

Adjunctive use of Ketorolac for Postoperative Pain Management in Elective Cardiac Surgery Patients: A Randomized Control Trial

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ABSTRACT

Objective: To compare between the efficacy of Ketorolac and Paracetamol in the management of post-operative pain following elective cardiac surgery.

Study Design: Randomized (single-blind) Control Trial (RCT NCT05361824.)

Place and Duration of Study: This study was conducted in the Surgical Intensive Care Unit (SICU) at the National Institute of Cardiovascular Diseases Hospital, Karachi Pakistan, From 1st Jan to 30th Jun 2021.

Methodology: Randomization of 60 patients undergoing elective cardiac surgery into either Paracetamol (30 control patients) or Ketorolac (30 treatment patients) was done. In addition, to a low dose, short duration background infusion of Nalbuphine, the control group was administered injection Paracetamol 1gm every six-hours. Whereas the treatment group was administered injection Ketorolac 30mg every eight-hours. Assessment of pain was done at 6, 12, 18 and 24 hours post-extubation, using a Visual analog scale (VAS). For the purpose of this study, a score of 4 or less was taken as a cut-off for adequate pain control.

Results: VAS score was significantly lower in Ketorolac group as compared to the Paracetamol group at all four-time points with an average rating of 3.2 ± 1.9 vs. 5.3 ± 1.7 ; $p < 0.001$, 3.5 ± 1.5 vs. 5 ± 1.7 ; $p < 0.001$, 3.3 ± 1 vs. 5.0 ± 1.4 ; $p < 0.001$, and 3.0 ± 1.4 vs. 4.3 ± 1.6 ; $p < 0.001$ at 6, 12, 18, and 24 hours respectively. The total dose of Nalbuphine administered (infusion + bolus doses) over 48 hours post-operatively was 15.3 ± 5.2 vs 25.7 ± 6.8 ml; $p < 0.001$ in the Ketorolac and Paracetamol groups, respectively.

Conclusion: The use of Ketorolac in conjunction with Nalbuphine gives better control over post-operative pain in elective cardiac surgeries than Paracetamol and Nalbuphine.

Keywords: Analgesia, Coronary artery bypass grafting, Coronary artery disease, Ketorolac, Paracetamol, Postoperative pain.

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INTRODUCTION

Postoperative pain is a particularly prevalent type of acute pain. Although a common and temporary occurrence, it is frequently ignored, resulting in postoperative complications and an extended hospital stay. Due to the complexity and multifactorial nature of its etiology,¹ it can effectively be controlled using a combination of multimodal and multidrug therapy. By using a cocktail of analgesics with a variety of mechanisms of action to minimize drug-related side effects. Additionally, reducing postoperative opioid use by adding non-opioid drugs has the advantage of reducing opioid-induced sedation and pulmonary complications. Thereby, ensuring stable respiratory status following surgery, allowing for early extubations.

To avoid hemodynamic disruptions due to unwarranted patient discomfort and to reduce morbidity, postoperative hospital stay, and overall costs, it is crucial to achieve optimal pain relief following any

cardiac surgery.² Moreso if not addressed timely it can lead to an even more distressing outcome persistent postoperative pain after cardiac surgery.³

Opioids have long been the mainstay of post-operative pain in cardiac patients; however, their use is now declining in this era of fast recovery after surgery.⁴ Ketorolac, a non-steroidal anti-inflammatory drug (NSAID) once used in conjunction with routine postoperative opioids for the short-term management of moderate to severe pain after cardiac surgery, fell out of favor after a boxed warning of increased risk of cardiovascular events in 2005 for 'all' NSAIDs in post-CABG patients. This was based on two studies done on the cyclooxygenase-2 (COX-2) selective inhibitors (Parecoxib and Valdecoxib, no longer on the market) that evaluated the significantly increased risk of complications (including myocardial infarction, stroke, cardiac arrest and pulmonary embolism) after CABG.^{5,6} Hence, despite its previous safe use in coronary artery disease patients⁷⁻⁹, the overall use of Ketorolac in cardiac surgery for post-operative pain management has declined or remains being used off-label.

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The theory behind this can be explained by the fact that COX-2 derived Prostacyclin, is a continuously released hormone, by the lungs into the blood circulation, which inhibits platelet aggregation by increasing cyclic AMP levels, thus maintaining normal blood fluidity. Whereas COX-1 derived Thromboxane A2 is a short-lived, intermediary produced by platelets from the phospholipid membrane (arachidonic acid) upon platelet activation (after injury). Its main role is in the amplification of platelet activation and recruitment of additional platelets to the site of injury (leading to clot formation).

