Intravenous Acetaminophen and Intravenous Ketorolac for Management of Pediatric Surgical Pain: A Literature Review

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Pediatric surgical patients are a population at risk of inadequate pain management. The American Society of Anesthesiologists' 2012 Practice Guidelines for Acute Pain Management in the Perioperative Setting recommend a multimodal approach as the most effective way to prevent and treat pain in children. A multimodal approach entails the use of 2 or more analgesic medications that act by different mechanisms, to maximally target a variety of pain receptors and reduce the potential for side effects. One method for incorporating a multimodal approach is to augment intravenous (IV) opioids with nonopioid IV analgesics. Ketorolac and acetaminophen are the 2 nonopioid IV analgesics currently available for use in the United States. This article provides a review of the literature of IV ketorolac and IV acetaminophen regarding their pharmacology, analgesic efficacy, limitations, and practical considerations, with a focus on patients 16 years of age and younger.

Keywords: Acetaminophen, anesthesia, ketorolac, multimodal analgesia, pediatric.

The historic undertreatment of pain in the pediatric population is a problem that anesthesia providers are challenged to eliminate. In the American Society of Anesthesiologists' (ASA's) 2012 *Practice Guidelines for Acute Pain Management in the Perioperative Setting*, pediatric patients are identified as a subpopulation at risk of inadequate pain control and requiring additional analgesic consideration.[1] The *Practice Guidelines* recommend a proactive approach to pain management with analgesic therapy based on age and weight, and embracing a multimodal approach.[1] A multimodal approach may be characterized by the use of 2 or more analgesic medications that act by different mechanisms, which can be administered via the same or different routes. It is believed that a combination of medications optimizes analgesic efficacy while minimizing adverse effects of any one medication used alone.[1]

Intravenous (IV) ketorolac and IV acetaminophen are 2 such nonopioid medications, whose administration combined with other analgesics addresses multimodal therapy, as well as the ASA's recommendation to initiate a regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX) 2–selective NSAIDS, or acetaminophen in pediatric surgical patients.[1] Intravenous acetaminophen and IV ketorolac have been used successfully, both alone and in conjunction with opioids, to manage surgical pain in various settings around the world.[2-4] Ketorolac has been widely administered in the United States since gaining Food and Drug Administration (FDA) approval in 1989. Overall, it has a well-established safety profile, but concerns have been raised regarding the potential to exacerbate hemorrhage. Acetaminophen (Tylenol) has been a mainstay of pain management for more than 50 years and is currently the most prescribed analgesic and antipyretic in children.[5] The parenteral formulation achieved FDA approval in 2010, but has been safely used in Europe for more than 20 years in adults and children.[6,7]

This article will review and compare IV ketorolac and IV acetaminophen regarding their pharmacologic profiles, analgesic potentials alone and in conjunction with opioids, their limitations, and considerations such as ease of administration and cost. It will provide a summary of each drugs' risks and benefits, to promote a more educated, individualized provision of multimodal pain management in surgical patients 16 years of age and younger.

Pharmacologic Profiles

• ***Ketorolac.*** Ketorolac tromethamine is the only IV NSAID currently available for use in the United States. It is administered as a racemic mixture; the S(–) isomer is responsible for the analgesic effects of the medication.[8] Ketorolac acts at central and peripheral sites in the body. It inhibits COX-1 and COX-2, with a slightly increased affinity for COX-1.[9] Both COX-1 and COX-2 are enzymes that play a role in the formation of chemical mediators in the body. Inhibition of these enzymes by ketorolac primarily prevents the production of prostaglandin-2

(PGE_2), a chemical mediator and subclass of prostaglandin active in many body functions, including nociception, inflammation, smooth muscle contraction and relaxation, gastric acid and mucus secretion, renal vasculature constriction and dilation, and febrile reactions.[9,10] Alterations to these body functions as a result of changes in PGE_2 production are responsible for both the desired and undesired effects of ketorolac.[9,10] Synthesis of thromboxane, a chemical mediator that promotes platelet aggregation, is also halted through COX-1 inhibition; this plays a part in ketorolac's known tendency to increase bleeding.[11] However, this effect on thromboxane, like the effect on PGE_2, is limited to the duration of action of the medication; platelet function should return to normal once the medication has been eliminated from the body.[8,11]

To have central nervous system (CNS) effects, ketorolac must cross the blood-brain barrier (BBB). In pediatric patients, ketorolac does penetrate the BBB, although in small amounts.[9] A study comparing cerebral spinal fluid (CSF) and plasma concentrations of ketorolac found that CSF concentrations were less than 0.05% of the plasma concentrations. However, CSF peak concentrations correlated positively with the peak analgesic effect of the medication, suggesting that this drug has a substantial CNS mechanism of action. This study further found that CSF concentrations of ketorolac vary inversely with age, height, weight, and body surface area, suggesting that younger and smaller patients have increased CNS levels of ketorolac, and possibly an increased CNS mechanism of action.[9]

For patients 2 years of age and older, the recommended dosage of IV ketorolac is 0.5 to 1 mg/kg per dose, up to the maximum of 30 mg per dose, given every 4 to 6 hours.[6,10] The recommended maximum duration of use in the United States is 5 days.[6,10] Several studies have verified the effectiveness of this dosing regimen and found few serious adverse effects, even in patients as young as 2 months of age.[6,10,12,13] Ketorolac has an onset of analgesic action of approximately 15 to 20 minutes, with a peak effect of 30 to 60 minutes[9,10] and a duration of action between 6 and 8 hours.[6,10] The average terminal half-life of ketorolac in pediatric patients is 6.1 hours. The mean volume of distribution at steady state is 0.26 L/kg, nearly twice that found in adult patients, presumably because of increased body water and slightly decreased protein binding.[6,14]

