Arch Crit Care Med. 2016 November; 1(4):e8278. doi: 10.17795/accm-8278.

Published online 2015 November 28. **Research Article**

Efficacy and Safety of Ketorolac for Pain Management After Congenital Heart Surgery: A Comparison to Paracetamol

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Received 2015 September 30; **Accepted** 2015 November 14.

Abstract

Background: Pain is an unpleasant complication commonly observed following congenital heart surgery, but is not often treated properly.
Objectives: The current study aimed to investigate the efficacy and safety of ketorolac to manage postoperative pain after pediatric heart surgery.
Methods: Eighty-one pediatric patients undergoing cardiac surgery received either ketorolac 0.5 mg/kg or paracetamol 15 mg/kg for postoperative pain control every six and eight hours on the first and second postoperative days, respectively. The critical-care pain observation tool (CPOT) and the face, legs, activity, cry, consolability (FLACC) scale were employed to investigate the pain severity. The patients were also investigated for additional analgesic requirements, and associated complications including acute kidney injury, gastrointestinal discomfort and bleeding in patients.
Results: Patients in the ketorolac group experienced less pain than the ones in the paracetamol group. More fentanyl was required for pain relief in the paracetamol than the ketorolac group. Use of ketorolac was not associated with more adverse effects in comparison to paracetamol.
Conclusions: Ketorolac is safe and effective to manage postoperative pain after congenital heart surgery. It is more effective than paracetamol for pain relief and requires less additional rescue analgesic.

Keywords: Postoperative Pain, Congenital Heart Surgery, Ketorolac, Paracetamol

1. Background

Pain is a common complication after congenital heart surgery with lots of challenges for the children, their parents and the health care providers.

Furthermore, it is often underdiagnosed and therefore not treated properly. Inappropriate management of postoperative pain is associated with deleterious effects including inadequate cough and clearance of pulmonary secretions and atelectasis especially in children, following heart surgery.

Opioids are often used to manage postoperative pain; nevertheless, they are associated with many adverse effects such as respiratory and cardiovascular depression. Therefore, use of non-opioid analgesics is popular among physicians caring for children undergoing cardiac surgery.

Paracetamol is a non-opioid analgesic commonly used to manage postoperative pain for different surgeries in children. It is used effectively and safely for pain relief after adult (1, 2) and pediatric heart surgeries (3).

Non-steroidal anti-inflammatory drugs (NSAID) are used to control postoperative pain. However, their safety is questioned in children undergoing heart surgery. Ketorolac has been used safely to manage postoperative pain in different pediatric surgeries (3-8) including congenital heart surgery (9-11) with no adverse effects.

2. Objectives

The current study aimed to compare paracetamol and ketorolac in management of postoperative pain in congenital heart surgery. The primary outcome was comparison of pain score in the two groups. The secondary outcome included investigation of additional postoperative analgesic requirements and adverse effects including postoperative

bleeding, acute kidney injury, gastrointestinal discomfort and bleeding following administration of the two drugs.

3. Methods

Eighty-one children over one year weighting more than 10 kg undergoing congenital heart surgery were recruited for the study. The ethics committee of Mashhad University of Medical Sciences approved the study and parents signed written informed consent forms before recruitment of their children. Using a computer based randomization, the patients were allocated to either intravenous paracetamol (n = 45) or ketorolac (n = 36) groups. The exclusion criteria were history of drug allergy, renal or hepatic insufficiency, unusual intraoperative or postoperative bleeding requiring blood products and peptic ulcer disease.

The patients in the paracetamol group received intravenous paracetamol 15 mg/kg every six and eight hours on days one and two, respectively.

Subjects in the ketorolac group received intravenous ketorolac 0.5 mg/kg every six and eight hours on days one and two, respectively.

The patients were evaluated for pain using critical pain objective tool (CPOT) (Figure 1) while intubated; and the face, legs, activity, cry, consolability (FLACC) scoring system (Table 1) when extubated at one hour intervals for 10 hours and every four hours up to 48 hours. They were given fentanyl 1μg/kg for CPOT of 6 - 8 and FLACC of 6 - 8 and 0.5 μg /kg for CPOT of 3 - 5 and FLACC of 3 - 5.

