhat mixed results. Van der Marel et al.[34] did not find a statistically significant difference in morphine consumption when rectal acetaminophen was given to infants on a scheduled basis following thoracic or abdominal surgery. However, Hong et al.[35] showed that IV ketorolac and acetaminophen administration during induction anesthesia for inguinal hernia repair was superior to placebo when evaluating post-operative fentanyl consumption and post-operative pain scores. Hong's study did occur in a slightly older patient population and in an outpatient setting, which may impact its validity in the NICU population. Recent evidence also speaks to the utility of IV acetaminophen (paracetamol) as an adjunctive therapy in the setting of major surgery.[36] At the EOL, newborns may receive acetaminophen orally or rectally for mild-to-moderate pain, or as an antipyretic. Data are lacking on the efficacy of NSAIDs for newborns more broadly at the end of life.

Ketamine

In recent years, the role of ketamine as a procedural analgesic or as an adjunct in operative and perioperative care has received some attention. It has anxiolytic, analgesic, and amnestic effects but is not used routinely in the NICU across most of North America. It has been employed as a premedication for tracheal intubation, eye examinations, dressing changes in epidermolysis bullosa, and in certain settings addressing chronic pain.[37,38] A single report suggests efficacy of an intranasal dosing route in adults.[39] To date, it has no specific use in EOL care in the NICU.

Dexmedetomidine and propofol

Principally used in sedation protocols, dexmedetomidine often reduces the need for concomitant opioid use. It is a central alpha-2 adrenergic agonist, requires IV access, and has a brief half-life (2 h). It does provide analgesic and anxiolytic effects and is a welcome addition to pediatric ICU and NICU regimens in recent years.[40] The greatest experience with this agent appears to be in the post-operative management of newborns and infants in the Cardiac ICU where it has been nicely studied for both its hemodynamic and respiratory effects.[41] In EOL settings, dexmedetomidine might be helpful if there is concern about opioid-mediated respiratory depression since the drug has limited effects on respiratory drive. This has not been studied, however, and no recommendation can currently be made.

The same may be said about propofol, another IV short-acting and non-respiratory suppressive sedative/analgesic. In limited studies, however, there is notable variability in response to bolus dosing with propofol and again, no recommendation can currently be made.[42]

Gabapentin

This agent, has recently been demonstrated to be of use in neurologically impaired infants and those with neuro-irritability, chronic pain, and suspected viscero-hyperalgesia. It has been associated with reduced opioid and sedative/anxiolytic use and been beneficial in certain painful procedures (e.g., dressing changes in epidermolysis bullosa).[43,44]

Non-pharmacological interventions

For mild and moderate pain, non-pharmacological methods of pain control are safe and important interventions in the NICU. Non-pharmacological options include swaddling, kangaroo (skin-to-skin) care, non-nutritive sucking, breastfeeding, and massage. Non-nutritive sucking, with or without the addition of sucrose, can improve pain scores and decrease crying time following acute episodes of mild pain, such as heel sticks, oral gastric tube insertion, or ROP screening. This effect is achieved by increasing the release of endogenous endorphins.[12] Additionally, a reduction in noxious stimuli—irritant touch, bright lights, noise—also should be pursued to mitigate pain and agitation of babies in the NICU. How procedures are performed, when they are performed, and whether or not they are necessary should all be considered part of non-pharmacologic pain management in the NICU. Following a redirection of care goals toward palliation, procedures should be minimized or not pursued unless they truly bring comfort or give symptom relief for dying

newborns. At the EOL, parents should be allowed to hold their infant—swaddled or skin-to-skin—as they desire and be supported in the provision of comforting touch, sounds and suckling if considered beneficial.

Special populations and circumstances

The chronic NICU patient

The identification and management of chronic pain is important in NICUs where long-term patients are treated. In particular, palliative clinicians and neonatologists alike should be aware of the specific benefits of using methadone, ketamine, or gabapentin in managing such patients and providing for long-term comfort in complex patients. Generally, chronic pain is a concern in newborns and young infants who receive long-term assisted ventilation (greater than 30 days), experience multiple invasive interventions or surgical procedures, or who exhibit refractory hyperalgesia (including viscero-hyperalgesia), neuro-irritability, disrupted sleep, or agitation. These patients may have neuropathic pain, which is generally due to nerve injury or some underlying neurologic disease state. Alternatively, they may have had other systemic disorders that impact their nervous system pathways, responses, and development. Many such patients have been managed with opioids and benzodiazepines for lengthy periods, at times resulting in hyperalgesia. Consequently, a rotation of opioids, or an assessment of opioid or benzodiazepine withdrawal should be made.

