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Pharmacologic Management of Pain in Intraoperative and Postoperative Periods in Pediatric Practice

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ABSTRACT

Pain management, along with the prevention of infectious complications, is among the primary objectives of the perioperative period. In infants and newborns, intense pain triggers a stress response. In similar surgical interventions, the stress response activated by afferent neuronal impulses from the site of injury in newborns is greater in magnitude but shorter compared with that in adults. Effective analgesia with opioids during cardiac surgery has been shown to improve surgical outcomes. Prolonged, high-intensity pain in a newborn with ineffective analgesia leads to the progression of such pathological conditions as hypoxia, metabolic acidosis, impaired liver and kidney function, an increased risk of sepsis, disseminated intravascular coagulation, and higher neonatal mortality. At present, the capabilities of traditional analgesia methods remain limited. In this regard, the main approaches to improving the efficacy of pain management in pediatric practice include various regimens combining non-opioid analgesics, supplemented with opioids if necessary, as well as the development of new effective and safe pharmacologic agents with analgesic activity.

Keywords: pain; perioperative analgesia; newborns; drug therapy; analgesics.

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Фармакологическая коррекция боли в интра- и послеоперационном периодах в педиатрической практике

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АННОТАЦИЯ

Обезболивание наряду с профилактикой инфекционных осложнений — основные задачи периоперационного периода. Известно, что у детей раннего возраста и новорожденных в ответ на интенсивную боль формируется стрессорная реакция. При аналогичных оперативных вмешательствах стресс-реакция, активируемая афферентными импульсами нейронов из места повреждения у новорожденных, является большей по величине, но меньшей по продолжительности, по сравнению со взрослыми. Показано, что эффективная аналгезия во время кардиохирургических операций с применением опиоидов связана с улучшением исходов оперативного вмешательства. Длительная боль высокой интенсивности у новорожденного при неэффективном обезболивании приводит к прогрессированию таких патологических состояний, как гипоксия, метаболический ацидоз, нарушения функции печени и почек, к возрастанию риска развития сепсиса, синдрома диссеминированного внутрисосудистого свертывания, к повышению неонатальной смертности. На сегодняшний момент, возможности традиционных методов аналгезии остаются ограниченными. В связи с этим в качестве основных направлений повышения эффективности обезбоживания в педиатрии применяют различные схемы комбинирования неопиоидных анальгетиков, при необходимости дополняемых опиоидами, а также разрабатывают новые эффективные и безопасные лекарственные средства с анальгетической активностью.

Ключевые слова: боль; периоперационное обезбоживание; новорожденные; фармакологическая коррекция; анальгетики.

Как цитировать

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NOCICEPTION IN NEWBORNS

Nociception, defined as neural processes of encoding and processing noxious stimuli, includes four consecutive phases: transduction, transmission, modulation, and perception [1]. The formation of these processes during ontogenesis determines the perception of pain in the neonatal period [2]. Structures responsible for the perception of pain and transmission of noxious stimuli begin to form from the sixth week of prenatal development. The majority of nociceptive neurotransmitters are detected at the gestational age of 12–14 weeks [3]. Compared to adults, newborns have more pronounced and prolonged nociceptive responses, higher density of nociceptors, and more closely located tactile and conduction fibers [4]. The key characteristics of pain perception in newborns are hyperalgesia and low pain threshold (with susceptibility to pain decreasing with gestational age), rapid habituation to a repeated noxious stimulus, depletion of compensatory mechanisms, and minimal external manifestations of pain [5]. In preterm newborns, nociceptive impulses are induced by milder stimuli and are transmitted more quickly than in adults [6].

PAIN MEDICATIONS IN THE INTRAOPERATIVE AND POSTOPERATIVE PERIOD

Pharmacological pain management in the postoperative period includes a multimodal approach and combination drug therapy with non-opioid and opioid analgesics, as well as local anesthetics [7]. Advantages of opioid analgesics include a nearly limitless analgesic efficacy, sedation, relative hemodynamic stability after intravenous injection, and reversible side effects. Morphine is more effective for sedation and vasodilation than fentanyl, with comparable clinical efficacy at recommended doses. Fentanyl has less impact on hemodynamics. However, long-term use of opioid analgesics increases the risk of tolerance, necessitating dose escalation. In addition to antinociceptive system activation, opioid analgesics cause sensitization as a result of excitatory neurotransmitter (glutamate and aspartate) activation [8].

