

# Nonopioid analgesics for perioperative and cardiac surgery pain in children: Current evidence and knowledge gaps

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## ABSTRACT

- Objective** : The purpose of this review is to present the available literature on the use of nonopioid analgesics such as nonsteroidal anti-inflammatory drugs in postcardiac surgery pediatric patients, mainly to focus on patients <1 year of age, and to provide the foundation for future research.
- Materials and Methods** : Published studies that address the use on nonopioid medications for postoperative sedation and analgesia in infants and children undergoing cardiac surgery were identified from online sources. Studies were reviewed by two authors independently to assess the quality of the data as well as the evidence. Due to limited availability of such studies, the review was then expanded to include use in noncardiac procedures as well as to expanded age groups. All studies that met the primary objective were included.
- Results/Data Synthesis** : Majority of the studies in the population of interest were related to use of ketorolac. Five studies specifically addressed ketorolac use in cardiac patients. In addition, studies were reviewed for nonopioid analgesia in noncardiac patients and included as a part of the available evidence as in the case of acetaminophen use. Newer agents as well as agents with very limited information were also acknowledged.
- Conclusion** : Nonopioid medications appear to show promise for analgesia in infants undergoing cardiac surgery, with ketorolac being the most potent agent as a potential substitute for opioids. These agents demonstrate a reasonable safety profile even in the very young. There continue to be significant gaps in knowledge before their adoption becomes routine. However, gives the awareness regarding short-term and long-term impact of opioid use in this vulnerable population, and studies of such agents are an urgent need.
- Keywords** : Analgesia, cardiac surgery, infants, nonopioid, nonsteroidal anti-inflammatory drugs, pediatric, postoperative care

## INTRODUCTION

Congenital heart disease (CHD) has a worldwide prevalence of 9.1/1000 live births affecting over one million infants each year.<sup>[1]</sup> Surgical intervention is

required for most children with CHD. More severe defects, namely, single-ventricle physiology and systemic outflow obstruction, need even multiple surgeries to correct the defect. Pain in the postoperative period can

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be due to surgery *per se* or due to various diagnostic and therapeutic procedures, namely, endotracheal intubation, suctioning, and IV placement.<sup>[2]</sup> Optimum pain management is essential to prevent long-term consequences associated with undertreatment when avoiding adverse effects associated with overtreatment. Some factors identified to contribute to inadequate pain management in infants and children include lack of training and experience, difficulties in identifying pain, inappropriate use of pain scales, differences in pharmacokinetics and pharmacodynamics, age-related drug licensing, and the lack of studies evaluating pediatric analgesia.<sup>[3]</sup> Poorly controlled pain in infants can have deleterious long-term consequences. Plasticity of central nervous system in the neonatal period may lead to structural expansion of dorsal horns afferent nerve terminals in the spinal cord of neonatal rats in response to chronic inflammation.<sup>[4]</sup> This could explain increased pain sensitivity to noxious stimuli in children who experienced painful procedures during the neonatal period.<sup>[5]</sup> Chronic postsurgical pain is another complication of inadequate pain control. It is reported in up to 11% of children, and the severity of acute pain in the first 24 h after surgery is a significant risk factor.<sup>[6]</sup> Thus, adequate pain control is an essential aspect of the postoperative care of children undergoing cardiac surgery. The World Health Organization advocates two-step strategy for the management of pain in pediatric patients. Acetaminophen and ibuprofen can be used for mild pain in children above 3 months of age. Opioids are recommended for moderate-to-severe pain.<sup>[7]</sup> Critically ill patients after cardiac surgery frequently receive a continuous infusion of opioids for pain management. Opioids cause respiratory depression and sedation and have been implicated in extubation failure following cardiac surgeries. Winch *et al.* studied extubation failure following early extubation in the OR, in children <1 year of age undergoing cardiac surgery. Respiratory depression secondary to narcotic use resulted in 45% (10/22) of extubation failures within 24 h.<sup>[8]</sup> Extubation failure is associated with a longer ICU stay, inhospital mortality, and greater resource utilization.<sup>[9]</sup> There is also a concern regarding the long-term neurodevelopmental impact of opioids in infants and children. Nonsteroidal anti-inflammatory drugs (NSAIDs) when used as an adjunct or primary analgesic can mitigate these problems. A growing body of literature has emerged on their use in postcardiac surgery pediatric patients. However, concerns regarding renal toxicity, gastrointestinal bleeding, and impaired hemostasis in this high-risk patient population translate into a gap in available literature and practice. The purpose of this review is to present the available literature on the use of nonopioid analgesics such as NSAIDs in postcardiac surgery pediatric patients,

mainly to focus on patients <1 year of age, and to provide the foundation for future research.