Ketorolac is metabolized primarily through hepatic conjugation with glucuronic acid to inactive metabolites, and excreted via the kidneys. The clearance of ketorolac in pediatric patients is 0.7 mL/kg/min, twice the clearance observed in adult patients.[6,14] A study in pediatric patients found that 56% of an administered IV dose of ketorolac was recovered unchanged in urine, suggesting that hepatic damage due to buildup of ketorolac is unlikely.[14] Two other studies also found increased clearance rates in pediatric patients aged 2 to 6 months[13] and aged 6 to 18 months[12] compared with adults. Results from these studies revealed rapid clearance of the S(–) isomer, with slower clearance of the R(+) isomer. In patients aged 2 to 6 months, mean clearance of the S(–) isomer was found to be 5 mL/min/kg, compared with 1.04 mL/min/kg for the R(+) isomer.[13] In patients aged 6 to 18 months, mean clearance of the S(–) isomer was 4.4 mL/min/kg, whereas mean clearance of the R(+) isomer was 1 mL/min/kg.[12] Based on these findings, regular use of ketorolac, and possibly more frequent dosing in infants may be tolerated. However, the authors hesitate to encourage this, as the effects of buildup of the R(+) isomer remain unknown.

• ***Acetaminophen.*** Acetaminophen, also known as paracetamol (the names are derived from different abbreviations of their identical chemical name), has been used as an analgesic and antipyretic for nearly 100 years. However, its exact mechanism of action is still not entirely understood.[15] Possible areas of activity include *N*-methyl-D-aspartate (NMDA) receptor inhibition,[15,16] serotonergic antagonism,[15,16] and, primarily, prostaglandin synthesis inhibition, namely PGE_2, both centrally and peripherally.[15,17] Through the inhibition of these various chemical mediators, the nociceptive pathway is blocked, and pain impulses are not transmitted. Acetaminophen appears to have a higher affinity for COX-2 than COX-1, which partly explains its lack of effect on platelets and bleeding time, because COX-2 has not been shown to play a role in the production of thromboxane.[15]

Like ketorolac, acetaminophen must be able to cross the BBB to exert CNS effects. One study has shown that acetaminophen readily crosses the BBB in children.[17] In that study, CSF levels of acetaminophen were detectable within 5 minutes of IV administration. In approximately 1 hour, measured CSF and plasma concentrations of acetaminophen were similar. This coincides with both the onset and peak analgesic effect of IV acetaminophen, which the manufacturer and other researchers state as being 5 to 15 minutes and 1 hour, respectively.[15-17] This study further revealed that, unlike ketorolac, there was no correlation between CSF concentrations of acetaminophen and patient age, height, or weight.

In the United States, IV acetaminophen is approved for use in patients 2 years of age and older. It has both an onset and peak effect of 15 minutes or less, and a duration of analgesic effect between 4 and 6 hours.[16] Dosing depends on patient weight and age, as well as the intended frequency of administration. For all patients 2 to12 years of age, and any patient weighing less than 50 kg, the dose is 12.5 mg/kg per dose if using an every-4-hour schedule, or 15 mg/kg per dose if using an every-6-hour schedule. The maximum single dose for these patients is 15 mg/kg, or 750 mg, given either dosing schedule. The maximum daily (24-hour) dose for these patients is 75 mg/kg, or 3,750 mg. For patients 13 years of age and older and

weighing 50 kg or greater, 1,000 mg of IV acetaminophen should be administered every 6 hours. The maximum daily (24-hour) dose for these patients is 4,000 mg.[16]

Intravenous acetaminophen administration in children less than 2 years of age is considered off-label use in the United States, and suggested dosages must therefore be gleaned from the results of studies from other countries. Several such studies have been completed, and they have largely found that IV acetaminophen is well tolerated in infants and small children, even as young as 28 weeks' gestation.[18-20] These studies showed that clearance rates of the drug increase as age increases, from 0.132 L/h/kg at 28 weeks' gestation, up to 0.21 L/h/kg at 42 weeks' gestation.[18] This correlates with increasing maturity of the hepatic system with increasing age. Mean clearance in the older pediatric patient is 0.27 L/h/kg.[16] Elimination half-life also decreases with age, from an average of 3.5 hours in the neonate to 1.5 to 2 hours in the pediatric patient.[15] The volume of distribution at steady state in the pediatric patient remains relatively constant, with a mean of 70.4 L/70 kg.[18]

Acetaminophen is metabolized via glucuronidation and sulfation in the liver.[15,16] In neonates and children up to 10 years of age, studies have shown preferential metabolism via sulfation, possibly indicating a decreased risk of hepatotoxicity, because hepatotoxicity is primarily due to the buildup of metabolites from glucuronidation.[15,19,20] However, even in the absence of supporting evidence, concerns about hepatotoxicity in infants continue to exist, possibly related to the 100% bioavailability of IV acetaminophen compared with the rectal and oral formulations. The authors of several studies suggest that a reduction in dosage (milligrams per kilogram) may be warranted, given the immature functioning of the neonatal liver.[19,20] In other countries, IV acetaminophen is often used for neonatal and infant pain management at dosages of 7.5 to 10 mg/kg.[18-20] Practitioners in the United States who choose to use IV acetaminophen off-label may want to consider this reduced dosage for pediatric patients less than 2 years of age.