The pharmacological activity of μ -opioid receptors is associated with glutamate transmission activation. Increased Ca^{2+} transport in the NMDA receptor complex enhances synaptic activity. Thus, opioid analgesics induce delayed dose-dependent hyperalgesia and allodynia. Despite their high efficacy, opioid analgesics have significant disadvantages: even short-term use is associated with the risk of tolerance, reducing their analgesic effect and necessitating dose escalation [9]. According to research, postoperative use of opioid analgesics may increase complication rates and treatment costs [8, 10].

Opioid tolerance and addiction, which can occur from the first days of therapy, bring the safety of these drugs into question [11, 12].

Fentanyl, morphine, and tramadol are opioid analgesics that are most commonly used in clinical practice for postoperative pain management. Moderate pain is typically treated using combination therapy with tramadol (1–2 mg/kg 4–6 times daily) and a non-opioid analgesic.

Tramadol is a potent opioid analgesic with low affinity for μ -opioid receptors; it inhibits the reuptake of norepinephrine and serotonin, which are antinociceptive transmission signaling molecules. Common adverse effects of tramadol include vomiting and dizziness; however, it has less impact on respiration than other opioids. When used for postoperative pain management in newborns, fentanyl 1–2 $\mu\text{g}/(\text{kg}\times\text{h})$ and tramadol 0.1–0.2 $\mu\text{g}/(\text{kg}\times\text{h})$ showed comparable efficacy within the first 72 h after surgery, with no superiority of fentanyl-based analgesia [13].

Morphine and fentanyl are drugs of choice in severe pain. Morphine, an opium alkaloid, is a highly effective opioid analgesic; it is used for pain management after surgery and during various interventions, as well as in patients on mechanical ventilation. A randomized controlled study [14] that assessed morphine versus placebo in 898 newborns (gestational age 23–32 weeks) found that morphine had a significant analgesic effect, but did not improve long-term outcomes. Specifically, it did not reduce the duration of mechanical ventilation and parenteral nutrition or improve hypertension [15, 16]. In Russia, morphine is approved for epidural administration and thus is typically used intraoperatively. It is currently believed that the use of morphine must be limited and only provided in the absence of hypertension, given the potential increased risk of intraventricular hemorrhage in preterm newborns with a very low body weight [17]. The use of morphine in the neonatal period may reduce body weight and impair cognitive functions [18, 19].

Fentanyl is most commonly used during and after surgery or during mechanical ventilation. It has a rapid onset and a relatively short duration of therapeutic action (30–90 min). Intravenous bolus injections of fentanyl may cause chest wall rigidity in 4% of newborns [20]. This effect can be avoided by slowly administering the drug or using muscle relaxants. Fentanyl is less likely to cause hemodynamic instability than morphine, making it a preferred option in patients with shock [18]. The daily dose of fentanyl depends on pain intensity, response to analgesia, and severity of adverse reactions, and amounts to 0.5 $\mu\text{g}/(\text{kg}\times\text{h})$ in children, following a bolus injection at a dose of 0.5 $\mu\text{g}/\text{kg}$ [7, 21].

It is now commonly accepted that the most effective pain management in newborns, which improves neonatal

surgery outcomes, is a multimodal approach that incorporates non-drug and drug therapies. It is preferable to use systemic analgesia in combination with local and/or regional anesthesia before, during, and after surgery, rather than opioid analgesics. The multimodal approach to pain management involves various antinociceptive mechanisms, providing optimal analgesia without the need for dose escalation and reducing the risk of side effects of individual drugs.

Ketamine, a non-opioid analgesic, provides effective analgesia while maintaining spontaneous breathing, muscle tone, and reflexes. Ketamine is used for induction of anesthesia, analgesia during short-term surgeries, and burn wound treatment, and provides short-term analgesia, amnesia, and sedation. It is effective both alone and in combination with benzodiazepines. Ketamine targets glutamate transmission by interacting with NMDA receptors. It reduces the intensity of pain potentiation and summation, facilitates antinociception by influencing monoaminergic transmission, and enhances the analgesic effect of opioids [8, 18, 22, 23]. The most significant side effects of ketamine are hallucinations (vivid dreams, including nightmares, psychomotor agitation, etc.) following anesthesia, hypersalivation, apnea, and laryngismus. There are few studies on the efficacy and long-term safety of ketamine in newborns. Its use in children is limited due to the reported neurotoxicity [24].

Gabapentin is an anticonvulsant used for neuropathic pain management; it targets post-surgical allodynia and hyperalgesia [25]. Gabapentin reduces pain by suppressing the activation of $\alpha 2\delta$ subunits of voltage-dependent Ca^{2+} channels of dorsal horn neurons, inhibiting glutamate transmission, and preventing pain wind-up [8, 26, 27]. Gabapentin is used in adults, but is not approved for neuropathic pain management in children.