## MATERIALS AND METHODS

In May 2018, published English-language literature was searched using PubMed, EMBASE, and Google Scholar for the following search terms and keywords: “congenital heart surgery,” “post-operative analgesia,” “non-steroidal anti-inflammatory drugs,” “opioid analgesics,” “cardiac intensive care,” “pain management,” “procedural sedation,” and “procedural analgesia.” Published studies that address the use on nonopioid medications for postoperative sedation and analgesia in infants and children undergoing cardiac surgery were assessed. Due to limited availability of such studies, the review was then expanded to include use in noncardiac procedures as well as to expanded age groups. Studies were reviewed by two authors independently to assess the quality of the data as well as the evidence. All studies that met the primary objective were included. In addition, we also reviewed the basic pain assessment tools which were integral to these studies.

## RESULTS AND DISCUSSION

### Assessment of pain in pediatric patients following cardiac surgery

Adequate pain management begins with an evaluation of the severity of pain. Verbal school-age children (>4 years) can report pain using standardized self-reporting tools such as visual analog scale or FACES scale. Pain assessment is more challenging in nonverbal and developmentally impaired patients due to dependence on third-person observation. Use of standardized pain assessment tools can reduce interobserver variability. Different tools are available and have been validated to assess pain severity in preverbal children. These scales use behavioral and physiological changes associated with pain such as crying, agitation, and changes in heart rate or blood pressure. Commonly used pain assessment tools in postoperative period include Face, Legs, Activity, Cry, and Consolability<sup>[10]</sup> and COMFORT<sup>[11]</sup> scales. It is worth noting that the COMFORT scales have been adapted for special populations such neonates/premature neonates<sup>[12]</sup> and children with Down syndrome.<sup>[13]</sup> Noncommunicative Children Pain Checklist-Postoperative version has been validated for use in cognitively impaired children.<sup>[14]</sup> Numeric rating scale-11 is an alternative numeric measure of pain in children and has been used in clinical studies. In the postoperative period, analysis of heart rate variability can be useful.<sup>[15]</sup> Nonetheless, frequent assessment of pain should be used to titrate the need for analgesic medications. There are certain limitations to the objectivity and accuracy of these pain measures, especially in the immediate postoperative

**Table 1: Summary of ketorolac use after cardiac surgery in infants**

Reference	Patient population	Study design	Outcomes	Results	Ketorolac dosing
Dawkins <i>et al.</i> <sup>[34]</sup>	Infants <6 months, postcardiac surgery <i>n</i> =38; (19 each in ketorolac and control group)	Case control retrospective chart review	BUN, serum creatinine, hemoglobin, platelet count and number of blood transfusions	No significant difference in outcome parameters compared to nonketorolac group	0.5 mg/kg IV every 6 h for 48 h
Moffett <i>et al.</i> <sup>[33]</sup>	Infants <6 months, postcardiac surgery. <i>n</i> =53	Retrospective chart review	BUN, serum creatinine, hemoglobin, hematocrit, and platelets	No significant difference in outcome parameters compared to nonketorolac group	0.44 mg/kg IV every 6 h
Inoue <i>et al.</i> <sup>[35]</sup>	Infants and children postlow-risk cardiac surgery. Ketorolac <i>n</i> =108 Control <i>n</i> =140	Case control retrospective chart review	BUN, serum creatinine, and urine output	No significant increase in BUN and serum creatinine or decrease in urine output	0.5 mg/kg IV every 6 h for 36 h
Gupta <i>et al.</i> <sup>[37]</sup>	Neonates, infants, and children, postcardiac surgery <i>n</i> =70; 35 in each group	Randomized controlled trial	Chest tube drainage, GI and wound bleeding	No significant risk of increased bleeding	0.5 mg/kg IV every 6 h for <48 h
Gupta <i>et al.</i> <sup>[38]</sup>	Infants and children, postcardiac surgery <i>n</i> =188; 94 each in ketorolac and control group	Case control retrospective chart review	Postoperative bleeding requiring reexploration	No significant risk of increased bleeding	0.5 mg/kg IV every 6 h for <48 h

BUN: Blood urea nitrogen, GI: Gastrointestinal, IV: Intravenous

period in sedated infants and has implications on the comparative evaluation of analgesics.

