Comparing the Effects of Ketorolac and Paracetamol on Postoperative Pain in Coronary Artery Bypass Graft surgery. A randomized clinical trial

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Abstract

Introduction Pain management after coronary artery bypass graft (CABG) surgery remains challenging. Objective This study aimed to compare the effects of Ketorolac and Paracetamol on postoperative CABG pain management.

Method This double-blind randomized clinical trial study was conducted in Ahvaz, Iran, from September 2018-December 2019. Two consecutive groups of 60 patients undergoing elective on-pump coronary artery bypass graft surgery. Intervention The patients were divided into 0.5 mg/kg of ketorolac mg/dl and 10 mg/kg of Paracetamol after surgery for pain management. Primary outcomes were: visual analog pain scale (VAS) at the time point immediately after extubation (baseline) and at 6, 12, 24 and 48 hours and the total dose of morphine consumption. Secondary outcomes included the hemodynamic variables, weaning time, chest tube derange, in-hospital mortality and myocardial infarction. Statistical analysis The data were analyzed using SPSS version 22(SPSS, Chicago, IL). The Mann-Whitney U-test was used to compare demographic data, VAS scores, vital signs, and side effects. Repeated measurements were tested within groups using Friedman's ANOVA and the Wilcoxon rank-sum test. Values were expressed as means ± standard deviations. Statistical significance was defined as a p-value < 0.05.

Results Compared with baseline scores, there were significant declines in VAS scores in both groups throughout the time sequence (P< 0.05). The statistical VAS score was slightly higher in the Paracetamol group at most time points, except for the time of 6 h. However, at 24 and 48 hours, the VAS score in group Paracetamol was significantly higher than in group Ketorolac. There were no significant differences between groups about hemodynamic variables.

Conclusion: The efficacy of ketorolac is comparable to that of Paracetamol in postoperative CABG pain management.

Introduction

Pain management after coronary artery bypass graft (CABG) surgery remains challenging. Incompetently controlled postoperative pain can increase catecholamine levels, triggering myocardial ischemia, stroke, and bleeding complications. Limiting patient mobility, poorly managed postoperative pain can increase the risk of deep vein thrombosis and pneumonia, in addition to harmful psychological consequences such as insomnia and demoralization (1, 2). Postoperative analgesia after cardiac surgery most commonly involves the use of intravenous and oral opioids. Intravenous (IV) opioids, such as morphine, are the analgesics commonly used to provide postoperative pain relief after CABG surgery (3, 4). However, adverse effects, such as drowsiness, respiratory depression, excessive sedation, biliary spasm, depression of gastrointestinal motility, nausea and vomiting, and, particularly in elderly, confusion caused by opioids may delay patient recovery and rehabilitation (3, 5). To limit these adverse effects without sacrificing adequate pain management, nonsteroidal anti-inflammatory drugs (NSAIDs), increasingly are being applied in the postoperative setting. Although NSAIDs have potential side effects (bleeding,

gastrointestinal ulceration, and renal dysfunction), several studies have noted low complication rates associated with their short-term use after CABG when administered to appropriately selected patients (6, 7)

Paracetamol is usually considered to be a frail inhibitor of the synthesis of prostaglandins (PGs). However, the in vivo effects of Paracetamol are alike to those of the discerning cyclooxygenase-2 (COX-2) inhibitors. It is the most commonly suggested pain-relieving for the treatment of acute pain (8). Its advantage over NSAIDs is its lack of interference with platelet functions. Moreover, it is safe to administer to patients with a history of peptic ulcers or asthma (9). Its mechanism of action may involve a central inhibition of COX-2 (10, 11), inhibition of nitric oxide generation via a blockade of the N-methyl-D-aspartate (NMDA) receptor, and activation of the descending serotonergic pathway. Paracetamol can cross the blood-brain barrier, producing a central analgesic effect (12, 13)

Ketorolac has been used for postoperative analgesia in combination with opioids. Several studies have reported that ketorolac is as effective as morphine or meperidine for analgesia after some types of surgical procedures (14). However, because many studies report significant side effects of ketorolac, including coagulopathy, gastrointestinal problems, and nephrotoxicity there is increasing interest in the use of other classes of non-opioid analgesics (15, 16). It remains unknown whether NSAID utilization rates after CABG have changed since the boxed warning was issued, although some groups have reported their continued use to select cardiac surgery patients (17, 18). Therefore, this study aimed to compare the effects of Ketorolac and Paracetamol on postoperative CABG pain management.

Material And Method:

Study design

This double –blind randomized clinical trial study was conducted in Golestan Hospital, Ahvaz, Iran, from September 2018-Desamber 2019(Ethics code: IR.AJUMS.REC.1398.050). Two consecutive groups of sixty patients undergoing elective on- pump coronary artery bypass graft surgery. After clearly explaining the objective and potential risks and benefits of the study, a written consent form for participation in the study was obtained from all patient. Setting and Patients: Inclusion criteria: Aged 30–70 years with ASA II- III, Ejection Fraction ≥ 30%, undergoing elective CABG.