• ***Analgesic Efficacy of Ketorolac and Acetaminophen.*** Pain management, an essential component of the anesthetic plan, is most commonly achieved via administration of opioids. The nonopioid analgesics ketorolac and acetaminophen are useful adjuncts that may help to improve pain control. In pediatric patients these medications may be beneficial, as there is some evidence to suggest that they aid in the reduction of opioid-related complications such as sedation.[1] Furthermore, the administration of opioid and nonopioid analgesics in combination is in keeping with the concept of multimodal pain management, which has been identified as a highly effective means of managing pain in pediatric patients.[1]

The Table presents a summary of 10 prospective, double-blind, randomized control trials that examined ketorolac and acetaminophen use alone, in combination with each other, and in combination with opioid analgesics. These studies were selected from peer-reviewed journals because of their focus on common pediatric surgical procedures and their IV administration of at least one of the drugs of interest for this literature review (acetaminophen or ketorolac). The primary dependent variable of all these studies was the analgesic efficacy of the administered medications. Additionally, these studies examined the effect of ketorolac and acetaminophen on postoperative complications such as sedation and postoperative nausea and vomiting (PONV). Nine of the studies focused specifically on pediatric patients ranging in age from 6 months to 16 years. One study examined adult patients ranging in age from 13 to 81 years but was deemed relevant in that strabismus surgery is a common pediatric procedure.

• *Ketorolac Clinical Trials.* Three studies (see Table) examined the efficacy of IV ketorolac at dosages of 0.5 to 1.0 mg/kg given at various times during the perioperative period. These studies found no decrease in opioid consumption with ketorolac administration compared with tramadol,[3] morphine,[11] or placebo.[12] The use of ketorolac did not appear to result in significant improvement in recovery or discharge times.[3,11,12] In addition, ketorolac administration was associated with a statistically significant increase in bleeding time in pediatric patients undergoing inguinal hernia repair,[3] as well as a clinically significant increase in bleeding episodes in pediatric patients undergoing tonsillectomy.[11]

• *Acetaminophen Clinical Trials.* Four studies (see Table) focused on the effect of IV acetaminophen on pain control, opioid consumption, and satisfaction scores. The methods for acetaminophen administration among these studies differed, but overall, the results suggested that IV acetaminophen is an effective adjunct to opioid analgesics.[2,4,21,22] However, IV acetaminophen was shown to be an inadequate replacement for opioids in pediatric patients undergoing dental restoration,[2] ureteroneocystostomy,[4] tonsillectomy,[21,22] and adenoidectomy.[22] The research further suggests that acetaminophen in combination with opioids may result in less postoperative sedation,[2,21] increased readiness for discharge from the postanesthesia care unit (PACU),[2,21] and favorable parent and staff satisfaction scores compared with opioids alone.[4]

• *Ketorolac versus Acetaminophen Clinical Trials.* Two studies (see Table) directly compared the analgesic effectiveness of acetaminophen and ketorolac. In the first study, of patients undergoing strabismus surgery, the authors reported that IV ketorolac, 60 mg, provided adequate pain control without additional analgesics.[23] In contrast, oral acetaminophen did not appear to be effective as a solo agent.[23] After this study's publication in 1994, the FDA revised ketorolac dosing recommendations to 30 mg per dose in adults, based on findings of

Year of publication/ Authors	Demographics	Surgical procedure analgesic comparisons and dosages	Anesthetic management	Postop adverse effects I: PONV II: Bleeding III: Respiratory Depression IV: Pulse Oximetry Values	Results
2011, El Deeb, El-Morsy[3]	• n=80 • Age 2-12 years • PS I and II • Exclusion criteria: renal dysfunction, coagulopathy, family history of bleeding disorders, required premedication	• Inguinal hernia repair • Group T: IV tramadol 1 mg/kg • Group K: IV ketorolac 1 mg/kg • Study drug given one time after induction	• No premedication • Induction: IV thiopental 4-6 mg/kg IV cisatracurium 0.09 mg/kg • Maintenance: 2% sevoflurane, 50/50 air/oxygen mixture • IV fentanyl 1 µg/kg given intra-op if BP or HR increased greater than 15% above pre-op values • No other sedatives or opioids given during the operation • NMB reversal at end with IV neostigmine 50 µg/kg and IV atropine 20 µg/kg • Deep extubation • PACU: Rectal acetaminophen and IV fentanyl rescue analgesics if needed	• I: no statistically significant difference between groups • II: intra-op bleeding time significantly longer in group K (*P*=.04) but still within normal limits	• Time to first rescue analgesic shorter in group K (*P*=.003) • Total opioid consumption higher in Group K (*P*=.001) • PACU pain scores higher in group K (*P*=.003) (FLACC scale) • No statistically significant difference between groups for sedation scores (4-point scale), PACU discharge times, or unplanned hospital admissions
2011, Uysal et al[22]	• n=64 • Age 6-16 years • PS I and II • Exclusion criteria: active and severe renal, respiratory, hepatic, cardiac, or neuromuscular disorders	• Tonsillectomy and adenoidectomy • Group A: IV acetaminophen 15 mg/kg • Group T: IV tramadol 1 mg/kg • Study drug given one time after induction	• PO midazolam 0.5 mg/kg given 30 minutes before surgery • Induction: IV propofol 2-3 mg/kg, IV fentanyl 1 µg/kg, IV vecuronium 0.1 mg/kg • Maintenance: 1.5-2.5% sevoflurane, 50/50 nitrous oxide/oxygen mixture • No additional opioids given intra-op • NMB reversal at end with IV neostigmine 0.04 mg/kg and IV atropine 0.02 mg/kg • Extubated when respirations regular and adequate in rate and depth • PACU: IV meperidine, PO ibuprofen, and PO acetaminophen rescue analgesics if needed	• I: no statistically significant difference between groups	• No statistically significant difference between groups for postop pain scores (modified Hannallah Pain Scale) or rescue analgesia requirements • No statistically significant difference between groups for Aldrete scores, sedation scores (4-point scale), parent and nurse satisfaction scores (4-point scale), or incidence of emergence agitation (PAED scale)