### Nonsteroidal anti-inflammatory drugs

NSAIDs are a heterogeneous group of drugs which act by competitive or noncompetitive inhibition of cyclooxygenase (COX), an enzyme involved in prostaglandins (PGs) biosynthesis from arachidonic acid. COX enzyme occurs in two isoforms: COX-1 is constitutively expressed in most tissues and is involved in housekeeping functions, whereas COX-2 is induced by cytokines and shear stress and is involved in PG formation in inflammation. Likewise, NSAIDs are classified as nonselective, which inhibit both COX-1 and COX-2, and COX-2 selective. Arachidonic acid is released into the cytoplasm by the action of phospholipase A<sub>2</sub> on cell membranes by various stimuli. It is acted upon by cytosolic PG G/H synthase which has both COX and hydroperoxidase activity, thus forming PGG<sub>2</sub> and PGH<sub>2</sub> in quick succession. PGH<sub>2</sub> is then converted by tissue-specific isomerases into various PGs, namely, PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, PGI<sub>2</sub>, and TxA<sub>2</sub>.<sup>[16]</sup> Once formed, PGs are transported out of the cells and act locally via G-protein-coupled receptors. PGE<sub>2</sub> is the most abundant PG produced in the body. It is produced constitutively by COX-1 and cytosolic PGE synthase and is induced by inflammation via COX-2 and microsomal PGE synthase. COX-1 preferentially couples with thromboxane, PGF<sub>2α</sub>, and cytosolic PGE<sub>2</sub> whereas COX-2 prefer microsomal PGE<sub>2</sub> and PGI<sub>2</sub>.<sup>[17]</sup>

PGE<sub>2</sub> and PGI<sub>2</sub> reduce the threshold for stimulation of nociceptors causing peripheral sensitization. PGE<sub>2</sub> primarily and PGD<sub>2</sub>, PGF<sub>2α</sub>, and PGI<sub>2</sub> to some extent increase the excitability of spinal dorsal horn neurons causing central sensitization.<sup>[18]</sup> Inhibition of PG synthesis by NSAIDs reverses the central and peripheral sensitization and represent the mechanistic basis for

their analgesic action.<sup>[19]</sup> Recently, NSAIDs have also been shown to cause COX-independent inhibition of caspases, which decrease cell death and generation of pro-inflammatory cytokines, which can further alter inflammatory and pain response.<sup>[20]</sup>

The various side effects of NSAIDs can also be attributed to inhibition of PG synthesis. Hemostasis begins with platelet aggregation which is mediated by thromboxane. In addition, PG-mediated gastric acid suppression plays a vital role in mucosal defense against gastric acid. NSAIDs, by suppressing PGs, increase the risk of gastric and other systemic bleeding.<sup>[21]</sup> PGs also play an essential part in maintaining renal blood flow by causing vasodilation of renal vessels. NSAIDs thus can reduce renal blood flow and clinically manifest as decreased urine output and elevated serum creatinine.<sup>[22]</sup> There is increased risk of experiencing these adverse effects in children undergoing cardiac surgery due to a low cardiac output state; disruption of homeostatic milieu; and concomitant use of drugs such as loop diuretics, aspirin, and thrombolytics.<sup>[21]</sup>

### Ketorolac

Ketorolac is a nonsteroidal anti-inflammatory drug acting by inhibition of COX as described earlier. Other mechanisms reported to contribute to its analgesic effect include local nitric oxide synthesis and interaction with cannabinoid receptors.<sup>[23]</sup> Ketorolac provides a degree of analgesia which is comparable to morphine. The combination of ketorolac and morphine is better than morphine alone and results in a 25%–50% reduction in morphine use in the first 24 h after surgery.<sup>[24]</sup> The FDA recommends ketorolac for short-term (<5 days) management of moderate and severe pain in adults that requires analgesia at the opioid level such as in a postoperative setting.<sup>[25]</sup> The drug is licensed for use in

