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Review Article

Acute perioperative pain in neonates: An evidence-based review of neurophysiology and management

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ABSTRACT

Current literature lacks systematic data on acute perioperative pain management in neonates and mainly focuses only on procedural pain management. In the current review, the neurophysiological basis of neonatal pain perception and the role of different analgesic drugs and techniques in perioperative pain management in neonates are systematically reviewed. Intravenous opioids such as morphine or fentanyl as either intermittent bolus or continuous infusion remain the most common modality for the treatment of perioperative pain. Paracetamol has a promising role in decreasing opioid requirement. However, routine use of ketorolac or other nonsteroidal anti-inflammatory drugs is not usually recommended. Epidural analgesia is safe in experienced hands and provides several benefits over systemic opioids such as early extubation and early return of bowel function.

1. Introduction

Pain is the most common complaint when a patient presents to a physician. Pain management in neonates warrants special consideration because the present knowledge of developmental neurophysiology is improving every day. Neonates are a special group of the population where a fine balance between optimal pain relief and adverse drug effects is of utmost importance. With the advancement of various surgical techniques and improved perioperative care, an increasing number of sick neonates undergo surgery, and optimal perioperative pain management may improve clinical outcomes in these neonates. In this evidence-based review, we have reviewed the neurophysiology of neonatal pain perception, long-term effects of suboptimal pain relief, and role of various drugs and techniques used in acute perioperative pain management in neonates.

2. Methods

Electronic searches were performed in MEDLINE, PubMed Central, Embase, and Scopus using the keywords “neonate”, “postoperative”, “pain”, and “acute pain”. The following professional society/organization’s web-based guidelines were also searched “Association of Pediatric Anesthesiologists”, “American Association of Pediatrics”, and “British Pain Society”.

The level of evidences (LOEs) was decided according to the following guidelines[1]:

Level I: Evidence obtained from at least one properly designed randomized controlled trial (RCT).
Level II-1: Evidence obtained from well-designed controlled trials without randomization.
Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

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3. Developmental neurobiology of pain

The immature nervous system develops from early gestation and continues to change in the postnatal period. Nociception involves peripheral sensory receptors, afferent sensory nerve fibers, the spinal dorsal horn, spinothalamic and thalamocortical tracts, and the sensory cortex. During maturation, C-fiber projections are the last group of primary afferents to enter the dorsal gray matter, after proprioceptive and low-threshold A fibers. By Week 30, nerve tracts are myelinated up to the thalamic level. Afferent neurons in the thalamus project axons migrating into the neocortex. Synaptic connections of these thalamocortical tracts might occur at 24 weeks' gestation. After reviewing the literature, Lee et al[2] concluded that direct thalamocortical fibers that are not specific for pain begin to emerge between 21 and 28 weeks' developmental age (23 and 30 weeks' gestational age). Fitzgerald stated that most pain responses in preterm infants, <32 weeks of age, including facial expressions, seem to be largely subcortical.[3] Involvement of fetal cerebral cortex in pain pathway may be minimal and predominantly brain stem is important.[4] However, premature neonates show behavioral and physiological reactions and hormonal stress responses to painful stimuli, and intravenous fentanyl has been found to attenuate the fetal stress response to intrahepatic vein needling (LOE II-3).[5]

4. Why should pain in neonates be treated?

Neonates in a hospital are routinely subjected to various degrees of painful procedures from very early in their lives ranging from venipuncture to major surgery. Apart from ethical reasons and expectation of the parents, there are several long-term and short-term effects of poorly managed acute pain in neonates.