2010, Hong et al[4]	• n=63 • Age 6-24 months • PS I and II • Exclusion criteria: kidney or liver dysfunction, required premedication	• Ureteroneocystostomy • Group FA: IV fentanyl 0.5 µg/kg and IV acetaminophen 15 mg/kg • Group F: IV fentanyl 0.5 µg/kg • Initial dose of study medications given at peritoneal closure • Post-op, all patients on PCNA pump with basal infusion rate, maximum duration of usage 72 hours • Group FA: IV fentanyl 0.25 µg/kg/hr and IV acetaminophen 1.5 µg/kg/hr • Group F: IV fentanyl 0.25 µg/kg/hr	• No premedication • Induction: IV thiopental 5 mg/kg, IV rocuronium 0.6 mg/kg • Maintenance: 1-4% end-tidal sevoflurane, air/oxygen mixture with inspired oxygen equal to 50% • IV fentanyl 1 µg/kg given to all patients after induction but before incision	• I: higher incidence in group F (P=.011)	• On both POD 1 and 2, total dose of fentanyl received by group FA was half that received by group F • Cumulative dose of fentanyl over 72 hours was significantly lower in group FA (P<.05) • Sedation scores higher in group F (P=.019) (modified Ramsey Sedation Scale) • No statistically significant difference in pain scores between groups (Children's Hospital of Eastern Ontario Pain Scale) • Parent satisfaction scores higher in group FA (P=.02) (4-point scale)
2010, Hong et al[4]	• n=55 • Age 1-5 years • Exclusion criteria: kidney or liver dysfunction, hemorrhagic diathesis, asthma, history of long-term analgesic use, required premedication	• Unilateral inguinal hernia repair • Group KA: IV ketorolac 1 mg/kg and IV acetaminophen 20 mg/kg • Group C: control, IV saline • Study drug given one time after induction	• No premedication • Induction: inhalation of 8% sevoflurane in oxygen, IV atracurium 0.5 mg/kg • Maintenance: 1-4% sevoflurane, air/oxygen mixture with inspired oxygen equal to 50% • IV fentanyl 1 µg/kg given to all patients after induction but before incision • No other opioids given intra-op • Awake extubation • PACU: IV fentanyl rescue analgesic if needed	• I: higher incidence in group C (P=.016) • III: no occurrence in either group	• Lower total consumption of fentanyl, fewer patients received rescue fentanyl in PACU in group KA (P=.001 for both) • Higher pain scores on arrival to PACU in group C (P=.041) (Wong-Baker FACES Scale) • Higher incidence of sedation in PACU in group C (P=.023) (modified Ramsey Sedation Scale) • No statistically significant difference in time to discharge between groups
2007, Alhashemi, Daghistani[2]	• n=40 • Age 3-16 years • PS I and II • Exclusion criteria: planned extractions, developmental delay, renal insufficiency, neurologic dysfunction	• Dental restorations • Group A: IV acetaminophen 15 mg/kg • Group Me: IM meperidine 1 mg/kg • Study drug given one time after induction	• PO midazolam 0.5 mg/kg given 30 minutes before surgery • Induction: sevoflurane inhalation or IV propofol 2-3 mg/kg • Maintenance: sevoflurane, oxygen/nitrous oxide mixture • IV fentanyl 1 µg/kg given to all patients immediately after induction • No other intra-op analgesics, local anesthetics, or anti-emetics given • Awake extubation • PACU: IV morphine rescue analgesic if needed	• I: no statistically significant difference between groups • III, IV: no occurrence in either group	• Lower PACU pain scores in group Me (P=.012) (OPS) • Increased incidence of sedation in PACU in group Me (P=.0130) (Ramsey Sedation Score) • Group A achieved Aldrete score of 10 and readiness for discharge faster than group Me (P=.009)