**Table 2: Summary of perioperative acetaminophen and ibuprofen use in children**

Reference	Patient population/age	Study design	Intervention	Opioid sparing effect Opioid dose mean±SD
Ceelie et al. <sup>[59]</sup>	Neonates and infants PMA 36 1/7 to 1 year of age; noncardiac surgery Acetaminophen n=33 Morphine n=38	Randomized controlled trial	Acetaminophen: 30 mg/kg/d IV Morphine: 2.5-5 µg/kg/h Rescue morphine boluses: 10-15 µg/kg	Acetaminophen: 121 µg/kg Morphine: 357 µg/kg 66% reduction in cumulative morphine dose in first 48 h postoperative Significant
Hong et al. <sup>[60]</sup>	Infants 6-24 months; ureteroneocystostomy Fentanyl + acetaminophen n=31 Fentanyl n=32	Randomized controlled trial	Fentanyl 0.5 µg/kg bolus and infusion at 0.25 µg/kg/h IV+acetaminophen: 15mg/kg bolus and infusion at 1.5 mg/kg/h IV Fentanyl 0.5 µg/kg bolus and infusion at 0.25 µg/kg/h IV	Acetaminophen: 8.3±3.7; 7±2.4 µg/kg Control: 18.1±4.6; 16.6 µg/kg Significant reduction in cumulative fentanyl dose on day 1 and 2 postoperative respectively
Dashti et al. <sup>[61]</sup>	7-15 years; adenotonsillectomy Acetaminophen n=53 Placebo n=51	Randomized controlled trial	Acetaminophen: 40 mg/kg PR after induction Placebo	Acetaminophen: 6.48±8.52 Placebo: 17.09±12.12 Significant reduction in cumulative pethidine dose in the first 24 h
Viitanen et al. <sup>[45]</sup>	1-6 years; adenoidectomy Acetaminophen n=40 Ibuprofen n=41 Combination n=40 Placebo n=38	Randomized controlled trial	Acetaminophen: 40 mg/kg PR Ibuprofen: 15 mg/kg PR Combination of acetaminophen and ibuprofen Placebo	Acetaminophen: 0.87±0.39 (19%) Ibuprofen: 0.78±0.37 (27%) Combination: 0.77±0.45 (28%) Placebo: 1.07±0.38 Significant reduction in cumulative meperidine dose
Korpela et al. <sup>[62]</sup>	1-7 years; adenoidectomy n=120; 30 in each group	Randomized controlled trial	Acetaminophen: 20 mg/kg PR Acetaminophen: 40 mg/kg PR Acetaminophen: 60 mg/kg PR Placebo	Acetaminophen 20 mg/kg: 63% Acetaminophen 40 mg/kg: 47% Acetaminophen 60 mg/kg: 20% Placebo: 80% Percentage of patients requiring rescue morphine in first 2 h postoperative Significant reduction at 40 and 60 mg/kg
Bremerich et al. <sup>[63]</sup>	Infants 11.4±9.9 months; cleft palate repair n=80; 20 in each group	Randomized controlled trial	Acetaminophen: 10 mg/kg PR Acetaminophen: 20 mg/kg PR Acetaminophen: 40 mg/kg PR Placebo	Acetaminophen 10 mg/kg: 2.8±1.2 Acetaminophen 20 mg/kg: 3.5±1.3 Acetaminophen 40 mg/kg: 3.3±1.0 Placebo: 2.7±1.6 No significant reduction in total dose of piritramide
van der Marel et al. <sup>[64]</sup>	0-9 months; noncardiac thoracic and abdominal surgery Acetaminophen n=29 Placebo n=25	Randomized controlled trial	Acetaminophen PR 30-40 mg/kg at induction and 20 mg/kg every 6-8 h Placebo	Acetaminophen: 7.91 µg/kg/h Placebo: 7.19 µg/kg/h No significant reduction in median total dose of morphine in the first 48 h
Maunuksela et al. <sup>[46]</sup>	4-12 years; ophthalmic, general or orthopedic surgery n=128; 64 in each group	Randomized controlled trial	Ibuprofen 40 mg/kg/d Placebo	Ortho surgery Ibuprofen: 0.46±0.52 Placebo: 0.82±0.67 Significant Other surgery Ibuprofen: 0.09±0.14 Placebo: 0.12±0.1 Significant reduction in total opioid dose in first 3 days postoperative