By selectively inhibiting 'only' COX-2, Parecoxib and Valdecoxib blocks the production of prostacyclin but have no effect on the production of thromboxane A2 produced via COX-1. Hence, this leads to uninhibited thromboxane production which results in platelet aggregation, causing thrombosis and serious adverse cardiovascular events. On the other hand, Ketorolac and Aspirin are both non-selective COX inhibitors and increase resistance to clot formation. Their antiplatelet effect can last up to 24 hours after a single dose. Thus, lowering the risk of graft closure after CABG surgery.⁷

Ketorolac is a highly effective pain reliever that can be used both safely and effectively during the perioperative period. Although a few retrospective studies exist which show that Ketorolac can be used in both children and adults following cardiac surgery.^{7,10-11} A recent prospective study conducted by Fatemeh. *et al.* also demonstrated the superiority of parenteral Ketorolac to Paracetamol in treating postoperative pain in CABG patients.¹² Additionally, off label use of Ketorolac for post-operative pain management in selected patients remained a common clinical practice, but limited data is available regarding its effectiveness, especially for our population. Therefore, there is a need for further prospective studies to provide scientific evidence regarding the safety and efficacy of Ketorolac in postoperative cardiac surgery patients to guide clinicians on evidence-based optimal post-operative pain management in surgical intensive care units (SICUs).

METHODOLOGY

After obtaining approval from the ethical committee of NICVD hospital (ERC-83/2020), written informed consent was taken from all patients meeting the inclusion criteria during the study period of six months (January 1, 2021 up to June 30, 2021). This Trial was registered at Clinical Trial.gov with Clinical Trials.gov ID of NCT05361824.

Sample Size: The sample size was calculated based on the study conducted by Javaherforooshzadeh *et al.*¹² which reported a mean VAS score of 121.1 ± 2.73 vs. 126.8 ± 3.41 ; $p=0.417$ after 24 hours of surgery in Paracetamol and Ketorolac group, respectively. Taking these statistics at a 5% level of significance and 80% power of test to detect the statistical difference between the two groups, the minimum calculated sample size required for the study was calculated to be 6 patients in each group. Considering the patient flow we recruited 30 patients in each group with a total sample of 60 patients (30 in Paracetamol and 30 in Ketorolac group).

Inclusion Criteria: The inclusion criteria included all consenting males and females from age 18 years above, undergoing elective cardiac surgeries, and having American Society of Anesthesiology (ASA) Physical Class-3 or 4.

Exclusion Criteria: On the other hand, all patients known to have allergy or sensitivity to nonsteroidal anti-inflammatory drugs, with a history of gastric ulcer, upper or lower gastrointestinal bleeding, hepatic dysfunction, or bleeding diathesis were excluded. As well as those patients, whose serum creatinine was 2.0 mg/dl preoperatively or had an increased serum creatinine of 0.5mg/dl (or 25% increase) from baseline, within the preceding 10 days were also excluded. In addition, patients with pre-operative ejection fraction < 30% or with a low cardiac output (cardiac index < 2.0 lit/min/m²) after coming off cardiopulmonary bypass (found on transesophageal echocardiography, done intraoperatively), patients already pre-planned for delayed extubation (due to moderate to severe pulmonary artery hypertension, poor right ventricular function, rhythm disturbances or unstable vitals) and those who were not comfortably ventilated or oxygenated, requiring high doses of sedation and neuromuscular blockade were excluded.

A total of sixty patients (30 in each group) were randomly assigned to receive either Paracetamol (control) or Ketorolac (treatment) for 48 hours postop, along with a background infusion of Nalbuphine. Computer randomization (using a predefined computer generated randomization schema with 1:1 ratio) was done for the numbers 1 to 60, having a 50% probability of being in either the treatment or control group. After randomization, the patients got allotted these numbers consecutively, as they presented for elective cardiac surgery. Thus, randomly allocating the presenting patient either into Ketorolac/treatment or Paracetamol/control group. The randomization

schema was accessible to a single investigator, not involved in patient management, and communicated to the primary operator on patient-to-patient basis to ensure concealment.