continues on page 58

continued from page 57

Year of publication/ Authors	Demographics	Surgical procedure analgesic comparisons and dosages	Anesthetic management	Postop adverse effects I: PONV II: Bleeding III: Respiratory Depression IV: Pulse Oximetry Values	Results
2007, Lynn et al[12]	• n= 37 • Age 6-18 months • Patients admitted after surgery • Exclusion criteria: < 36 weeks gestation at birth, history of GI bleed, hepatic or renal impairment, coagulopathy in patient or family member	• Craniectomy, other neurosurgery, general, plastic, urologic, and cardiac surgical procedures • Group P: IV placebo • Group K0.5: IV ketorolac 0.5 mg/kg • Group K1: IV ketorolac 1 mg/kg • Study drug given one time on POD 1 • All patients placed on continuous infusion of IV morphine at 5-30 µg/kg/hr	• No details of anesthetic management provided	• II, IV: no statistically significant difference among groups • No statistically significant difference in BUN, creatinine, AST, ALT, or urine analysis results among groups	• No statistically significant difference in morphine consumption between groups • Authors suggest this was possibly due to a reluctance to wean medication based on satisfactory pain scores (FLACC scale) and lack of adverse effects
2006, Alhashemi, Daghistani[21]	• n=80 • Age 3-16 years • PS I and II • Exclusion criteria: developmental delay, neurologic dysfunction, renal insufficiency	• Tonsillectomy • Group A: IV acetaminophen 15 mg/kg • Group Me: IM meperidine 1 mg/kg • Study drug given onetime after induction	• PO midazolam 0.5 mg/kg given 30 minutes before surgery • Induction: sevoflurane inhalation or IV propofol 2-3 mg/kg • Maintenance: sevoflurane, oxygen/nitrous oxide mixture • IV fentanyl 1 µg/kg given to all patients immediately after induction • No other intra-op analgesics given • PACU: IV morphine rescue analgesic if needed	• I, II, III, IV: no statistically significant differences between groups	• No statistically significant difference in pain scores between groups (OPS) • Group A had a greater number of patients requiring rescue analgesia in PACU • Increased incidence of sedation in group Me (P=.031) (Ramsey Sedation Scale) • Aldrete score of 10 and readiness for discharge achieved sooner in group A (P=.005 for both) • No statistically significant difference between groups for PACU RN satisfaction with analgesia (7-point scale)
1995, Gunter et al[11]	• n= 96 • Age 1-12 years • Exclusion criteria: significant underlying medical conditions, airway abnormalities, asthma, bleeding disorders, family history of bleeding disorders	• Tonsillectomy • Group Mo: IV morphine 0.1 mg/kg • Group K: IV ketorolac 1 mg/kg • One-time dose of study medications given after surgery completed and hemostasis achieved	• No premedication • Induction: halothane inhalation in 66% nitrous oxide/33% oxygen • Maintenance: halothane and nitrous oxide • No additional intra-op analgesics given • Deep extubation • PACU: Rectal acetaminophen given to all patients on arrival; IV morphine rescue analgesic if needed	• I: lower incidence in group K (P=.006) • II: higher incidence in group K • Study stopped early due to increased incidence of major bleeding and bleeding episodes in first 24 hours after surgery	• No statistically significant difference between groups for supplemental morphine requirements in PACU • No statistically significant difference between groups in time to awakening, recovery, or discharge • No statistically significant difference between groups for unplanned admissions to the hospital

1995, Rusy et al[24]	• n=50 • Age 2-15 years • PS I and II • Exclusion criteria: renal dysfunction, egg allergy, bleeding disorders, family history of bleeding disorders	• Tonsillectomy with or without adenoidectomy • Group K: IV ketorolac 1 mg/kg • Group A: rectal acetaminophen 35 mg/kg • Study drug given given once various times intraoperatively	• No premedication • Induction: halothane inhalation in oxygen/nitrous oxide mixture, IV atracurium 0.5 mg/kg • Maintenance: 70/30 nitrous oxide/oxygen mixture, IV propofol 75-300 µg/kg/min • No opioids given pre- or intra-op • NMB reversal at end with IV neostigmine 0.05 mg/kg and IV glycopyrrolate 0.01 mg/kg • Awake extubation • PACU: IV morphine rescue analgesic if needed	• II: higher incidence in group K (*P*=.025) • 8/25 patients in group K required additional measures to achieve hemostasis • 1/25 patients in group A required additional measures	• No significant difference in pain scores between groups (OPS) • Majority of patients in both groups required additional analgesia in PACU
1994, Morrison, Repka[a23]	• n= 60 • Age 13-18 years • Exclusion criteria: history of peptic ulcer disease, platelet disorders, sensitivity to NSAIDs, >3 previous eye surgeries	• Strabismus surgery • Group A: PO acetaminophen 650 mg • Group I: PO ibuprofen 600 mg • Group K: IV ketorolac 60 mg administered at the end of surgery, plus PO placebo • PO medications given one time in PACU 35-40 minutes after surgery completed	• General inhalational anesthesia or local periocular anesthesia Intra-op sedation and IV analgesia "held constant" (p.916) regardless of anesthetic type • No additional details given regarding induction or maintenance • IV droperidol 75 µg/kg administered to all patients before surgery for PONV prophylaxis • PACU: PO acetaminophen with and without oxycodone rescue analgesic if needed	• I: 2 occurrences each in group A and group I, no occurrence in group K • II: no statistically significant difference among groups	• Lower pain scores in group K compared with group A and group I (*P*=.001) (VAS) • 63% group K required no additional pain medication, 100% group I and 80% group A required additional analgesics (*P*= .0001) • No statistically significant difference in sedation scores among groups (VAS)

Table. Studies Evaluating the Postoperative Analgesic Efficacy of IV Ketorolac and IV Acetaminophen in Common Pediatric Procedures

Abbreviations: n, number of study participants; PS, physical status; IV, intravenous; BP, blood pressure; HR, heart rate; NMB, neuromuscular blockade; PACU, post anesthesia care unit; FLACC, face legs activity cry consolability; PO, per os/by mouth; PAED, pediatric anesthesia emergence delirium; PCNA, parent/nurse-controlled analgesia; POD, postoperative day; OPS, objective pain scale; PONV, postoperative nausea and vomiting; NSAIDs, non-steroidal anti-inflammatory drugs; VAS, visual analog scale.

[a] Study enrolled teenagers and adult subjects

limited analgesic efficacy above 30 mg with an increased risk of side effects.[10]

In the second study, rectal acetaminophen was found to be equally effective to IV ketorolac in pediatric patients undergoing tonsillectomy.[24] Neither agent was found to be sufficient as a solo analgesic, because both groups required additional morphine in the PACU. Increased bleeding occurred in the patients receiving ketorolac.

• *Combined Ketorolac-Acetaminophen Clinical Trials.* One study (see Table) examined the efficacy of a combination of IV acetaminophen and IV ketorolac on total fentanyl requirements in pediatric patients undergoing inguinal hernia repair.[25] The authors reported reduced fentanyl consumption, improved satisfaction scores, less vomiting, and less sedation in the acetaminophen-ketorolac group vs the saline control group. Also, no adverse effects in the acetaminophen-ketorolac group were reported.

