Mechanism of Action, Cellular Targets and Clinical Importance of Analgesic Therapy in Postoperative Pediatric Patients: A Brief Observation

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Authors' contributions

This work was carried out in collaboration among all authors. Author AMRYP designed the study and wrote the first draft of the manuscript. Author ICI managed the literature searches. Authors NM and RBS reviewed and managed to analyzed the study. All authors read and approved the final manuscript.

Article Information

Minireview Article

ABSTRACT

Pain is a distressing sensation that has the potential to induce changes in multiple organ systems, especially in pediatric patients following surgical procedures. Efficient pain management is of the utmost importance for patients who wish to reduce or eliminate pain and distress with minimal adverse effects. The objective of this review is to investigate the clinical outcome, cellular targets,

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and mechanism of action of pain relief treatment in pediatric surgical patients after an operation. The literature search for this review was performed by accessing the Pubmed and Google Scholar databases; as a result, thirty publications were obtained for use as references. In compiling this review, the authors have categorized analgesic pharmaceuticals into three distinct groups: NSAIDs, opioids, and acetaminophen. In accordance with the review's stated objective, three distinct indicators are employed to compare these categories. This succinct investigation revealed that a consensus among clinicians and researchers was reached regarding the optimal strategy for managing postoperative pain in children. It was concluded that acetaminophen should be the initial course of treatment, followed by nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids being reserved as the last choice.

Keywords: Analgetic therapy; Pediatric surgery; post-operative management.

1. INTRODUCTION

Pain in children is identical to that in adults and can harm the body. Anticipating and treating pediatric pain is critical. An unpleasant experience like pain can affect all physiological systems. Pain can be precisely quantified in children utilizing age-specific pain scoring systems. Analgesics should be used early and in sufficient amounts to work. A multimodal approach combining milder analgesics and localized blocks can control pain and prevent severe side effects from potent analgesics. Recent advances in analgesic pharmacology allow for broad use with minimal adverse effects. The use of various analgesics should be done early and in adequate doses for them to be effective. The use of multimodal approach with weaker analgesics along with regional blocks is an effective modality to control pain and prevent severe adverse effects associated with higher doses of potent analgesics [1]. Pain alleviation has physiological benefits, therefore monitoring it is becoming a key postoperative quality measure. Pain management after surgery aims to relieve discomfort with minimal side effects [2,3].

Postoperative pain therapy is crucial for hospitals for many reasons. Proper therapy affects patient care, hospital costs, and comorbidities. Acute postoperative pain remains a barrier for modern medicine despite pharmacological and technological improvements. However, acute postoperative pain should be treated based on the intensity of the surgical procedure, the analgesics, and adequate combinations that enhance analgesic effects rather than side effects, as well as local and regional techniques associated with the surgical site [4,5]. This study aims to investigate the mechanism of action, cellular targets, and clinical outcome of analgetic therapy in post-operative pediatric surgical patients.

2. METHODOLOGY

The literature search in this review was carried out Using Pubmed and Google Scholar databases with three main keywords: pediatric surgery, analgetic therapy, and post-operative management. The articles were selected based on language, type of publication, suitability of methods, case characteristics, exposure, and outcome. All references that match the inclusion criteria are processed using the Mendeley® citation manager, whereas 30 articles are obtained as references. In this review, authors include three types of analgetic drug: Acetaminophen, NSAID, and opioids with three indicators of comparison: Mechanism of action, cellular targets and the clinical outcome of the patient.

3. RESULTS AND DISCUSSION

3.1 Acetaminophen

- **Mechanism of action**

Paracetamol as the most common use acetaminophen drug is a first-line oral analgesic for long-term usage. Acetaminophen is extensively utilized in children due to its well-established safety and efficacy. While the likelihood of children experiencing toxic reactions to acetaminophen is often lower than in adults, intentional overdoses can nevertheless lead to severe events in pediatric patients. Occasionally, acetaminophen poisoning can occur due to unintentional incorrect dosing or the failure to identify children who are more susceptible to it, even when they have been given the recommended quantities of acetaminophen. Due to the

generic nature of the symptoms of acetaminophen intoxication, the diagnosis and treatment of inadvertent cases of toxicity are more likely to be delayed. This statement outlines many circumstances and factors that might lead to acetaminophen poisoning, excluding cases involving deliberate self-harm. Children's paracetamol use requires specific attention and age-appropriate dosage, unlike adults'. Paracetamol metabolism determines toxicity, notably hepatotoxicity, hence children's dosage is based on this. Younger children use the sulfation pathway to eliminate paracetamol, which is mature at birth, while the glucuronidation pathway takes two years to mature. In humans, paracetamol is metabolized in the liver through glucuronidation (50- 60%), sulfation (25-30%), and oxidation (<10%). Central function of paracetamol is its stimulation of descending serotoninergic pathways, which reduce pain. In vivo tests on animals and humans validated this notion, showing that this drug's central antinociceptive impact involves the 5-HT3 subtype of serotonin receptors [6,7].