Patients meeting the inclusion criteria had received standard general anesthesia and underwent elective cardiac surgery. After which they were shifted to SICU, where they got administered their allocated analgesic therapy. Both groups upon arrival into the ICU were initially started on a maintenance infusion of Nalbuphine at 2.5mg/hr, which was stopped at the time of extubation. In addition to this, the treatment group was administered injection Ketorolac 30mg, 8 hourly for the first 48 hours, and the control group injection Paracetamol 1gm, 6 hourly for the first 48 hours. Bolus doses of Nalbuphine 10mg were given as rescue analgesia if needed by either group. In order to maintain (patient) blinding, the drugs were prepared in 100 ml infusion bottles identical in every aspect, except for a unique label on them which was only known to the primary investigator.

The primary outcome of the study was post-operative pain intensity. This was measured using a Visual Analogue Scale (VAS) consisting of a straight 10cm line divided into 10 equal parts with the end-points defining extreme limits such as 'no pain at all' (at 0) and 'worst pain possible' (at 10). The scale was explained to the patients twice: one day prior to surgery (at preoperative interview) and after they recovered their alert state (post-extubation). The patients were asked to mark the intensity of pain experienced on the line between the two endpoints (0 to 10). The mark that the patient pointed to, defined the patient's pain. For the purposes of this study "adequate pain relief" was defined as achieving a pain score of four or less, this designation was also included on the VAS scale and explained to the patients (every time VAS was shown) so that they may indicate numbers higher than four if they felt any pain. To evaluate the efficacy of either therapy, the first post-operative analgesia assessment was performed using VAS at 6 hours and then at 12, 18, and 24 hours post-extubation. Additionally, the total number of rescue analgesia doses needed and the total amount of Nalbuphine administered (infusion+rescue bolus dose) to each patient were recorded as secondary outcomes. The time taken to extubation, and the total chest tube drainage were also recorded over 48hours postoperatively.

Data was entered and analyzed using SPSS version-25. Shapiro-Wilk test was applied to check the

hypothesis of normality for continuous variables and was expressed using descriptive statistics such as Mean±SD, median (IQR), maximum and minimum. Frequency and percentages were then calculated for categorical variables. VAS score was compared to patients' characteristics by conducting t-test or Mann-Whitney U test appropriately. A two-sided *p*-value of ≤ 0.05 was taken as significant.

RESULTS

The mean age in Paracetamol group was 54±10.6 years and 58.4±9.1 years in Ketorolac group. The females were 7(23.3%) vs. 2(6.7%) in Paracetamol and Ketorolac group, respectively. All patients were in ASA class 4. Demographic and clinical characteristics of the Paracetamol and Ketorolac are summarized in Table-I.

Table-I: Distribution of Baseline Demographic and Clinical Characteristics stratified by the Treatment Group

Characteristics	Therapy		<i>p</i> -value
	Paracetamol	Ketorolac	
Total (N)	30	30	-
Gender			
Male	76.7% (23)	93.3% (28)	0.071
Female	23.3% (7)	6.7% (2)	
Age (years)	54 ± 10.64	58.43 ± 9.13	0.088
Weight (kg)	73 ± 11.3	76.4 ± 12	0.264
Height (cm)	165.4 ± 10.4	167.8 ± 9.8	0.361
Body mass index (kg/m ²)	26.9 ± 4.5	27.2 ± 4.3	0.760
Diagnosis			
Left main+3vessel disease	75.6% (59)	71.8% (56)	0.157
3 vessel disease	15.4% (12)	16.7% (13)	
2 vessel disease+ atrial septal defect	7.7% (6)	10.3% (8)	
Ejection Fraction (%)			
30 to 50%	40% (12)	60% (18)	0.121
>50%	60% (18)	40% (12)	

The extubation time was 5.4±1.5 vs. 5.3±1.5 hours in Paracetamol and Ketorolac group, respectively. Average total dose of Nalbuphine was 25.7±6.9 vs 15.3±5.2 mg in Paracetamol and Ketorolac group, respectively. Significantly lower VAS pain rating was observed in Ketorolac group as compared to the Paracetamol group at all four-time points. Adequate pain control (VAS≤4) was observed to be 43.3% (13) vs 90% (27); *p*<0.001 at 6 hours, 46.7% (14) vs 86.7% (26); *p*<0.001 at 12 hours, 46.7% (14) vs 93.3% (28); *p*<0.001 at 18 hours, and 70% (21) vs 93.3% (28); *p*<0.001 at 24 hours for Paracetamol and Ketorolac group respectively (Table-II).