While no specific or singular definition of chronic pain in the neonate exists,[45] certain patients have been reported to have benefited from pharmacologic management that addresses the NMDA (N-methyl-D-aspartate) receptor. This receptor is the locus of action for ketamine and methadone both. Hence, these drugs may be beneficial in trying to break the cycle of chronic pain. Methadone can be given intravenously or enterally with good bioavailability. Ketamine, again not a commonly used drug in neonatal units across North America, has proven efficacy intravenously, and also may be given enterally to treat chronic pain. Gabapentin has also been used successfully to treat neuropathic and chronic pain in newborns and infants.[44]

Neonatal abstinence syndrome

Patient receiving opioids for greater than 7–10 days often develop physiologic tolerance, requiring escalation of doses in order to attain the desired effect of sedation or analgesia. This phenomenon occurs more rapidly with fentanyl than it does with morphine.[46] When attempts are made to wean the opioid, opioid withdrawal ensues, with readily identified characteristics and generally requires a resumption of an opioid to be treated. The most widely recognized manifestation of this in the newborn and young infant is called neonatal abstinence syndrome (NAS), which occurs after a newborn is delivered of a woman who has used opioids throughout the latter part of gestation, or upon the iatrogenic receipt of opioids while in the ICU.[47] The development of tolerance and the interaction of the opioid analgesic on the central nervous system can be anticipated and treated with a variety of medications. Recent experience indicates that opioid withdrawal is best treated with an opioid (not a benzodiazepine or barbiturate). Consequently, protocols routinely employ the use of intravenous or oral morphine, methadone (due to its longer half-life, bioavailability, and beneficial effect on neuropathic pain), or more recently buprenorphine.[48–50] In addition, the adjunctive use of clonidine may prove helpful in reducing many of the centrally mediated sympathetic and neuroendocrine manifestations of opioid withdrawal.[51,52]

The dying neonate

Often, caregivers may express concern or feel uncomfortable administering various analgesics to a dying neonate, particularly if participation in palliative care is not their norm. An underlying fear that the provider is contributing to, or in some way facilitating, the infant's death may be present. Partridge and Wall[25] reported as early as 1997 that infants receiving adequate pain control at the time of life-support withdrawal spent more time alive than did those patients who were not adequately treated. Chan et al.[53] found that the use of anxiolytics similarly increased time spent alive following discontinuation of ventilator support. Ethically, the rule of double effect is applicable in this setting—so long as the intent is to do good, foreseeable yet undesirable consequences are acceptable. If the goal is to minimize pain and suffering for the dying neonate, subsequent unintended respiratory depression is ethically acceptable.[54] The rule (or doctrine) of double effect originates from the Catholic tradition of moral philosophy and theology. Its applicability is not uniformly agreed upon by some clinicians and ethicists in certain contexts of palliative care. While some clinicians still feel uncomfortable with medication dosing that risks respiratory depression —even at the EOL[55]—it remains important to parents that their dying newborn or young infant not experience pain.

Informed providers, educated in pain assessment and pain management, as well as palliative care precepts, are inclined to be present through the dying process and can confidently assist and assure parents that their loved one is not being abandoned. When treatment goals have become primarily palliative, rather than life-sustaining clinicians should help parents understand and anticipate changes in the baby's tone, color, perfusion, temperature, and responsiveness. Anticipated changes in the baby's respiratory pattern are important to share and facilitating parental use of oral or pharyngeal suction is generally valued. Parents who are accompanied through this time with staff that can inform and assist them in providing EOL care often express gratitude and tend to evidence less complicated grief.[56]

Conclusion

The anticipation of pain and agitation for certain newborns and young infants being withdrawn from life-sustaining technologies should be a part of the neonatologist's and palliative clinician's approach to patients at the EOL. The fundamental desire for all persons not to die alone or in pain is as present in the NICU as anywhere. Parents need the

surety that their baby is comfortable, that they can be present and provide comforting touch and interactions at the EOL, and that pain and agitation are treated effectively. Today there is greater knowledge about all drugs used in the NICU than at any time in recent decades, yet barriers remain to effective pain assessment and management. Informed and educated clinicians can help shape policy and broaden the impact of daily pain management as well as effective EOL comfort for vulnerable patients and their families.

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