Limitations

• ***Ketorolac.*** The analgesic effect of ketorolac is derived from the drug's ability to inhibit prostaglandin synthesis, which is also the primary source of the drug's limitations. Like other NSAIDs, ketorolac is responsible for 2 categories of side effects, those that are predictable and caused by the inhibition of prostaglandins, and those that are unpredictable and caused for unknown reasons. Numerous studies demonstrate that NSAIDs' suppression of prostaglandin synthesis can result in gastrointestinal ulcerations and erosions, nephrotoxicity, and abnormal bleeding.[26-28] However, most of these studies did not focus on pediatric patients, nor did they test short-term intraoperative use of IV ketorolac.

• *Side Effects.* The most troublesome side effect of ketorolac is the potential for hemorrhage due to blockade of the COX-1 system. A 2001 comprehensive review of the risks and benefits of NSAID use in children specified that ketorolac has been studied primarily in children older than 1 year of age undergoing minor surgeries such as tonsillectomy, strabismus correction, myringotomy, hernia repair, and dental work.[26] The studies reviewed include IV ketorolac administered preoperatively or postoperatively as a single dose ranging from 0.5 to 1.5 mg/kg. Although many studies found no increased risk of hemorrhage after ketorolac administration, several described a correlation between ketorolac administration and postoperative hemorrhage. The authors of the review article recommended that during surgeries with the potential for substantial blood loss, such as tonsillectomy, ketorolac may be administered, 0.5 to 1.5 mg/kg, postoperatively after hemostasis has been achieved. Only a handful of studies have examined the use of ketorolac in children undergoing orthopedic, genitourinary, cardiac, or reconstructive surgeries, but notably there are no reports of any increase in bleeding complications in these more extensive procedures.[26]

Seven studies from the anesthesia, pediatric, and surgical (specifically ear, nose, and throat) literature link IV ketorolac administration with the potential for increased hemorrhage. All of the studies examined hemorrhage or coagulopathy as one of the primary outcome measures. Of these 7 studies, 2 indicated negligible increased risk of hemorrhage[12,29] and 5 demonstrated some degree of coagulopathy.[7,11,24,30,31]

Several studies highlighted the safety of ketorolac and the lack of adverse bleeding effects.[12,29] A double-blind, placebo-controlled study involving 37 patients 6 to 18 months of age demonstrated no association between ketorolac administration and bleeding.[12] The details of this study can be found in the Table. Similarly, a retrospective review of 310 pediatric patients' medical records found no significant difference in frequency of postoperative hemorrhage between patients receiving a 1-time dose of IV ketorolac in the normal dose range (ie, 0.5-1 mg/kg) compared with patients who did not receive ketorolac (2.3% for ketorolac group vs 3.1% for nonketorolac group, $P = 0.71$).[29]

Five studies were identified that suggested an association between ketorolac and bleeding,[7,11,24,30,31] including a frequently cited article from 1995, which was one of the first studies to demonstrate the adverse hemostatic effects of ketorolac in pediatric patients.[24] In this study, additional hemostatic measures (eg, packing with phenylephrine) were required more frequently in the ketorolac group than the acetaminophen group (8 vs 1, $P = .012$). Furthermore, measured blood loss was found to be greater in patients who received ketorolac than those who did not (3 ± 2 mL/kg vs 1 ± 1 mL/kg, $P = .025$). Although the blood loss in the ketorolac group was deemed clinically significant because it required extra time and work for the otolaryngologist to correct (the study labeled the bleeding "nuisance bleeding"), there were no effects on hemodynamic compromise or patient morbidity.[24] Details of the study appear in the Table. Similarly, a randomized, prospective, placebo-controlled study of 90 children undergoing elective general, orthopedic, or genitourinary procedures found that compared with bleeding times before administration of a single dose of 0.75 mg/kg intramuscular (IM) ketorolac, bleeding times at 180 minutes after study drug administration increased 53 ± 75 seconds ($P = .006$).[30] The ketorolac groups' mean bleeding time was still within the normal range and no bleeding problems or adverse effects occurred during the study. Likewise, a chart review of 258 adult and pediatric patients undergoing tonsillectomy with or without adenoidectomy reported an increased incidence of postoperative hemorrhage, operationalized as an unquantified amount of bleeding requiring surgical or medical intervention, in patients treated with perioperative IV ketorolac: 10.1% in the ketorolac group vs 2.2% in the narcotic analgesia group.[31]

In addition to the 3 studies discussed in the previous

paragraph demonstrating an association between ketorolac administration and some degree of coagulopathy, 2 studies were terminated after researchers concluded that there was an undue risk of excessive bleeding in pediatric patients treated with ketorolac undergoing tonsillectomy.[7,11] The preliminary findings from the first study[7] showed that intraoperative blood loss was significantly higher in the group that received 1 mg/kg IV ketorolac vs 1.5 mg/kg IM codeine (2.2 ± 1.9 mL/kg vs 1.3 ± 0.8 mL/kg, $P < .05$). Furthermore, 5 of the 35 patients treated with ketorolac experienced bleeding that led to unscheduled hospital admissions.[7] The second study was terminated after 49 children treated with 1 mg/kg of IV ketorolac experienced more bleeding problems than 47 children receiving 0.1 mg/kg of IV morphine.[11] Specifically, the ketorolac group experienced more bleeding that required intervention (5/49 vs 0/47, $P = .03$) and more bleeding episodes in the first 24 hours postoperatively (0.22 episodes per subject vs 0.04 episodes per subject, $P < .05$).

