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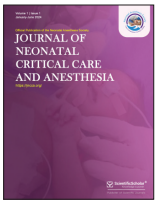

Narrative Review

Feasibility of "Opioid-Free Anesthesia" in Neonates: Evaluating the Risks and Benefits

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ABSTRACT

Opioids have been the mainstay of perioperative analgesia for centuries. The excellent analgesic profile along with innumerable benefits spiked up the inadvertent and irrational use of different opioids leading to increasing incidence of opioid addiction and respiratory depression leading to morbidity and mortality. Moreover, hence emerged the concept of "opioid-free anesthesia" (OFA). The concept of OFA escalated with advancements in pharmacotherapy, equipment, and monitoring facilities. Various newer anesthetic agents have shown promising effects in providing sedation and analgesia in the adult population, gradually replacing opioids in the perioperative management protocols. Various studies have demonstrated highly effective and safe OFA techniques in the adult population. However, owing to the difference in pharmacokinetic and pharmacodynamic profiles in neonates, the use of these agents in the neonatal population may not have similar effects. Hence, the applicability of OFA in the neonatal age group cannot be blindly accepted. In this review article, I intend to discuss the various aspects of opioid use as an essential part of anesthesia management in the neonatal age group.

Keywords: Opioids, Opioid-free anesthesia, Neonate, Opioid-sparing anesthesia

INTRODUCTION

The anesthesia armamentarium has been enormously refined over the past few decades. The introduction of newer pharmacological agents, machines, and monitoring devices has revolutionized the concept of perioperative care. With the emergence of enhanced recovery after surgery protocols, long-acting drugs have been replaced with short-acting and ultra-short-acting anesthetics and analgesics. Since time immemorial, opioids have been used for perioperative care. They very well complement other anesthetic agents and smoothen the course of the perioperative period. Newer agents such as fentanyl and remifentanil allow rapid recovery along with the other benefits of opioid therapy. Opioids offer various benefits in all age groups with diverse comorbidities. The idea of omitting opioids completely from the perioperative management protocols creates a dilemma for anesthesiologists. As a perioperative pain physician, an anesthesiologist needs to establish a fine balance between the effects and adverse effects of opioids and use multimodal therapy for the benefit of the patient.

PAIN – THE GIGANTIC PROBLEM

According to the International Association for the Study of Pain, pain is defined as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[1]

Different studies on neurophysiological development have shown that the ascending pathway for pain is completely developed by 25 weeks of gestation,[2] while the anti-nociceptive pathway development takes place at a later stage. Hence, pre-term infants have been shown to be more sensitive to pain as compared to term infants. Pain due to any reason during the neonatal age can have various short-term and long-term consequences. Minimal pain in neonates during procedures such as laboratory testing and intravenous line placement has the potential to lead to adverse metabolic, behavioral, and clinical responses in later life.[3] Untreated acute pain leads to an increase in 30-day infection rates and poor recovery profiles. Sleep disturbances due to pain may have long-term developmental impacts and cause a decline in cognitive function. Poor pain control alters the perception and sensitization (peripheral and central) to pain leading to higher chances of chronic pain in adult life. Studies have demonstrated brain dysmaturation in adults with painful experiences in neonatal age. These findings highlight the importance of perioperative analgesia since birth or even before.[3]

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Pain evaluation and management have always been a major concern for perioperative caretakers. The process is relatively easy and well taken care of in adults due to the availability of objective methods of assessment and a multitude of interventional and pharmacological therapies. About 30–80% of adult patients report pain on the first post-operative day despite the administration of routine analgesic agents.[4] Adding more to the complexity of the situation, assessment of pain in neonates is challenging due to the absence of any specific objective signs. Multiple scales such as Premature Infant Pain Profile-Revised, Neonatal Infant Pain Scale, Neonatal Facial Coding System-Revised, Pain Assessment Tool, Scale for Use in Newborns, Bernese Pain Scale Neonates, Comfort Assessment Neo, Neonatal Pain, Agitation, and Sedation Scale and many others are used for pain assessment in neonates. All of these scales objectively measure the level of nociception; missing out on the subjective experience of the individual suffering, and contradicting the World Health Organization definition of pain.[2] This exposes them to a higher risk of untreated pain leading to adverse consequences.