Exclusion criteria included

Severe hepatic and renal disease, consumption of the anti-inflammatory drugs or antipyretic drugs before the study, redo surgery, history of cerebrovascular accident (CVA).
Randomization: randomization was performed using a computer –generated random digits to ensure that patients and investigators were blind to the treatment assignment before study entry; and the allocation was done 1:1 to receive either ketorolac or Paracetamol. Randomization was not performed until electronically confirming the eligibility criteria in the web-based case report form. Randomization

was performed centrally without stratification. The sequence was generated by an independent statistician using a random number generator with a 1:1 allocation using random block sizes of 2.

Sample size

The study population consisted of 60 patients. Based on the previous data(19) the study required a sample size of 30 patients per intervention group to provide the statistical power of 90% with a two-sided significance level of 0.05.

Anesthesia protocol

After arrival to the operation room, standard monitoring included five-lead electrocardiography, pulse oximetry and arterial line for continuous blood pressure monitoring and blood gases were inserted.. Induction of anesthesia was induced (i.e., 0.25 mg/kg midazolam, 2 µg/kg fentanyl, 1 mg/kg propofol, and 0.5 mg/kg cisatracurium). Isoflurane 1%, 4 µg/kg/h fentanyl, 0.25 mg/kg/h midazolam, and 0.3 mg/kg/h cisatracurium were used for maintaining general anesthesia. After induction of general anesthesia, a central venous catheter was introduced. For initiation of cardiopulmonary bypass, 350 u/kg heparin was injected to all patients. Heparin dosage was attuned based on goal ACT 450–480 second. After the bypass was terminated, protamine was given for reversal of heparin. Cardiac surgery and postoperative management were standardized.

After surgery, all the patients were admitted to the cardiovascular ICU, with a standard protocol for sedation, analgesia, and management of mechanical ventilation.

Intervention

Immediately after the transfer of patients to ICU, intervention began. The patients in the ketorolac group were administered 0.5 mg/kg of ketorolac (mixed with normal saline to a total volume of 100 ml) for 30 minutes each 6 hours for 24 hours. The patients in the Paracetamol group were given 10 mg/kg of Paracetamol (mixed with normal saline to a total volume of 100 ml) for 30 minutes each 6 hours for 24 hours.
Patients were extubated according to the following criteria: responsive and cooperative, pO2 of 80–100, oxygenation index of pO2/FiO2 > 300, and hemodynamic stability. Patients in the Intensive Care Unit (ICU) were sedated with propofol (0.5 mg/kg/h) until extubation. Analgesia was provided based on need with intravenous morphine infusion. The amount of morphine consumption were recorded.

Primary outcomes were: visual analogue pain scale (VAS) at the time point immediately after extubation (baseline) and at 6, 12, 24 and 48 hours and the total dose of morphine consumption. Secondary outcomes included the hemodynamic variables, weaning time, chest tube derange, in hospital mortality and myocardial infarction.

VAS score assessment

Pain intensity levels were subjectively measured using a 10 cm visual analogue pain scale (VAS, 0 = no pain to 10 = unbearable pain). We assessed VAS and hemodynamic variables (systolic blood pressure, diastolic blood pressure, heart rate and other parameters) of each regimen immediately after extubation (baseline) and at 6, 12, 24, and 48 hours .

Statistical analysis

The data were analyzed using SPSS version 22(SPSS, Chicago, IL). The Mannhitney U-test was used to compare demographic data, VAS scores, vital signs, and side effects. Repeated measurements were tested within groups using Friedman's ANOVA and the Wilcoxon rank sum test. Values were expressed as means ± standard deviations. Statistical significance was defined as a p-value < 0.05.

Results

During the study period from September 2018-Desamber 2019, 100 patients undergoing elective on-pump CABG surgery were eligible to participate in the trial. 40 patients did not have inclusion criteria Finally, 60 patients were enrolled in the study and were assigned into two groups of ketorolac and Paracetamol, 30 patients each. (Fig.1)

There were no significant differences between two groups in terms of demographic characteristics including age, male/female ratio ,platelet count ,bleeding time , duration of cross clamp time, and chest tube derange (P> 0.05) (Table 1).