The tolerability profile of ketorolac is similar to that of other NSAIDs. In addition to effects on hematologic function, the most clinically important adverse events include damage to renal function[10] and the gastrointestinal tract.[27] Like other NSAIDs, ketorolac has also been linked to allergic or hypersensitivity reactions,[10] but with the increased knowledge about appropriate dosing regimens and contraindications to NSAID administration, side effects are exceedingly rare. The safety profile and favorable clinical reputation of ketorolac have been well established since the mid-1990s.[32,33] The incidence of gastrointestinal and renal adverse effects is comparable to that of placebo when the recommended dosage guidelines of IV ketorolac are followed (0.5-1 mg/kg every 4-6 hours, with a maximum use of 5 days).[32]

• *Contraindications.* Ketorolac should not be given to patients with sensitivity reactions (eg, bronchospasm) precipitated by other NSAIDs or aspirin. Ketorolac should be used with caution, and in communication with the surgeon, in children with renal or hepatic impairment, uncorrected hypovolemia or hypotension, quantitative or qualitative platelet dysfunction, ongoing or substantial bleeding, coagulation disorders, and peptic ulcer disease.[27,28] Ketorolac has been used successfully with newborns, neurosurgical patients, children with asthma, and the critically ill, although the provider should err on the side of caution when weighing the risks and benefits of ketorolac administration in these vulnerable populations.[28]

• ***Acetaminophen.*** For more than 5 decades, acetaminophen has been used in oral and rectal preparations for the management of pediatric pain and fever in the United States, and has developed a reputation for safety and efficacy. The IV preparation of acetaminophen (Ofirmev) was approved by the FDA in 2010 for use in adults and children 2 years of age and older. Although relatively new to the United States, IV acetaminophen has been in use since 2000 in nearly 80 countries.[5] Furthermore, more than 440 million units of the medication were distributed in Europe from 2002 through April 2010, representing an estimated 65 million patient exposures.[16] Although the history of IV acetaminophen use in the United States is relatively short, there is considerable safety data to draw on from European studies and the FDA approval process.

• *Side Effects.* Premarketing clinical trials conducted by the manufacturer of IV acetaminophen included 2 active-controlled and 3 open-label safety and pharmacokinetic studies, which enrolled a total of 355 pediatric subjects.[16] The most common adverse reactions (reported in ≥ 5% of patients) found were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.[16] Other reactions reported in at least 1or 2 children included anemia, tachycardia, abdominal pain, diarrhea, injection site pain, edema, hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia, muscle spasm, headache, insomnia, oliguria, pulmonary edema, pleural effusion, stridor, wheezing, rash, hypotension, or hypertension. However, these reactions could not be directly traced to IV acetaminophen administration. It was also not stated during what timeframe these reactions occurred. In contrast to side effects reported in the ketorolac literature, there were no reports of platelet inhibition or surgical site bleeding. Additionally, there were no cases of respiratory depression, postoperative ileus, sedation, cognitive impairment, upper gastrointestinal bleeding, renal toxicity, or cardiovascular thrombotic events.[16]

Independent reviews of IV acetaminophen have been favorable in their reports of tolerability and minimal side effects. A 2009 review of 8 double-blind, placebo-controlled clinical trials stated that in patients less than 16 years of age, IV paracetamol has a tolerability profile similar to in adults or with placebo.[15] Adverse reactions were rare (> 1/10,000 but < 1/1,000) for effects such as malaise, hypotension, and increased levels of hepatic transaminases and very rare (< 1/10,000) for reactions such as thrombocytopenia; appropriate acetaminophen dosing is not associated with hepatotoxicity.[15]

Two literature reviews published in 2010[34] and 2011[5] also speak to the overall safety profile of IV acetaminophen. The first, from 2010, evaluated prospective, randomized, controlled trials of IV acetaminophen vs a comparable nonopioid analgesic or placebo in the Medline and Cochrane libraries from 2000 to 2010. Sixteen articles from 9 countries published between 2005 and 2010 met inclusion criteria and included 1,464 patients. In all of the articles reviewed, no increased incidence of adverse effects was found with IV acetaminophen compared with placebo. Similarly, the second focused literature review from 2011 found that the overall risk of adverse effects or hepatotoxicity is extremely rare with therapeutic acetaminophen dosing.[5]

Several studies support that daily maximum dose recom-

mendations and concerns about hepatotoxicity are largely driven by damage caused by uncontrolled outpatient use.[5,19,20] Even in premature neonates receiving infusions of IV acetaminophen for up to 4 days, there is no evidence of hepatotoxicity.[18,20] There is a suggestion that unconjugated hyperbilirubinemia can slow clearance and thus mandate a dose reduction, although the authors do not specify a recommended dose reduction amount.[18] Currently, the manufacturers of Ofirmev are pursuing FDA approval in children younger than 2 years old, and the authors of this review found no studies that indicate increased incidence of adverse advents in neonates or infants.

• *Contraindications.* Intravenous acetaminophen should not be given to children with sensitivity reactions to acetaminophen in any form. It also should not be given to patients with known hypersensitivity to any of the inactive ingredients in the IV formulation, which include mannitol, dibasic sodium phosphate, sodium hydroxide, and hydrochloric acid.[16] Parenteral acetaminophen is absolutely contraindicated in patients with severe hepatic impairment or severe active liver disease. Caution should be exercised when administering acetaminophen to children with hepatic injury, alcohol consumption, chronic malnutrition or long-term fasting, severe hypovolemia, or severe renal impairment.

Practical Concerns

• ***Ketorolac.*** Hospital acquisition prices for ketorolac vary based on manufacturer and size of the unit sold; they range from approximately $1.25 to $5.22 for a single dose 60 mg/2 mL or 30 mg/mL vial.[35] Ketorolac does not require refrigeration and can be easily stored in the operating room (OR) wherever anesthesia medications are kept.