OPIOIDS: CORNERSTONE OF PERIOPERATIVE PAIN MANAGEMENT

The first natural opioid was discovered in 1803 and the first successful use of opioids has been described as early as 1844, wherein morphine was successfully used by Francis Rynd to treat facial pain. Thereafter, opioids became an integral part of anesthesia from pre-medication to post-operative pain relief. During the Second World War, owing to tremendous demand, a number of synthetic opioids were synthesized. However, the use was restricted due to the high incidence of respiratory depression leading to morbidity and mortality. This drawback was overcome with the invention of endotracheal tubes and ventilators, thereby adding to the safety profile of opioids. Since then, various natural, synthetic, and semisynthetic opioids have been an inextricable part of perioperative analgesia and sedation protocols.

Opioids have a diverse pharmacologic profile, provide excellent analgesia with hemodynamic stability, and can safely be used in all age groups. A wide variety of opioids have been developed over the years with diverse pharmacological profiles from long-acting morphine to ultra-short-acting remifentanil. They have been a blessing for the anesthesiologists and pain physicians. They can be administered by various routes – intravenous (IV), intramuscular (IM), oral, transmucosal, transdermal, intrathecal, and perineural. By suppressing the autonomic nervous system's response to surgical stress, opioids allay pre-operative anxiety and pain. Intraoperative opioid infusions have been used to complement the effect of different inhalational and intravenous anesthetic agents and maintain a stable hemodynamic profile of the patient. The supreme analgesia provided by different opioids soothes the post-operative experience for the patient. Cost-effectiveness and excellent analgesia help maintain patient compliance. Titrated doses of opioid analgesics have been proven safe in patients of different age groups with multiple comorbidities.

The four components of balanced anesthesia include sedation, analgesia, amnesia, and muscle relaxation. A smooth perioperative course requires adequate management of all of these components. Various opioids individually possess the ability to provide excellent analgesia and also complement other anesthetic agents, enhancing the sedation, amnesia, and muscle relaxation provided by them. Opioids have been dependable adjuncts to general anesthesia and regional anesthesia in all forms and all age groups.

THE INTRODUCTION OF OPIOID-FREE ANESTHESIA (OFA)

The medical field is one of the most rapidly progressing areas. Newer techniques, drugs, and equipment are continuously replacing the older ones. The trends keep changing and updating themselves. Although opioids are tried and tested analgesics trusted by medical professionals, easy availability and irrational marketing led to surplus misuse of this exotic pharmacotherapy. Unethical high and prolonged dosages highlighted the various side effects of opioids such as nausea, vomiting, constipation, and respiratory depression. Prolonged use of opioids leads to tolerance, addiction, hyperalgesia, cancer progression, and development of chronic pain.[5] Furthermore, the immense sense of well-being provided by opioids led to addiction, ultimately causing an opioid crisis.[6] Hence, various restrictions were laid by the government over the manufacturing, storage, dispatch, and use of opioids. Alongside began the search for other alternatives to replace opioids and emerged the concept of OFA.

OFA is a tailor-made technique that utilizes multiple pharmacological agents. It requires modifications as per the patient profile. A combination of regional anesthesia along with α-2 agonists, N-methyl-D-aspartate (NMDA) antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), and benzodiazepines has been used in adult patients with considerable success.