IV: Intravenous, SD: Standard deviation, PMA: post menstrual age, PR: Per rectum

children older than 2 years in the USA, although it remains unlicensed in Europe for use in children under 16 years. Its use in children after cardiac surgery is contentious owing to their compromised physiological status. In light of growing body of literature, it is imperative to revisit the use of ketorolac in this setting [Table 1].

Ketorolac can be administered by intravenous, intramuscular, oral, sublingual, and intranasal route which makes it a versatile drug. Time to peak plasma concentration is 5 min after intravenous

administration and 20–60 min with the oral and intramuscular route. The systemic bioavailability after oral administration is 100 + 20% which is similar to intramuscular administration.<sup>[26]</sup> Ketorolac is largely protein bound (>99%). The drug has a steady state volume of distribution of 113 + 33 mL/kg in children aged 1–16 years<sup>[27]</sup> compared to 236 ml/kg in infants.<sup>[28]</sup> Metabolism is mainly by hydroxylation and glucuronide conjugation in the liver followed by excretion by kidneys approximately 40% as metabolites and 60%



unchanged.<sup>[26]</sup> The elimination clearance of ketorolac is  $0.57 + 0.17$  ml/kg/min in children above 1 year of age compared to 1.52 ml/kg/min in neonates and infants. The difference, however, is not appreciated after allometric scaling.<sup>[28,29]</sup> The half-life of ketorolac is 4–6 h. Based on this pharmacokinetic profile, a dosing regimen of 0.5 mg/kg every 6 h is sufficient to maintain a trough concentration greater  $EC_{50}$  for analgesia, which is 0.37 mg/L based on adult data.<sup>[30]</sup>

Ketorolac is a very potent analgesic. Ketorolac single dose (0.6 mg/kg) has been shown to provide comparable postoperative pain relief to morphine (0.1 mg/kg) in children admitted to the intensive care unit.<sup>[31]</sup> In comparison to paracetamol, use of ketorolac for pain management after cardiac surgery in children resulted in better pain relief and less use of rescue fentanyl on first 2 postoperative days. This randomized control trial included 81 children over 1 year weighing more than 10 kg who received either paracetamol 15 mg/kg or ketorolac 0.5 mg/kg every 6–8 h up to 48 h. Pain scores were significantly lower, and no of rescue fentanyl was used in the ketorolac group compared to paracetamol with a comparable incidence of side effects.<sup>[32]</sup>

Many studies have evaluated the safety of ketorolac in cardiac surgical infants. Moffett *et al.* conducted a retrospective chart review of 53 infants younger than 6 months including 11 neonates who received ketorolac for 48 h following cardiac surgery. Cardiopulmonary bypass was used for 83% of patients. Thirty percent (16/53) of patients had a significant increase in serum creatinine and blood urea nitrogen from baseline. However, the clinical significance of this increase was questionable as all values remained within the normal range for age. The values returned to baseline subsequently negating concerns of persistent renal injury.<sup>[33]</sup> Similarly, Dawkins *et al.* studied 19 infants <6 months of age and compared them with matched controls and did not find any significant difference in the renal functions from baseline. The study did not include patients with single-ventricle physiology or preoperative renal impairment.<sup>[34]</sup> Studies involving older children also show similar results.<sup>[35]</sup> A small retrospective case–control study conducted on 14 infants younger than 6 months identified the concomitant use of aspirin and bidirectional Glenn procedure to be associated with worsening of renal functions after ketorolac use.<sup>[36]</sup>