Table-II: Comparison of Clinical Parameters and VAS Pain Rating Between Paracetamol and Ketorolac

Characteristics	Therapy		p-value	
	Paracetamol	Ketorolac		
Total (n)	30	30	-	
Time taken to extubation (minutes)	5.4 ± 1.5	5.3 ± 1.5	0.741	
Total Number of Rescue Dose				
0	0% (0)	66.7% (20)	<0.001*	
1	20% (6)	23.3% (7)		
2	23.3% (7)	6.7% (2)		
3	40% (12)	0% (0)		
4	10% (3)	3.3% (1)		
5	6.7% (2)	0% (0)		
Nalbuphine infusion (mg)	12.4 ± 3.5	12.8 ± 3.5	0.649	
Total Nalbuphine dose (mg)	25.7 ± 6.9	15.3 ± 5.2	<0.001*	
Drain output (ml)	660 [460-900]	770 [500-960]	0.877	
At 6 hours	VAS pain rating	5.3 ± 1.7	3.2 ± 1.9	<0.001*
	≤4	43.3% (13)	90% (27)	<0.001*
	5 - 10	56.7% (17)	10% (3)	
At 12 hours	VAS pain rating	5.0 ± 1.7	3.5 ± 1.5	<0.001*
	≤4	46.7% (14)	86.7% (26)	0.001*
	5 - 10	53.3% (16)	13.3% (4)	
At 18 hours	VAS pain rating	5 ± 1.4	3.3 ± 1.0	<0.001*
	≤4	46.7% (14)	93.3% (28)	<0.001*
	5 - 10	53.3% (16)	6.7% (2)	
At 24 hours	VAS pain rating	4.3 ± 1.6	3.0 ± 1.4	<0.001*
	≤4	70% (21)	93.3% (28)	0.02*
	5 to 10	30% (9)	6.7% (2)	

VAS=visual analog scale *Significant at 5%

DISCUSSION

As a result of improvements in the cardiopulmonary bypass technique, cardiac surgery is now a common procedure; however, it causes patient discomfort, just like other operations, because of the pain and the consequences of the pain. Patients undergoing cardiac surgery are usually older, and the number of comorbidities they have is increasing. For patients who have had a cardiac procedure, preventing and controlling pain in the postoperative care setting is critical^{1,2}. As it is the era of fast-track recovery following surgery, research is being done to provide effective analgesia with minimal opioid usage in cardiac surgery patients.¹³⁻¹⁵ Therefore, the aim of this study was to compare the efficacy of Ketorolac in postoperative pain management in cardiac surgery patients.

According to the study's main finding, patients undergoing elective cardiac surgery who were given Ketorolac instead of Paracetamol experienced less postoperative pain, on average at all four-time points. VAS scores in the Ketorolac group at 6,12,18 and 24 hours post-extubation were less than 4 (adequate pain

control), in comparison to the Paracetamol group whose VAS ratings were 5 or more at 6,12 and 18 hours post-extubation, the only exception being at 24 hours post-extubation where they also had a score of less than 4 (Table -II).

Opioids used alone or in large doses for an extended period of time, can cause acute tolerance and opioid dependence postoperatively.¹⁶ In light of this, a multimodal approach incorporating non-opioid agents into opioid-based regimens appears to be a promising alternative. One of the goals of this research was to compare the total number of opioid rescue doses needed by the patients postoperatively, along with the total amount of Nalbuphine administered to each patient in SICU. In the study's result, Ketorolac appears to have reduced both the number of rescue doses needed, as well as the total postoperative Nalbuphine requirement when compared to Paracetamol.

Ketorolac can be administered both enteral and parenterally, either alone or with opioids, despite its route it has no significant impact on the cardiovascular or respiratory systems¹⁷ and can limit the adverse effects of opioids while also facilitating early extubation and mobilization following cardiac surgery.⁸⁻¹² This could be due to the fact that the study patients underwent elective cardiac surgery and had overall similar demographics, both Ketorolac and Paracetamol group had a comparable time of extubation which was approximately around 5 hours (Table II).