Neonates, even the premature ones, also feel pain and elicit stress response, which was first scientifically described in a landmark study by Anand et al[6] in 1987. They also concluded that blunting the stress response by fentanyl may be associated with improved outcomes. Subsequently in 1992, Anand and Hickey[7] showed that management of postoperative pain after cardiac surgery by potent opioids is associated with improved outcomes. The stress response, activated by afferent neuronal impulses from the site of injury, was found to be greater in magnitude but shorter in duration in neonates compared with adults during the same operation.[8] The stress response initiates a series of metabolic changes leading to catabolism of protein, fat, and carbohydrate. In premature or sick infants, this might cause metabolic acidosis, hypoglycemia, hyperglycemia, and electrolyte imbalances leading to increased morbidity and mortality.[9]

Altered and heightened pain responses in the subsequent painful procedures are the most common long-term effect (LOE II-1),[10,11] and this may persist until adolescence[12] (LOE II-2). A proper analgesic regimen may also prevent heightened pain response.[10] Behavioral response may also be altered by stress exposure in the neonatal intensive care unit (NICU).[13] The current consensus is that neonatal pain must be managed regardless of their age and severity of coexisting illness.[14]

5. Neonates feel more pain than their older counterparts

Clinical and laboratory investigations of neonatal pain suggest that preterm neonates have an increased sensitivity to pain.[15] Anatomic studies have shown that the density of nociceptive nerve endings in the skin of newborns is similar to or greater than that in adult skin.[16] Lack of myelination was suggested as an argument to support the hypothesis that neonates are not capable of perceiving pain. However, nociceptive impulses in the peripheral nerves are conducted through unmyelinated (C fibers) and thinly myelinated fibers (A-δ fibers).[17] Lower pain thresholds and the lack of inhibitory controls contribute to hypersensitivity in the most premature neonates. Repeated tactile stimulation leads to a significant lowering of the threshold (sensitization) in neonates up to 35 weeks' postconceptional age (PCA).[18] The low pain threshold in preterm neonates is accentuated by an increased excitability of nociceptive neurons in the dorsal horn of the spinal cord after exposure to any painful stimulus (wind-up phenomenon). In neonates, prolonged activity in the nociceptive pathways may be perceived as chronic noxious stimulation.

6. Preoperative issues

An appropriate pain management plan should be formulated in the preoperative visit and communicated to the parents to minimize their anxiety. Unnecessary laboratory investigations should be avoided to minimize pain associated with invasive procedures. Fasting period beyond the stipulated guidelines should not be extended to avoid unnecessary discomfort. Patient's present clinical conditions, presence of other coexisting medical illness, nature of the surgical procedure to be done, and the area where the neonate will be managed in the postoperative period should be taken into consideration.

For blood sampling, the heel is preferable, as it is less painful (LOE I) and mother should be encouraged to breast-feed the baby whenever feasible or sucrose solution should be used (LOE I). Topical anesthesia (LOE I) or morphine (LOE II) alone is insufficient for lancinating pain. However, a topical local anesthetic cream (eutectic mixture of local anesthetic) may be used during venous/arterial puncture and insertion of peripherally inserted central catheter in neonates aged more than 26 weeks and it is safe in single dose (LOE I).[19]

Since then, numerous studies and reviews have addressed the issue of procedural pain in neonates, and the primary aim of this article is to highlight acute postoperative pain.

7. Assessment of pain in neonates

Because preverbal age children are not able to vocalize, the anesthesiologist has to rely on behavioral and physiological markers of acute pain. Various reliable pain measures exist to assess pain in full-term and preterm neonates. Behavioral indicators of pain (e.g., crying, facial activity, body language, complex behavioral responses) and physiological indicators of pain (e.g., changes in heart rate, respiratory rate, blood pressure, oxygen saturation, vagal tone, palmar sweating, and plasma cortisol or catecholamine levels) can be used to assess pain in neonates.

7.1. Behavioral indicators

Facial expression is regarded as the most sensitive indicator of acute and short-term pain in neonates. Total facial activity and a cluster of specific facial features (brow bulge, eye squeeze, nasolabial furrow, and open mouth) have been shown to be significantly associated with acute and postoperative pain.[20] Body movement as a pain indicator focuses on the observation of arm and leg activities. Increased activity is thought to indicate more pain. Posture and muscle tone are thought to be tenser when pain is present. Cry features have been extensively studied using spectrographic devices. Short latency to onset of cry, longer duration of the first cry cycle, higher fundamental frequency, and greater intensity in the upper ranges are pain-specific cry features.[21]