The patients were also evaluated for development of adverse drug effects including postoperative bleeding, acute kidney injury using modified pediatric RIFLE (risk, injury, failure, loss of kidney function and end-stage kidney disease) criteria (Table 2), and gastrointestinal discomfort and bleeding.

The patients underwent a standard anesthesia with ketamine 1 mg/kg, midazolam 0.1 mg/kg, and fentanyl 1-5 μg/kg for induction and atracurium 0.6 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane 1.2 - 2.5 minimum alveolar concentration (MAC) and additional fentanyl 5 μg/kg to maintain blood pressure and heart rates at 20% from baseline. Atracurium was given as 0.2 - 0.4 mg/kg/hour. The patients were transferred to the intensive care unit (ICU) while intubated where they were weaned from mechanical ventilation and extubated under a standard protocol. The children were under a standard monitoring including electrocardiography, invasive blood pressure, central venous pressure, end-tidal CO_2, hear rates, respiratory rates and temperature.

A difference of 20% in pain intensity was considered clinically significant. A sample size of 68 was required to detect such a difference between the groups for a power of 90% at a significance level of 5%. The sample size was increased to 80 in case of missing data. Data analyses were performed by SPSS software for Windows, version 16 (SPSS Inc, Chicago, IL, USA). Mean and standard deviation values for different variables were calculated. Independent Student T-test was used to compare continuous variables exhibiting normal distribution, and Chi-square or the Fisher exact tests for non-continuous variables. A P-value < 0.05 was considered significant.

4. Results

Eighty-one patients were recruited for the study with the mean age of 50.40 $\pm$ 23.80 months. The patients were similar in both groups with respect to demographic characteristics (Table 3).

There were no significant differences between the two groups regarding duration of surgery, frequency of on pump surgery, cardiopulmonary pump and cross clamp time (Table 3).

Based on CPOT scale, pain score was significantly lower in the ketorolac (3.25 $\pm$ 2.48) than paracetamol group (5.22 $\pm$ 5.48) (P-value = 0.049) (Figure 2).

The mean FLACC scores were 5.33 $\pm$ 3.77 and 8.02 $\pm$ 7.44 in the ketorolac and paracetamol groups, respectively (P-value = 0.05) on the first postoperative day. On the second day, patients in the ketorolac group had FLACC score of 0.55 $\pm$ 1.99 and the ones in the paracetamol group had FLACC score of 2.82 $\pm$ 3.88 (P-value = 0.01) (Figure 3).

Patients in the ketorolac group required less fentanyl (11.41 $\pm$ 20.87 μg/kg) than the ones in the paracetamol group (16.45 $\pm$ 15.90 μg/kg) on the first postoperative day (P-value = 0.33). No patients in the ketorolac group required additional fentanyl on the second postoperative day while those in the paracetamol group received fentanyl 2.44 $\pm$ 4.95 μg/kg (P-value = 0.032).

Duration of mechanical ventilation was 2.4 + 3.2 hours and 5.4 + 5.2 hours in the ketorolac and paracetamol groups, respectively (P-value = 0.11).

The patients were similar with respect to development of acute kidney injury (AKI). No cases of gastrointestinal discomfort and bleeding were observed in the groups.

5. Discussion

The current study revealed that ketorolac was more effective than paracetamol to manage postoperative pain in children undergoing cardiac surgery. In addition, it can reduce postoperative additional analgesic requirement in comparison to paracetamol with no additional adverse effects.