The risk of bleeding associated with ketorolac use is low. Gupta *et al.* performed a randomized controlled trial to evaluate the risk of bleeding with ketorolac use after cardiac surgery in 70 pediatric patients including infants <6 months of age. Bleeding risk was assessed by chest tube drainage, wound bleeding as measured by visual inspection and dressings, and GI bleeding. No significant difference was found in the chest tube

drainage (median output 13.3 in ketorolac vs. 16.5 in the nonketorolac group) and wound bleeding between the groups. One patient had GI bleed without any change in hematocrit. The study excluded patients with a history of recent GI bleed, bleeding in first 6 postoperative h, cardiac transplantation, or delayed sternal closure.<sup>[37]</sup> Moffett *et al.* reported episodes of minor bleeding in 4/53 infants without any hemodynamic instability, the need for blood transfusion or significant change in hemoglobin and platelet count.<sup>[33]</sup> Dawkins *et al.* found no significant difference in hemoglobin, hematocrit, platelet counts, or number of blood transfusions in patients who received ketorolac compared to the nonketorolac group.<sup>[34]</sup> Gupta *et al.* performed a retrospective case–control study on 94 patients and looked at the rates of clinically significant bleeding requiring surgical exploration and found no significant difference between ketorolac and nonketorolac group. This study was, however, performed on older children with a mean age of  $8.5 \pm 6.1$  and  $6.7 \pm 5.6$  in the two groups.<sup>[38]</sup>

Even though these studies provide important data on the efficacy and safety profile of ketorolac in cardiac surgery patients, there are many important considerations to the interpretation of these data. Majority of these studies are retrospective and have relatively small sample sizes. They lack uniformity in patient selection and outcome parameters. Patients with single-ventricle physiology and those undergoing cardiac transplantation are at high risk of adverse effects and are often excluded. Data on neonates continue to be limited. Concomitant use of aspirin and anticoagulation is common in patients undergoing cardiac surgery, but has not been adequately discussed in the literature.

### Ibuprofen

Ibuprofen is a propionic acid derivative, which is commonly used in the management of pain and fever in neonates and infants. Ibuprofen comprises R and S enantiomers with S-enantiomer responsible for its analgesic activity.<sup>[39]</sup> It is available in oral, rectal, and intravenous preparations. Ibuprofen is completely absorbed after oral administration with time to maximum concentration ( $T_{max}$ ) of 2 h with tablet form and <0.25 h with oral solutions.<sup>[40]</sup> Rectally administered ibuprofen has less bioavailability and longer  $T_{max}$  compared to oral preparation.<sup>[39]</sup> Ibuprofen is >98% protein bound<sup>[41]</sup> and has a volume of distribution between 6.37 and 23.5 L.<sup>[39]</sup> The drug is extensively metabolized in the liver by cytochrome 2C9 and glucuronide conjugation.<sup>[17]</sup> Approximately 70%–90% of ibuprofen and its metabolites are excreted by the kidneys translating into a  $t_{1/2}$  of about 2 h.<sup>[39]</sup> Pharmacokinetics of ibuprofen in children 3 months to 10.4 years of age is similar to that in adults.<sup>[42]</sup> However, preterm infants have a substantially prolonged  $t_{1/2}$  (34.3 h) and slower clearance (3.5 ml/kg/h) for

S enantiomer which can be attributed to immature cytochrome 2C9 enzyme system in premature infants.<sup>[43]</sup> The recommended dose of ibuprofen is 10 mg/kg every 6 h in children to attain  $EC_{50}$  of 24.4 + 1.2 mg/L. For rectal administration, a dose of 20 mg/kg is required to achieve therapeutic levels.<sup>[44]</sup> In preterm infants, a loading dose of 10 mg/kg is followed by 5 mg/kg every 24 h.

There is some evidence for the efficacy of ibuprofen as an opioid-sparing agent in the perioperative period [Table 2]. Viitanen *et al.* found significant opioid-sparing effects of ibuprofen in children 1–6 years of age undergoing adenoidectomy. Ibuprofen 15 mg/kg administered rectally just after induction of anesthesia resulted in a significant reduction in cumulative meperidine requirements (0.78 vs. 1.07 mg/kg) compared to placebo. Earlier fulfillment of discharge criteria was also reported.<sup>[45]</sup> In children 4–12 years of age undergoing noncardiac surgery, per rectal ibuprofen at a dose of 40 mg/kg/d beginning in the preoperative period resulted in significant reduction in the need for opioids in the first 3 days after surgery. No adverse effects associated with ibuprofen use were reported in this study.<sup>[46]</sup> Intravenous ibuprofen has been found to be useful in postoperative pain management in adults. However, studies on the use of intravenous ibuprofen lack in the pediatric population.<sup>[47]</sup> Ibuprofen has the same side effect profile as ketorolac with concerns of renal injury and bleeding following cardiac surgery. There are no studies available which have looked at its use in this specific population group.