- **Cellular targets**

The mechanisms of acetaminophen's clinical selectivity remain unknown. Traditional NSAIDs block or change the active site of cyclo-oxygenase, however acetaminophen may not. Two main theories exist. First, acetaminophen may preferentially block a central nervous system cyclooxygenase isoform, maybe the canine brain's putative cyclooxygenase-3. Second, acetaminophen may impede cyclo-oxygenase action by converting its active oxidized form to an inactive form rather than binding to its active site. Thus, low peroxide concentrations make acetaminophen inhibition more effective. This theory explains acetaminophen's nerve-specific therapeutic selectivity. Nerves, which are sensitive to intracellular oxidants, actively minimize oxidation. The inflammatory location may have high oxidant levels, making acetaminophen's lowering effects ineffective. Acetaminophen preferentially inhibits cyclo-oxygenase activity in endothelial cells but not platelets, and increasing intracellular peroxide levels prevents its inhibitory effects [8].

Another possibility for cellular selectivity in acetaminophen response is that the drug's metabolic destiny changes among cells, which could affect its efficacy by forming an active metabolite or accelerating drug inactivation.

Acetaminophen biotransformation data is plentiful and suggests selectivity.Acetaminophen is metabolized in the liver by glucuronidation and sulfate conjugation. Acetaminophen is deacetylated to produce p-aminophenol, a powerful nephrotoxicant. Substance of p-aminophenol inhibits thromboxane A2 production in washed platelets more than acetaminophen, based on this and evidence that it inhibits PGHS in the rat renal medulla. These findings provide a clear rationale for determining the extent of acetaminophen deacetylation in relation to cellular selectivity, but the role of cell- or tissue-specific deacetylation in clinical behavior remains to be explored. A recent study suggests that acetaminophen's analgesic qualities come from a downstream metabolite of p-aminophenol. Additional research is needed to prove that this metabolic pathway for acetaminophen is necessary for its analgesic effects and that humans have such pathways [9].

- **Clinical outcome**

Acetaminophen can damage the liver in large doses, however liver failure risk depends on health and other factors. Because an intricate system of intra- and extracellular molecular signaling regulates APAP-induced liver injury and recovery, we aim to quantify the importance of specific modules in determining the outcome after an APAP insult and of potential targets for therapies that mitigate adversity [10]. Because it inhibits prostaglandin synthesis, acetaminophen has extremely selective analgesic and antipyretic effects. Arachidonic acid-derived PGs are key mediators of inflammation, fever, and discomfort. A practical investigation showed that intraoperative IV acetaminophen was safe and beneficial for postoperative pain following pediatric skin laser irradiation. In that study, the acetaminophen IV group had lower pain levels than the placebo group up to 2 hours postoperatively, except for emergence [11].

3.2 Non-Steroid Anti Inflamatory Drugs (NSAID)

- **Mechanism of action**

Non-steroidal anti-inflammatory drugs (NSAIDs) are utilized for their powerful analgesic, anti-inflammatory, and antipyretic properties. NSAIDs work by inhibiting COX enzyme, which biosynthesizes prostaglandins and thromboxane. Fever, pain, and inflammation are mediated by PGs and TXs. pathophysiology of many diseases

involves inflammation. PGs, coagulation cascade-derived peptides, IL-2, IL-6, and TNF are affected by NSAIDs. Arachidonic acid-derived prostanoids promote inflammation [12,13].

The immune system is directly activated by surgical injury through the binding of danger-associated molecular patterns to pattern recognition receptors in the innate immune system. Additionally, the neuroendocrine system is indirectly activated through the hypothalamic-pituitary-adrenal axis. Upon activation, a cascade of hormones, cytokines, chemokines, and prostanoids are produced in order to restore the body's internal balance, promote tissue healing, and combat infections. Anti-inflammatory nonsteroidal anti-inflammatory drugs (NSAIDs) may be beneficial for this condition as they inhibit the sensitivity of both the peripheral and central nociceptive pathways. Ibuprofen, diclofenac, ketorolac, naproxen, and flurbiprofen were employed, however COX-2 inhibitors shown a greater reduction in postoperative analgesic consumption compared to nonselective NSAIDs [14].