OFA: PRACTICAL APPLICATIONS IN NEONATES

Neonates have several anatomic and physiological differences as compared to adults. The various organ systems are immature and in the developing phase. The circulatory system is in the transitional phase between fetal and adult circulation. Hepatic and renal functions are poorly developed. This alters the pharmacodynamic and

pharmacokinetic properties of drugs. Hence, any drug used in the pediatric and adult population cannot be used in neonates expecting similar effects. As clinicians, it becomes our prime responsibility to ensure the safety and efficacy of any modern treatment that we provide to our patients. To date, there is a sparsity of literature supporting the benefits of OFA in neonates. The excellent analgesia provided with the use of opioids remains unsurpassed. Furthermore, as OFA usually requires multidrug therapy with precise dose titrations, the availability of expert and specific equipment is mandatory for its practical application in neonates. Complete omission of opioids from the perioperative period would escalate the financial burden on the patient and the health-care system, without any substantial benefits.

The majority of procedures performed in neonates are emergency procedures and the condition of the patient is often suboptimal. This contraindicates multiple drugs used in OFA in the neonatal population. In-depth knowledge of dose titrations and drug interactions is mandatory for providing OFA to neonates.

NON-OPIOID ANALGESICS IN NEONATES

Multiple drugs have been used to provide analgesia in the perioperative period [Table 1]. One of the most common drugs used is acetaminophen. It is used orally, IV, or rectally for the treatment of mild–to–moderate pain. However, its analgesic potency is questionable in the treatment of severe pain experienced during surgery.[7-11]

NSAIDs, by virtue of their mechanism of action, that is, inhibition of prostaglandin synthesis, adversely affect the development of cardiovascular, renal, and central nervous systems, when used in the neonatal age group.[2] Stone and Aldrink *et al.* recommend a minimum postnatal age of 21 days and a post-conceptional age of at least 37 weeks for the use of ketorolac. Continuous monitoring of renal and coagulation profiles is essential if the neonate is to be given NSAID.[12,13]

Dexmedetomidine, a selective α-2 agonist, is widely used in the adult population to provide sedation and analgesia in OFA. It provides sympatholysis, sedation, anxiolysis, and analgesia without respiratory depression. Dexmedetomidine is metabolized in the liver by glucuronidation and through Cytochrome P450 2A6 (CYP2A6) and the metabolites are excreted by the kidney. Both the hepatic and renal systems being immature, the pharmacokinetic profile of the drug in neonates remains unpredictable. Studies have demonstrated a lower clearance rate and longer half-life of the drug in neonates.[14-17] In a study comparing different doses of dexmedetomidine infusion in neonates after open heart surgery, severe cardiovascular adverse effects were observed at doses 0.5 μg/kg/h and above.[18] Looking at the pharmacodynamics, neonates have a predominant parasympathetic tone governing the cardiac output. This when coupled with sympathetic blockade by α-2 agonists, can lead to fatal bradycardia. In a study conducted by Beloeil *et al.*, comparing balanced OFA using dexmedetomidine and remifentanil in the neonates undergoing non-cardiac surgery, fatal bradycardia leading to asystole was demonstrated in two neonates receiving dexmedetomidine, due to which the study had to be prematurely discontinued.[19] A few studies do demonstrate the neuroprotective and sedato-analgesic action of dexmedetomidine in neonates, routine administration mandates further research for safety in term and preterm neonates.[20,21]

Ketamine, a potent NMDA antagonist forms the cornerstone of pediatric anesthesia. Administration of ketamine to infant mice in subanesthetic doses has been shown to produce neuroapoptosis and no study has conclusively reported the incidence of similar neurodegeneration in humans. Hence, the safety of ketamine remains under a gray area in neonates.[13,14]

Benzodiazepines such as lorazepam and midazolam act on gamma-aminobutyric acid receptors and produce sedation required for various procedures in the operation theater and intensive care unit. A Cochrane review published in 2000 demonstrates a higher incidence of adverse neurological events including intraventricular hemorrhage, periventricular leukoplakia, and even death.[22] The use of benzodiazepines in neonates has also been associated with a higher occurrence of cardiorespiratory adverse events such as hypotension, respiratory depression, and bronchospasm. In comparison with opioids, benzodiazepines are antianalgesics with chances of potentially life-threatening complications when used in the peri-operative period in neonates.[23]