### Acetaminophen

Acetaminophen is an analgesic and antipyretic acting via inhibition of peroxidase activity of COX-1 and COX-2 enzymes. The analgesic effect of this drug is weak in comparison to other NSAIDs, but it has a better safety profile with good gastrointestinal tolerance and minimal antiplatelet activity.<sup>[48]</sup> Its efficacy is well established for the treatment of fever in pediatric patients and patent ductus arteriosus in preterm neonates.<sup>[49,50]</sup> Acetaminophen is also used for pain management involving a variety of painful procedures, albeit the evidence for its analgesic effect is less concrete [Table 2].

Acetaminophen can be administered via the oral, rectal, and intravenous route. Peak concentration is attained at 45–60 min after oral administration and 3.5–4.5 h after rectal administration.<sup>[17]</sup> Population pharmacokinetic analysis of acetaminophen involving 943 observations from 158 neonates reports notable differences with weight and gestational age in various parameters. Clearance was 5 L/h/kg compared to 16.2 L/kg/h in adults which was attained at 1 year of age. Likewise, the volume of distribution decreased from 51.9 L/70 kg to adult values of 35.4 L/70 kg by 6 months of age.<sup>[51,52]</sup> Acetaminophen has a  $t_{1/2}$  of 277 min in premature

infants compared to 172 min in term infants.<sup>[53]</sup> A pharmacodynamic study of the analgesic effect of acetaminophen in children after tonsillectomy showed a plasma concentration of 10 mg/l to be sufficient to have an optimal analgesic effect.<sup>[54]</sup> With the backdrop of above-described pharmacokinetic parameters, dosing regimen for intravenous acetaminophen should consist of a loading dose of 20 mg/kg followed by 10 mg/kg every 6 h in neonates and infants between 32 and 44 weeks and 15 mg/kg every 6 h for older infants.<sup>[51,52]</sup> The dosing interval should be increased to 12 h below 31 weeks.<sup>[55]</sup> A dose of 40 mg/kg is recommended for per rectal use.<sup>[56]</sup> The liver metabolizes acetaminophen by glucuronyl transferase (52%–57%) and sulfation (30%–44%). A minor pathway involving oxidation (5%–10%) via CYP2E1 results in the synthesis of a toxic metabolite N-acetyl-p-benzoquinone imine, which is responsible for its hepatotoxicity. Immaturity of CYP2E1 in neonates makes them less susceptible to acetaminophen hepatotoxicity.<sup>[17]</sup>

Acetaminophen is a relatively safe drug to use after cardiac surgery because it is devoid of the risk of renal dysfunction and bleeding associated with other NSAIDs. Data on hepatic tolerance after repeated intravenous administration in neonates also suggest a favorable profile and no significant changes in hepatic enzymes with therapeutic doses of acetaminophen.<sup>[57]</sup> Acetaminophen is a weak analgesic. In a recently published systematic review, acetaminophen has been found comparable to placebo for heel lance and eye examination in neonates.<sup>[58]</sup> However, opioid-sparing effect with the perioperative use of acetaminophen has been observed in both neonates and older children. Ceelie *et al.* conducted a randomized controlled trial comparing morphine to paracetamol for postoperative analgesia. This trial included seventy neonates and infants undergoing noncardiac thoracic or abdominal surgery. They found a 66% reduction in cumulative morphine dose (121 vs. 357 ug/kg) in the paracetamol group compared to the morphine group when attaining a similar degree of pain relief.<sup>[59]</sup> Hong *et al.* performed a randomized controlled trial to evaluate the role of acetaminophen as an adjunct to fentanyl after ureteroneocystostomy. The study enrolled 63 infants of 6–24 months of age. Fifty percent reduction in the cumulative dose of fentanyl occurred with the concurrent use of acetaminophen on the first 3 postoperative days. Significant reduction in the incidence of vomiting and sedation was also reported.<sup>[60]</sup> Similar results, albeit in older children, have been published following adenotonsillectomy<sup>[45,61]</sup> and day case surgeries.<sup>[62]</sup> The results have been inconsistent, and many studies fail to show similar benefits in reducing opioid use in the perioperative period.<sup>[63,64]</sup> One possible explanation for such varied results could be differences in the preparations and route of administration of the drug in