- **Cellular targets**

NSAIDs are highly effective analgesics and are among the most commonly purchased medications. It is necessary to investigate the molecular interactions that are responsible for both the physiological activity and the detrimental effects of these substances. Ibuprofen, naproxen, and diclofenac, which are widely used NSAIDs, have an interaction with dimyristoylphosphatidylserine, a prominent phospholipid found in eukaryotic cells. Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) are employed to observe the change from gel to liquid crystalline phase of the acyl chains, both in the absence and presence of the NSAID. The interactions between NSAIDs and functional groups in the DMPS spectrum, such as the ester carbonyl and phosphate vibrational bands, are detected and recorded using Fourier Transform Infrared Spectroscopy (FTIR) in reflection mode with Attenuated Total Reflection (ATR) technique. The thermodynamics of the interaction between NSAID-DMPS liposomes are assessed using isothermal titration calorimetry (ITC) and Förster resonance energy transfer (FRET). The data indicate that the NSAID interacts with this lipid in a specific manner, while exhibiting distinct differences in other parameters. This provides a comprehensive understanding of the interaction processes. Our investigation revealed that NSAIDs such as ibuprofen, naproxen, and diclofenac caused the destabilization of DMPS bilayers, resulting in detrimental effects on their thermodynamic properties. Drug-membrane interaction is influenced by multiple aspects. Hydration is essential for the stabilization of bilayers. The presence of a hydration shell and the arrangement of lipids can have an impact on cell membranes, influencing their semipermeable properties, the rate and efficiency of cell development, and the activity of enzymes linked with the membrane [15].

- **Clinical outcome**

Ibuprofen is the most extensively researched and utilized nonsteroidal anti-inflammatory drug (NSAID) in children for the treatment of sudden pain, and it is the sole NSAID authorized for use in children as young as 6 months. All of the studies on ibuprofen examined adverse events (AEs) and other factors related to safety and tolerability, such as nausea, vomiting, drowsiness, and dizziness [16]. The ideal pediatric ibuprofen dose is 10 mg/kg body weight every 8h, with the maximum single dose and daily dose being 800 mg and 2400 mg, respectively. Severe ibuprofen toxicity in children at doses less than 100 mg/kg by history throughout treatment is rare. More than 400 mg/kg body weight can cause serious or life-threatening toxicities include gastrointestinal hemorrhage, thrombocytopenia, pulmonary edema, severe acute kidney failure, and metabolic acidosis. Since there is no antidote, main supportive measures should be used [17].

NSAIDs have many advantage and disadvantage due to the organ system. In the urinary system, NSAIDs inhibit kidney COX-1 and intravascular volume-dependent inducible COX-2. While COX-1 controls glomerular filtration rate and renal hemodynamics, COX-2 controls salt and water excretion. In the nervous system, NSAIDs may delay Alzheimer's. Inhibiting COX-2 disrupts the β-amyloid cascade, which suppresses memory and synaptic plasticity [18]. Moreover, NSAIDs can affect the GI system by deteriorating this process. These harms can be caused by PG or non-PG methods. A gastric lesion caused by increased mucosal permeability and myeloperoxidase activity increases gastric hypermotility. In the cardiovascular system, selective COX inhibitors lower PGI2, which is

essential for endothelial cell vasodilation and platelet inhibition, increasing the risk of thrombosis. PGI2 and TXA2, a vasoconstrictor, can become imbalanced, causing platelet aggregation and thrombus development [12].

In the general population, 0.3% of adults and 0.5% of children have hypersensitivity reactions to NSAIDs. Ibuprofen was the most commonly implicated NSAID (7,6% of cases). Treatment duration and drug doses should be frequently assessed and manufacturer or expert committee maximum dose limits and other guidelines followed. The medical team should start NSAID medication with the lowest age- or weight-based dose to improve safety in newborns and children. Because NSAIDs are used by a significant number of children, hypersensitivity should always be considered as a drug-induced adverse event that must be monitored and handled [19–21].

3.3 Opioids

- **Mechanism of action**

Opioids affect the afferent and efferent pain pathways. They block pain transmission from primary afferent to ascending neurones by lowering neurotransmitter release. Kþ and Ca2þ channels play a major role in these processes, with activation increasing Kþ efflux and hyperpolarization, while inhibition decreases Ca2þ influx and limits transmitter release. Second-to-third-order transmission and descending inhibitory control activities are enhanced by reducing GABAergic inhibitory transmission. Plasticity exists in NOP receptor and pain processing [22]. NOP, MOP (m), KOP (k), and DOP (d) are classical opioid receptors according to IUPHAR. All four G-protein-coupled receptors have a seven-transmembrane topology. Instead of directly communicating with effector proteins, G-protein-coupled receptors (GPCRs) convey the message. MOP with morphine closes voltage-sensitive calcium channels (VSCCs), stimulates potassium efflux, hyperpolarizes cells, and reduces cyclic adenosine monophosphate (cAMP) production by inhibiting adenylyl cyclase. All four receptor subtypes preferentially couple to inhibitory G-proteins. This decreases neuronal cell excitability, reducing nerve impulse transmission and neurotransmitter release [23].