Regional anesthesia with the help of fluoroscopy and ultrasonography has revolutionized perioperative pain relief in pediatrics and adults. However, as compared to older children, the conduction of nerve blocks in neonates is technically more challenging and requires well-trained staff. Incomplete ossification of bones offers little resistance to needles and may cause permanent damage. Incomplete myelination affects the dose and duration of local anesthetics. Administration of peripheral nerve blocks for pain relief requires the administration of general anesthesia, masking the early signs of local anesthetic toxicity.[24]

In a nutshell, none of the available pharmacotherapy and technology seems to override the efficacy and advantages of opioids providing effective perioperative analgesia without any complications in neonates.

RATIONAL USE OF OPIOIDS

A patient and the anesthesiologist gain multiple benefits from the use of opioids as a part of the perioperative management protocol. It helps treat pain, blunt the sympathetic stress

Table 1: Recommendations for opioid-sparing anesthesia in neonates.

Sr. No.	Drug	Mode of administration	Dose
1.	Injection morphine[25,26]	IV infusion	1–30 μg/kg/h
		IV intermittent	0.05–0.20 mg/kg 4–6 hourly
2.	Injection fentanyl[25,26]	Intravenous	0.3–4 μg/kg every 2–4 hourly
		IV infusion	0.3–5 μg/kg/h
3.	Injection remifentanil[27]	IV	5 μg/kg
		IV infusion	0.25 μg/kg/min
4.	Injection midazolam[27]	Intravenous	50–150 μg/kg
		IV infusion	10–60 μg/kg/h
		Intramuscular	200 μg/kg
		Intranasal	200–300 μg/kg
5.	Injection ketamine[27]	Intravenous	0.5–2 mg/kg
		IV infusion	1 mg/kg loading followed by 0.5 mg/kg/h
		Intramuscular	4 mg/kg
		Per-rectal	5 mg/kg
6.	Injection dexmedetomidine[28]	IV infusion	Maximum dose: 0.3 μg/kg/h
7.	Injection ketorolac[29]	Intravenous	0.5 mg/kg every 6 h
8.	Injection acetaminophen[30,31]	Oral/rectal	Up to 30-week gestation: 25–30 mg/kg/day Up to 34-week gestation: 45 mg/kg/day Term neonates: 60 mg/kg/day
		Intravenous	20 mg/kg followed by 10 mg/kg every 6 h

IV: Intravenous

response, and provide adequate sedation, all in a small, economical dose. Effective pain control smoothens the post-operative course leading to early recovery and discharge, complementing the surgeon's efficacy. As a perioperative pain physician, one would definitely promote the use of opioid-sparing anesthesia techniques rather than a blanket OFA protocol. The various adverse effects of opioids such as nausea, vomiting, hyperalgesia, respiratory depression, urinary retention, etc. depend on the dose and duration of opioid administration. Hence, one should promote the use of the lowest required dose of opioids for the minimum duration for excellent patient satisfaction. The use of multimodal techniques can help us counter the adverse effects of opioids without depriving the patient of perioperative analgesia.[5]

RECOMMENDATIONS FOR OPIOID-SPARING ANESTHESIA

Perioperative pain management is as important a component of balanced anesthesia in neonates as in adults. Based on the available literature review, none of the available pharmacological agents used in neonatal anesthesia have shown safety and efficacy similar to opioids. Although, the majority of them can be used to complement the beneficial effects of opioids. The use of drug combinations can help reduce the dose and duration of opioid use, thereby avoiding its adverse effects.[32,33] Regional anesthesia should be used whenever a trained person is available. The scarcity of studies conducted in neonates makes it difficult to propose an ideal drug regimen. Based on available research, the following drugs can be used in neonates for perioperative sedation and analgesia [Table 1].

CONCLUSION

Clinical use of OFA in neonates needs more research to evaluate its safety and efficacy. Op ioid-sparing an esthesia se ems to be more safe, feasible, and practically applicable as compared to OFA.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent is not required, as there are no patients in this study.

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Conflicts of interest

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the

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