Magnesium sulfate exhibits analgesic activity by targeting NMDA receptors; it enhances the analgesic effect of opioids and reduces opioid tolerance [28]. The efficacy of magnesium sulfate depends on various factors, such as baseline plasma Mg^{2+} levels, dose, duration of treatment, severity of condition, and extent of surgery [8].

Sucrose (glucose) is primarily used during short-term interventions associated with mild or moderate pain. The maximum effect, lasting for approximately 4 min, is achieved when the drug is administered 2 min before intervention. Sucrose provides effective analgesia in newborns during venipuncture and intramuscular injections [29]. Oral glucose provides a good analgesic effect in neonates, including preterm newborns [30].

Analgesics for newborns are selected based on the extent of surgery, gestational and postconceptional age, severity of condition, need for long-term respiratory support, individual pain perception, and contraindications to specific drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs). Neonatal characteristics that directly

influence the pharmacodynamics and pharmacokinetics of analgesics play a significant role. These include fetal albumin concentrations with a significantly lower affinity for drug products; serum protein levels; ability to reduce free plasma xenobiotic levels and their adverse effects; higher indirect bilirubin levels compared to adults, which may impair drug binding to albumins; risk of acidosis, which may alter the degree of ionization of drug substance molecules; and others [31]. The use of NSAIDs for pain management reduces the need for opioids and provides adequate analgesia in the perioperative period [32].

Paracetamol is one of the most commonly used analgesics in newborns owing to its high efficacy and favorable safety profile [33]. Oral paracetamol is administered at a dose of 10 mg/kg every 6 h or 15 mg/kg every 8 h. It should be noted that newborns have reduced xenobiotic clearance [34]. Data on intravenous use of paracetamol in newborns are limited. The recommended doses include a loading dose of 20 mg/kg, followed by a maintenance dose of 10 mg/kg every 6 h [35]. The cumulative daily doses for newborns are 0–60 mg/(kg×day) (<1 month) and 60–75 mg/(kg×day) (1–3 months) [36]. Rectal paracetamol must be administered at a dose of 20 mg/kg every 6–8 h. Low-dose paracetamol is safe for newborns; however, rare side effects, including hepatotoxicity and nephrotoxicity, must be taken into account [37]. Paracetamol can also be used in combination with morphine. This combination has minimal side effects and reduces the need for opioid analgesics [38]. Importantly, NSAIDs must not be used simultaneously with anticoagulants, steroids, and nephrotoxic agents. The most common side effects of NSAIDs are hemorrhages, gastrointestinal disorders, hepatotoxicity, and renal toxicity [39].

Epidural anesthesia is used in newborns weighing 700 g and more, aged several hours and more, during various surgeries, as well as for multimodal analgesia or alone in the postoperative period (in children with esophageal or small bowel atresia, tracheoesophageal fistula, umbilical hernia and gastroschisis, diaphragmatic hernia, or intestinal obstruction). In this case, the anesthetic acts by entering the subarachnoid space and blocking nociceptive impulses [40]. Toxic effects of epidural opioids in newborns and infants are significantly less common than in older children and adults, especially when using low-dose anesthetics [41–44]. Therefore, epidural anesthesia does not influence cerebral perfusion in newborns and minimizes the risk of neurotoxicity by reducing the need for centrally acting anesthetics [45, 46].

CONCLUSION

Conventional anesthetic techniques remain limited. There is still a significant need for minimizing the use of opioid analgesics in the intraoperative and postoperative

period. Improved pain management requires introducing various combination analgesia techniques using opioid and non-opioid analgesics into clinical practice, as well as developing effective and safe novel analgesics.

Pain management, along with the prevention of infectious complications, is among the primary objectives of the perioperative period [47]. In infants and newborns, intense pain triggers a stress response [48]. In similar surgical interventions, the stress response activated by afferent neuronal impulses from the site of injury in newborns is greater in magnitude but shorter than in adults. Effective analgesia with opioids during cardiac surgery has been shown to improve surgical outcomes [15]. Prolonged, severe pain in newborns with ineffective analgesia leads to the progression of such disorders as hypoxia, metabolic acidosis, hepatic insufficiency, and renal insufficiency, increased risk of sepsis and disseminated intravascular coagulation, and higher neonatal mortality [8, 49–51]. At present, the capabilities of conventional analgesia remain limited. In this regard, the main approaches to improving the efficacy of pain management in pediatric practice include various regimens combining non-opioid analgesics, supplemented with opioids if necessary, as well as the development of effective and safe novel analgesics.

ADDITIONAL INFO

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