A large retrospective cohort study conducted by Kimmel, *et al.*⁷ in 35 hospitals showed that patients who had received IV Ketorolac for pain management for up to 3 days after CABG surgery had a 30% lower risk of developing myocardial infarction (MI) than those who received only IV opioids. Although not recorded as an outcome and only being administered to a limited number of (30) patients undergoing elective cardiac in our study, not one was noted to have developed a graft blockage, postoperative MI, or any respiratory complication, showing consistency with the results found by Kimmel, *et al.*⁷

A review article on the safe use of Ketorolac for postoperative pain highlighted that, it can decrease platelet aggregation capability and lengthen the bleeding duration but not bleeding volume¹⁸. As hemorrhagic amount can vary due to a number of reasons ranging from, the type of surgery (major vs. minor), site of operation (cardiovascular vs superficial), surgical hand (surgeon dependent), pre-existing coagulopathy (congenital or drug-induced) in the patient

themselves, to the total length of operative time, etc. Although almost all the patients studied here underwent elective coronary artery bypass surgery for three or two-vessel disease which lasted for a total of three to four hours (from skin incision to skin closure) and had a comparable bypass time (maximum being 90 minutes). However, they were conducted by eight different cardiac surgeons whose cardiac surgery experience varied from a minimum of 8 to a maximum of 25 years. Despite this and the fact that the patients were computer randomized into two groups, the total chest drain output over 48 hours was not significantly different (an average of 100ml difference) between the Paracetamol group (an average drain output of 660ml) and the Ketorolac group (an average drain output of 770ml). No patient was taken back for reopening in either group (Table-II).

As a result of the development of new pharmacological and interventional approaches, postoperative analgesia has improved. Overall, the most cost-effective and comfortable method of postoperative analgesia should be chosen, as well as one with the fewest complications and side effects while also shortening the patient's postoperative stay. After surgery, patients experience both physical and psychological discomfort, which limits their ability to exercise, reduces their respiratory capacity and increases their risk of developing pulmonary issues. On the other hand, effective postoperative pain management can reduce the risk of these complications and shorten ICU stay.

To manage postoperative pain after cardiac surgeries clinicians often turn to opioids, which act on the opioid receptors and provide analgesia. Acting as an opioid agonist-antagonist, Nalbuphine is commonly used in controlling mild to moderate pain. It has been shown to have an analgesic effect by acting on the central nervous system's μ and κ -receptors. With a lower incidence of postoperative nausea and vomiting and minimal effects on patient hemodynamics, Nalbuphine is an effective analgesic after cardiac surgery.¹⁹

However, the use of opioids necessitates the use of other analgesic adjuncts to reduce the overall dose requirements due to their side effects, such as respiratory depression, sedation, bradycardia, nausea, and vomiting. Antipyretic and analgesic in nature, Paracetamol's (Acetaminophen) primary mechanism of action is still a matter of debate, but it may work by inhibiting prostaglandin (PG) synthesis, as its analgesic and antipyretic effects are similar to those of Aspirin, or by influencing cannabinoid receptors via an active

metabolite (*p*-Aminophenol). There has also been speculation that its action is mediated by activation of descending serotonergic pathways. Whatever the mechanism, after cardiac surgery, Paracetamol because of its safety profile is commonly used in conjunction with opioids as a postoperative pain reliever in cardiac surgery.^{20,21} Despite this, the efficacy of Ketorolac in alleviating postoperative pain and decreasing opioid consumption surpasses that of Paracetamol thus making it a promising postoperative analgesic option.

LIMITATIONS OF STUDY

The study was limited to a single center and had a small sample size (60 patients). It is proposed to conduct this study in multi centers, having a larger sample size, which includes both on and off-pump CABG, and a longer follow-up period, for concrete results.

CONCLUSION

Ketorolac ensures better pain control in comparison to Paracetamol when used in carefully selected cardiac patients for a short period. Furthermore, it also decreases the overall opioid consumption, thus avoiding opioid-induced side effects such as sedation, respiratory depression, and delayed extubation.

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Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MM: Manuscript writing, concept, review

AMK: Idea, intellectual contribution, final approval

AA: Proof reading, critical review, interpretation

RI: Intellectual contribution, study design, reference setting

HTC: Critical review, data collection, analysis

RS: Final approval, proof reading, critical analysis

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Zubrzycki M, Liebold A, Skrabal C, Reinelt H, Ziegler M, Perdas E, et al. Assessment and pathophysiology of pain in cardiac surgery. *J Pain Res* 2018; 11(1): 1599-1611
2. Jayakumar S, Borrelli M. Optimizing pain management protocols following cardiac surgery: A protocol for a national quality improvement study. *Int J Surg Protoc* 2019;14(1): 1-8.