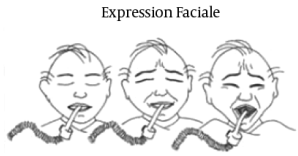
Indicator	Score		Description
Facial expression  Caroline Arbour, RN, B.Sc., PhD(student) School of Nursing, McGill University	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening and levator contraction or any other change (e.g. opening eyes or tearing during nociceptive procedures)
	Grimacing	2	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open or biting the endotracheal tube)
Body movements	Absence of movements or normal position	0	Does not move at all (doesn't necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	Protection	1	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements
	Restlessness/Agitation	2	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
Compliance with the ventilator (intubated patients)	Tolerating ventilator or movement	0	Alarms not activated, easy ventilation
	Coughing but tolerating	1	Coughing, alarms may be activated but stop spontaneously
	Fighting ventilator	2	Asynchrony: blocking ventilation, alarms frequently activated
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	0	Talking in normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Crying out, sobbing	2	Crying out, sobbing
Muscle tension Evaluation by passive flexion and extension of upper limbs when patient is at rest or evaluation when patient is being turned	Relaxed	0	No resistance to passive movements
	Tense, rigid	1	Resistance to passive movements
	Very tense or rigid	2	Strong resistance to passive movements or incapacity to complete them
TOTAL	___ / **8**		

Figure 1. The CPOT Scale

Table 1. The FLACC Scale

Criteria	Score - 0	Score - 1	Score - 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moving easily	Squirming, shifting back and forth, tense	Rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to distract	Difficult to console or comfort

Abbreviation: FLACC, the face, legs, activity, cry, consolability scale.

Table 2. Modified Pediatric RIFLE Criteria

Category	Estimated Creatinine Clearance	
Urine Output		
Risk	Decrease by 25%	< 0.5 mL/kg/hour for 8 hours
Injury	Decrease by 50%	< 0.5 mL/kg/hour for 16 hours
Failure	Decrease by 75% or < 35 mL/minute/1.73 m^2	< 0.3 mL/kg/hour for 24 hours or anuric uremia for 12 hours
Loss	Loss of renal function > 4 weeks	
End-Stage	End stage renal disease	

Abbreviation: RIFLE, risk, injury, failure, loss of kidney function and end-stage kidney disease

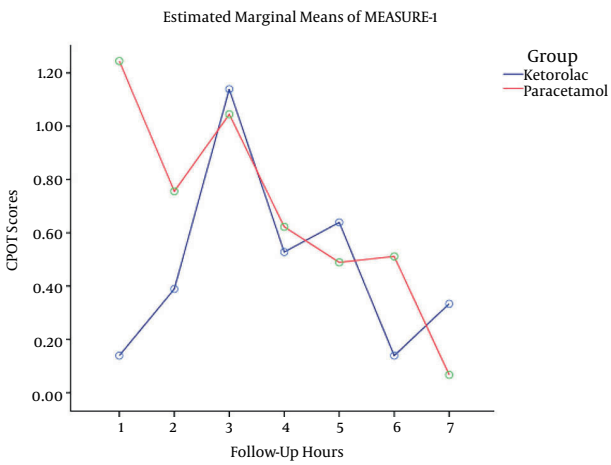


Figure 2. Pain Severity According to CPOT Scale in Patients Receiving Ketorolac and Paracetamol

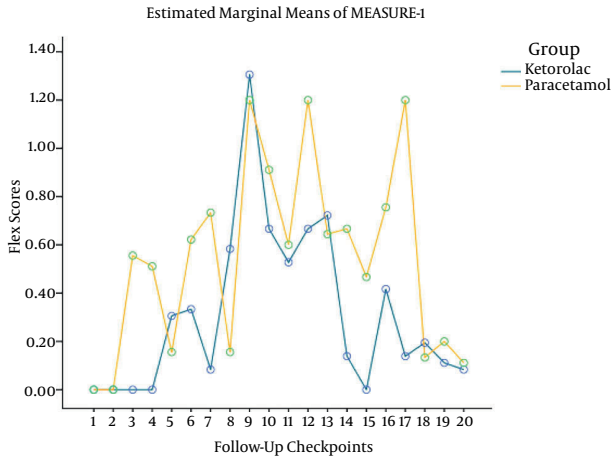


Figure 3. Pain Severity According to FLACC Scale in Patients Receiving Ketorolac and Paracetamol

Similar to the current study findings, some studies reported that paracetamol and ketorolac were both effective to manage postoperative pain following thyroidectomy (12) and parathyroidectomy (13). However, in the current series ketorolac was more effective in reducing pain; indicating that ketorolac was more effective in reducing moderate to severe pain experienced during cardiac surgery.