- **Cellular targets**

Numerous physiological functions depend on opioid receptors, which are widely distributed in the body. These include central and peripheral nervous system pain signaling, reproduction, growth, breathing, and immunological response. Physiologically and pathophysiologically, opioid receptors are important in the GI tract. GPCRs are targets for about one-third of FDA- approved blockbuster medications, including analgesics, antihistamines, neuroleptics, and numerous cardiovascular therapies. The opioid receptor family is key GPCR. MOP, DOP, and KOP are prototypical naloxone-sensitive opioid receptors. This family also includes the nonclassical nociceptin/orphanin FQ (N/OFQ) receptor. Naloxone does not affect this receptor. Opioids bind to Gi/Go G-proteins, causing neuron hyperpolarization, closing voltage-gated Ca2þ channels, and inhibiting adenylyl cyclase to reduce cyclic adenosine monophosphate formation and membrane repolarization. The b-arrestin pathway inhibits signaling. These coordinated cellular activities allow all family members to produce analgesia (anti-nociception in non-humans) to varied degrees and locales. G-protein and independent b-arrestin pathways link opioid receptors to mitogen-activated protein kinases such ESRPK, p38, and Jun Nterminal kinase. All members of the family can provide analgesia, but MOP receptor agonists are the mainstay in the clinic, with some developing instances addressed next. The list includes morphine, fentanyl, and oxycodone. Opioids have many side effects, including ventilatory depression, nausea and vomiting, constipation, tolerance, and dependency. Tolerance causes dose escalation (particularly in palliative care) and dependence, which is associated to premature death and crime globally [24,25].

- **Clinical outcome**

Studies suggest non-opioid medications are equally effective in controlling post-operative pain after pediatric herniorrhaphy compared to opioid medications. Routine opioid administration does not appear to positively affect postoperative pain management in this population and is associated with a higher rate of medication related side effects. Most study suggests that opioid prescriptions are more likely to cause harm in the form of worsened nausea and vomiting than provide improved pain control [26].

Dixit et al. 2022 reported that surgery as a risk factor for opioid use, persistence, and misuse in

children. In the experiment, 849 (63.1%) of 1344 pediatric ambulatory surgery patients responded. Survey respondents were 60% male, 55% 2–12-year-olds, and 90% ASA 1 or 2 patients. The average procedure took 1 h. 32.4% of 275 discharged patients received opioids. 164 (59.6%) postoperative opioid users did not use them on POD 1. Orthopedic and plastic surgery had 28–29% wasted opioid prescribing, while dentistry and ophthalmology had 3–4%. Neurosurgical patients received 55% opioids and all used them on POD 1. Obstetrics, dental and maxillofacial surgery, orthopedic surgery, and plastic surgery discharged at least 60% of patients on opioids, with 33–42% not using opioids on POD 1. Operative and patient-specific opioid days and OMEs per kilogram differed substantially. Some children had 3- to 7-day opioid prescriptions after tonsillectomy and adenoidectomy, while one received >15 days. Some patients received opioids for 10 days after orchiopexy. Most got 2–4 days. These findings represent oral morphine equivalents per kilogram. Older patients, those with private insurance, those with longer surgeries, and those furthest from the hospital were prescribed more opioids. Medical opioid exposure makes adolescents more likely to use recreationally, share, and develop drug dependence and misuse. Opioid exposure and chronic usage are linked to surgery, with 6-10% of opioid-naïve persons consuming opioids for beyond 3 months or even a year after surgery. After cholecystectomy,arthroscopic knee surgery, colectomy, and wisdom tooth extraction, 5% of pediatric patients fill opioid prescriptions 2–6 months later [27].

Other opioid-related issues, such as opioid use disorder, stem from opioid usage. In 2016, there are about 153,000 children in 12–17-year-olds in the US reported opioid use disorder. Most opioid use disorder cases (99%) involved prescription opioids, with heroin accounting for 1%. Opioids are the leading cause of serious injury or death in children, and accidental opioid overdoses in the US doubled from 1999 to 2008. In 2008, opioid-related accidental deaths were 0.1 per 100,000 for children 0–14 and 3.7 per 100,000 for teenagers 15–18. After 2008, opioid-related adolescent mortality dropped to2.0 per 100,000 in 2011 and 2.5 per 100,000 in 2015 [28–30].

4. CONCLUSION

This brief review showed that all researcher and clinician agreed that post operative analgesia management for children still must be started by using acetaminophen as initial teraphy, then NSAID and Opioids as the last choice.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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