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3. Guimarães-Pereira L, Reis P, Abelha F, Azevedo L, Castro-Lopes J. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. *Pain* 2017; 158(10): 1869-1885.
4. Markham T, Wegner R, Hernandez N, Lee J, Choi W, Eltzschig H et al. Assessment of a multimodal analgesia protocol to allow the implementation of enhanced recovery after cardiac surgery: Retrospective analysis of patient outcomes. *J Clin Anesth* 2019; 54(1): 76-80
5. Ott E, Nussmeier N, Duke P, Feneck R, Alston R, Snabes M, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003; 125(6): 1481-1492.
6. Nussmeier N, Whelton A, Brown M. Complications of the COX-II inhibitors parecoxib and valdecoxib after cardiac surgery. *J Vasc Surg* 2005; 42(2): 380.
7. Kimmel S, Berlin J, Kinman J, Hennessy S, Feldman H, Carson J, et al. Parenteral ketorolac and risk of myocardial infarction. *Pharmacoepidemiol Drug Saf* 2002; 11(2): 113-119.
8. Maddali M, Kurian E, Fahr J. Extubation time, hemodynamic stability, and postoperative pain control in patients undergoing coronary artery bypass surgery: an evaluation of fentanyl, remifentanyl, and nonsteroidal antiinflammatory drugs with propofol for perioperative and postoperative management. *J Clin Anesth* 2006; 18(8): 605-610.
9. Inoue M, Caldarone C, Frndova H, Cox P, Ito S, Taddio A, et al. Safety and efficacy of ketorolac in children after cardiac surgery. *Intensive Care Med* 2009; 35(9): 1584-1592.
10. Engoren M, Hadaway J, Schwann T. Ketorolac Improves Graft Patency After Coronary Artery Bypass Grafting: A Propensity-Matched Analysis. *Ann Thorac Card Surg* 2011; 92(2): 603-609.
11. Howard M, Warhurst R, Sheehan C. Safety of Continuous Infusion Ketorolac in Postoperative Coronary Artery Bypass Graft Surgery Patients. *Pharmacy* 2016; 4(3): 22-26.
12. Javaherforooshzadeh F, Abdalbeygi H, Janatmakan F, Gholizadeh B. Comparing the effects of ketorolac and Paracetamol on postoperative pain relief after coronary artery bypass graft surgery. A randomized clinical trial. *J Cardio Surg* 2020; 15(1): 80.
13. García Araque H, Cepeda Pinzón L, Quintero Beltrán O, Barros Campo J. Opioid-free anesthesia in coronary artery bypass grafting (cabg) surgery, during a drug shortages period in the covid 19 pandemic. *J Cardiothorac Vasc Anesth* 2021; 35(1): S22.
14. Kamdar N, Hoftman N, Rahman S, Cannesson M. Opioid-Free Analgesia in the Era of Enhanced Recovery After Surgery and the Surgical Home. *Anesth Analg* 2017; 125(4): 1089-1091.
15. Landry E, Burns S, Pelletier M, Muehlschlegel J. A Successful Opioid-Free Anesthetic in a Patient Undergoing Cardiac Surgery. *J Cardiothorac Vasc Anesth* 2019; 33(9): 2517-2520.
16. Brown C, Chen Z, Khurshan F, Groeneveld P, Desai N. Development of Persistent Opioid Use After Cardiac Surgery. *JAMA Cardiol* 2020; 5(8): 889-892.
17. Kenny GN, McArdle CS, Aitken HH. Parenteral ketorolac: opiatesparing effect and lack of cardiorespiratory depression in the perioperative patient. *Pharmacoth* 1990; 10(6P2): 127S-31S.
18. Maslin B, Lipana L, Roth B, Kodumudi G, Vadivelu N. Safety Considerations in the Use of Ketorolac for Postoperative Pain. *Curr. Drug Saf* 2017; 12(1): 67-73.
19. Saiyed A, Sharma S, Hussain A. Comparison of analgesic and hemodynamic effects of nalbuphine versus fentanyl: a randomized, double-blinded interventional study in patients on cardiopulmonary bypass. *Egypt J Anaesth* 2020; 14(2): 44-48.
20. Mahjoubifard M, Moeini Y, Feizabad E, Abdolrazaghnejad A. The Effect of Paracetamol on the Patient-Controlled Pain After Coronary Artery Bypass Surgery: A Randomized Clinical Trial Study. *J Pharm Care* 2021; 9(4): 176-182.
21. Jannati M, Attar A. Analgesia and sedation post-coronary artery bypass graft surgery: a review of the literature. *Ther Clin Risk Manag* 2019; 15(1): 773-781.