The obtained results showed that ketorolac reduced additional analgesic requirement postoperatively even better than paracetamol. It was in agreement with the report of Inoue et al. (10). Similar to the current study but in a different population, Burd et al. (14) and Chauhan et al. (15) also found that ketorolac was able to reduce the amount of additional postoperative opioid required after surgery in infants (14, 15).

In contrast to the current study, it was reported that patients with renal colic receiving paracetamol required less additional opioids in comparison to the ones in the ketorolac group (16). Different types of surgeries might explain this discrepancy.

Table 3. Patients' Demographic and Surgical Data[a]

Characteristic	Ketorolac	Paracetamol	P Value
Age	4.4 ± 4.5	3.2 ± 2.8	0.8
Gender			0.1
Male	42.9	59.1	
Female	57.1	40.9	
Weight, Kg	15.1 ± 5.3	16.4 ± 7.8	0.39
Height, Cm	102.4 ± 20.6	101.06 ± 22.8	0.7
Off Pump, No. (%)	2 (5.6)	0	0.10
On Pump, No. (%)	34 (94.4)	44 (100)	0.11
Pump time, Minute[b]	42.88 ± 24.3	39.58 ± 29.6	0.53

[a] Values are expressed as mean ± SD unless otherwise indicated.
[b] Cross clamp time.

Application of nonsteroidal anti-inflammatory drugs (NSAIDs) in the perioperative period can be associated with hemostasis disturbance, pulmonary, gastrointestinal and renal dysfunction (11, 13, 17). However, several investigations demonstrated safety of ketorolac regarding renal dysfunction following pediatric heart surgery (10, 11).

It is reported that single use of ketorolac is effective and safe in infants less than two years (14, 18). Furthermore, ketorolac had no adverse effects on wound healing (19) and perioperative bleeding (19, 20) in infants undergoing cardiac surgery.

Use of ketorolac was not associated with increased risk of renal dysfunction in the current series. It was confirmed by other studies (10, 11). In agreement with the current study, Jalkut et al. suggested that ketorolac could be used in specific pediatric patients after cardiac surgery with minimal risk of bleeding or renal dysfunction with appropriate dosing and duration of use (9).

In contrast, it is reported that the concomitant use of aspirin with ketorolac is associated with increased renal morbidity in small infants' post-cardiac surgery (21). However, the current study did not evaluate the effect of this combination on renal dysfunction.

Bleeding is proposed as a potential adverse effect of NSAIDs. However, there are a number of studies indicating that using ketorolac to manage postoperative pain in children after cardiac surgery does not increase the risk of postoperative bleeding (11, 19, 22, 23). Similarly, in our patients no significant postoperative bleeding was noticed in the ketorolac in comparison to the paracetamol group.

The current study had a few limitations. Distribution of surgeries was not similar in the two groups that might affect the nature and intensity of pain. Furthermore, amount of intraoperative opioids was not investigated in the two groups that might affect their postoperative pain and analgesic requirements.

It was concluded that both ketorolac and paracetamol can reduce pain intensity effectively and safely after pediatric heart surgery with no preference. However, more additional analgesic was required in the paracetamol group in the first two postoperative days. Furthermore, ketorolac was not associated with increased risk of renal dysfunction, gastrointestinal discomfort and postoperative bleeding.

Acknowledgments

Authors would like to thank nursing staff at Imam Reza cardiac surgery ICU, especially Mr. Ali Bahush and Ms. Akram Kiani, for their contribution to the study.

Footnotes

Authors' Contribution: Shahram Amini, study design and manuscript preparation and writing; Ehsan Mahdavi, study design and manuscript preparation; Ghasem Soltani, study design and writing; Nahid Zirak, data collection; Mohammad Abbasi Tashnizi, data collection; Vida Vakili, data analysis; Farideh Golhasani, manuscript preparation

Financial Disclosure: The authors declared no financial disclosure regarding the current study.

Funding/Support: The study was supported financially by deputy research of Mashhad University of Medical Sciences, Mashhad, Iran.

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