different studies. The literature on acetaminophen use after cardiac surgery in children is sparse. Nevertheless, there is some evidence favoring its role as an adjunct to opioids. Furthermore, the drug has an excellent safety profile. A potential role of acetaminophen in preventing hemolysis and acute kidney injury during cardiopulmonary bypass is also being explored in recent studies.<sup>[65]</sup> Further studies are warranted to investigate its use in infants following surgery for CHD. A multicenter randomized controlled trial is currently underway comparing morphine to acetaminophen in neonates and infants after cardiac surgery.<sup>[66]</sup>

### Other nonsteroidal anti-inflammatory drugs

Ketoprofen is another propionic acid derivative which when used as an adjunct can reduce perioperative opioid use. Ketoprofen is available in intravenous, rectal, and oral preparations. Pharmacokinetic studies of ketoprofen in children 7 months to 16 years of age after intravenous administration of 1 mg/kg revealed a volume of distribution 0.16 L/Kg (0.12–0.21 L/kg), clearance 0.09 L/kg/h (0.06–0.13 L/kg/h), and  $t_{1/2}$  1.3 h (0.8–1.7 h).<sup>[67]</sup> Bioavailability after the oral and rectal dose is about 75% with similar pharmacokinetic properties.<sup>[68,69]</sup> Ketoprofen provides a good degree of analgesia and reduces postoperative opioid analgesia in children over 1 year of age after noncardiac surgeries, particularly in the setting of adenotonsillectomy. The drug is overall well tolerated without untoward side effects.<sup>[70,71]</sup> The oral and intramuscular route is comparable to the intravenous administration for pain management.<sup>[72,73]</sup> Comparison with paracetamol and tramadol found ketoprofen to be more effective than either of the drug.<sup>[74,75]</sup> Other NSAIDs sporadically studied in the pediatric population in the setting of surgical management include intravenous indomethacin, rectal diclofenac, oral rofecoxib, and naproxen. Data are weak and involve older and stable children undergoing noncardiac surgeries.

In addition to NSAIDs, there is also interest in various NMDA receptor antagonists as potential analgesics. Ketamine and dextromethorphan have strong evidence to support their use for the management of postoperative pain in adults.<sup>[76]</sup> Similarly, a meta-analysis of pediatric studies showed ketamine to be effective in decreasing postoperative pain intensity and need for nonopioid analgesics, but did not demonstrate efficacy as an opioid-sparing agent. However, the studies evaluated in this meta-analysis involved noncardiac day surgeries such as adenoidectomy and circumcision.<sup>[77]</sup> There are no data for these agents in the setting of cardiac surgeries in neonates and infants.

## CONCLUSIONS

Opioid analgesics continue to be the mainstay of postoperative analgesia after cardiac surgery in infant

and neonates. However, there is increasing awareness of the long-term adverse impact of their use and therefore a strong interest in evaluating nonopioid options. Nonsteroidal anti-inflammatory agents show promise in this regard, with ketorolac being the most potent agent as a potential substitute for opioids. Agents such as acetaminophen and ibuprofen appear to have at least an opioid-sparing role in postoperative analgesia. Overall, all of these agents have a reasonable safety profile even in the very young. There continue to be significant gaps in knowledge before their adoption becomes routine. Further studies need to systematically evaluate the comparative analgesic efficacy of ketorolac compared to opioid in neonatal and pediatric cardiac surgery. Studies to assess opioid-free regimens in cardiac surgery need to be conducted. Similarly, systematic studies are needed to assess the opioid-sparing effect of routine acetaminophen or ibuprofen in this population. There is also a need for improved understanding of the long-term impact of opioid and nonopioid analgesics in neonatal and pediatric cardiac populations. This review provides a current state of knowledge and hopefully underscores the needs to improve postoperative care of children.

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### Conflicts of interest

There are no conflicts of interest.

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