If ketorolac is administered intraoperatively, it should not be given until after surgical hemostasis is achieved; several studies demonstrated increased bleeding when ketorolac was given before hemostasis was achieved.[3,11,24] In certain surgical populations with risk of substantial bleeding, such as patients undergoing tonsillectomy,[11] as well as patients with preexisting coagulation disorders, ketorolac use may be inappropriate. Ketorolac should be used cautiously in combination with other NSAIDs such as ibuprofen that may be administered to pediatric patients postoperatively; synergism between the medications may worsen side effects.[35] Administration of the drug should be communicated to the provider or parent assuming care of the patient, to correctly deliver subsequent doses of ketorolac and/or other NSAIDs, watch for adverse effects, and appropriately plan for other analgesic medications.

• ***Acetaminophen.*** Acetaminophen injection comes in a single-dose vial of 1,000 mg/100 mL; the hospital acquisition cost is approximately $10.18 per vial.[36] Single-dose vials of IV acetaminophen can be easily stored in the OR wherever anesthesia medications are kept. No refrigeration is required. Once opened, vials are good for 6 hours per manufacturer guidelines.[16] Intravenous acetaminophen should be administered as a 15-minute infusion, and doses less than the total amount in the vial should be drawn up in a separate syringe to prevent accidental overdose.[16] Because acetaminophen does not interfere with hemostasis, the IV preparation may be given in the preoperative area if it facilitates administration. However, dosing should be timed to ensure that the analgesic effects are still present during the initial recovery period.

Rectal acetaminophen, ranging in cost from approximately $0.44 to $2.55 per suppository depending on dosage and manufacturer,[35] is much cheaper than the IV preparation. However, it has less predictable absorption and serum concentration levels, and it may be inappropriate for certain types of pediatric patients such as immunocompromised patients or those undergoing bowel surgery, in whom intestinal absorption may be impaired. Difficulties also arise in delivering exact doses with rectal acetaminophen, because of nonhomogeneous spread of the medication throughout the suppository, and manufacturer recommendations that suppositories not be divided.

When administering IV acetaminophen, anesthesia providers should adhere to recommended maximum allowable daily (24-hour) doses for acetaminophen: 75 mg/kg, or 3,750 mg for children 2 to 12 years of age or anyone weighing under 50 kg; 4,000 mg for anyone weighing 50 kg or greater and 13 years of age or older.[16] All forms of acetaminophen that may be given to the patient, such as oxycodone-acetaminophen (Percocet), Tylenol with codeine, or Tylenol suppositories, must be considered and included in the daily maximum allowable dose. Administration of IV acetaminophen should be documented and reported to the provider or parent assuming care of the pediatric patient so that subsequent doses of IV, oral, and/or rectal forms of acetaminophen can be planned accordingly, and the maximum daily allowable dose of acetaminophen is not exceeded.

Summary

Based on the studies reviewed, for pediatric surgical patients 15 years of age and younger, ketorolac was not found to improve discharge times,[3,11,25] decrease the incidence of unplanned hospital admissions,[11] or consistently cut down on total opioid consumption.[3,11,12] Therefore, it does not seem likely that its routine use would be beneficial in reducing overall surgical costs for the patient or the hospital. However, ketorolac may not be any less effective than morphine in providing analgesia,[11] and its use may help decrease the incidence of opioid-induced PONV.[11,23] In the appropriate patient population then, ketorolac may still be an attractive option for anesthesia providers interested in an analgesic with a longer duration of action and a decreased incidence of PONV than what many opioids offer.

For pediatric patients undergoing unilateral hernia

repair, ketorolac use in combination with IV acetaminophen did appear to decrease opioid requirements in the PACU.[25] Further investigation with other pediatric surgical populations is warranted, but the analgesic effectiveness of ketorolac and acetaminophen in combination may extend to other surgeries as well; certainly the concept is fitting with the multimodal recommendations of the ASA's 2012 *Practice Guidelines for Acute Pain Management in the Perioperative Setting*. For *adult* patients undergoing strabismus surgery, ketorolac was found to decrease opioid consumption in the PACU.[23] This study also included patients as young as 13 years of age (the number of 13-year-olds was not specified), patients potentially classifiable as pediatric patients; therefore the findings may be extendable to younger patients undergoing similar surgeries.

The studies focusing on acetaminophen suggest that IV acetaminophen may contribute to shortened PACU stays,[2,21] less sedation in the PACU,[2,4,21] decreased opioid consumption,[4] and fewer opioid-related adverse effects4 requiring treatment and intervention. These findings may justify the high cost of the medication. Improved parent and nurse pain management satisfaction scores[4] may also make IV acetaminophen a desirable choice. However, based on the studies examined, IV acetaminophen is not an appropriate replacement for opioids, because most patients required opioid analgesics in addition to acetaminophen.[2,21,22] Instead, it should be used as an adjunctive medication to provide a multimodal approach to analgesic management.

Pediatric surgical patients are a population identified as being at risk of the undertreatment of pain.[1] Fear of oversedation and narcotic dependency, and unfamiliarity in recognizing and treating pain in pediatric patients contribute to this problem.[1] The ASA's 2012 *Practice Guidelines for Acute Pain Management in the Perioperative Setting* offers a potential solution of multimodal therapy. For anesthesia providers, the simplest method for using a multimodal approach to pediatric pain management is to administer nonopioid IV analgesics in combination with IV opioids. Two frequently used nonopioid IV analgesics that may be beneficial for pediatric patients are ketorolac and acetaminophen. Ultimately, anesthesia providers must individualize care for each patient, taking into consideration patient characteristics, desired analgesic outcomes, the type of surgery being performed, associated risks and complications, and the surgical setting.

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