Table 1. Demographic Data of patients in two groups

Parameter	Paracetamol (n=30)	Ketorolac group (n=30)	P-value
Male/Female (%)	18/12 (60/40)	19/11 (63.33/36.67/)	0.453
Age (year)	58.41 ± 1.82	61.83 ± 1.54	0.159
Weight(kg)	70.63 (10.102)	74.80 (31.142)	0.475
Height(cm)	173.03 (10.165)	163.29 (27.207)	0.063
Outpatient use of NSAIDs or antiplatelet, n (%)	20(67)	21(70)	0.21
Euro Score ‖ (%), mean ± SD	2.63 ± 2.65	2.86 ± 2.83	0.489
BT in 24 hr (S)	121.1± 2.73	126.8± 3.41	0.417
BT in 48 hr (S)	129.6 ± 34.56	132.4 ± 23.87	0.356
Duration of Aortic cross-clamp time(min) mean±SD	55.11 ± 38.61	49.47 ± 30.73	0.09

SD:Standard deviation; BT:Bleeding Time

Compared with baseline scores, there were significant declines in VAS scores in both groups throughout the time sequence (P 0.05). The statistical VAS score was slightly higher in the paracetamol group at most time points, except for the time of 6 h. However, at 24 and 48 hours the VAS score in group Paracetamol was significant higher than in group Ketorolac (Fig. 2).

There was significant differences about morphine consumption in two groups at 24(2.9±0.41 mg in Paracetamol group versus 1.71±0.53mg in ketorolac group p=0.027) and 48 hours (2.2±0.15 mg in Paracetamol versus 2.18±0.52 mg in ketorolac group p=0.007) after extubation.

Fig. 2. VAS score after operation. There was significant VAS score declines in both groups (P < 0.05).

Comparison of the two groups receiving ketorolac and Paracetamol showed that there was no significant difference between the two groups in terms hemodynamic parameters and oxygen saturation percentage at different times (P> 0.05) (Table2).

No significant difference in the hospital mortality rate was found between the two groups. (P>0.05)

No patients in either group experienced a postoperative MI. There was no difference between groups with respect to clinically significant bleeding and change in platelets. Weaning time significantly lower in Paracetamol group than ketorolac group (p=0.003). (Table2)

Table 2. Effect of administration of ketorolac and Paracetamol on hemodynamic variables and outcomes

parameter	Paracetamol (n=30)	Ketorolac(n=30)	P-value
MAP	87.742 (11.026)	86.451 (8.958)	0.59
HR	86.2±7.2	85.5±11.7	0.44
SAO2	98.4±1.4	98.4±1.3	0.8
Chesttub drainage(cc)	285.25±65.6	302.05±68.76	0.65
Decrease in platlet,median(IQR)	74 (11–121)	72 (19–153)	0.17
Weaning time(hr.)	11.76±1.21	18.56±1.14	0.003
Myocardial infarction	0	0	-
Mortality	0	0	-

HR: heart rate; MAP: Mean arterial blood pressure; CTD: Chest Tube Drainage; SAT O_2: oxygen saturation; IQR: interquartile range

Discussion

Pain management in the postoperative care setting is of utmost importance for patients who underwent CABG. Therefore, pharmacological and interventional approaches have been developed for postoperative analgesia. Currently, there is an increase in the mean age of the patients, and in the number of comorbidities in patients undergoing CABG. Overall, a method of postoperative analgesia which is cost-effective and comfortable for the patient with minimum complication rates and side effects which also shortens the duration of postoperative stay should be chosen. However, postoperative pain managing is often incomplete by the side effects of opioids; especially when used alone in large doses for an extensive period, opioids can lead to acute tolerance and, more seriously, respiratory depression and hypotension. For these reasons, multimodal approaches that add non-opioid agents to opioid-based regimens are favorable. This study aimed to compare the effects of Ketorolac and Paracetamol on postoperative pain management. The main finding in the present study was confirmation of the beneficial analgesic effect of ketorolac and Paracetamol, which alleviated pain in all of the patients. Such effects seem to be less marked with Paracetamol, possibly because of the low dose selected.

NSAIDs block the synthesis of prostaglandins through the inhibition of COX-1 and COX-2, thus lowering the production of acute inflammatory response mediators. By decreasing the inflammatory response to surgical trauma, NSAIDs reduce peripheral nociception. NSAIDs also appear to have a central analgesic mechanism, possibly through the inhibition of prostaglandin synthesis within the spinal cord. In general, NSAIDs have a low side-effect profile when administered for the short-term purpose of perioperative analgesia after cardiac surgery (20, 21).

Ketorolac is effective at reducing pain, and several studies have reported its safety and efficacy in the perioperative period. In many reports, the use of ketorolac as an adjuvant to a PCA opioid resulted in an opioid-sparing effect ranging from 16–33% (22). The hypothesis by which ketorolac exerts these possible beneficial effects is proposed to be related to its COX-1 selectivity and minimal inhibition of COX-2 (23). As previously discussed, the boxed warning for NSAIDs arose from specific data for the COX-2 selective NSAID, valecoxib (24) COX-2 inhibitors selectively reduce prostacyclin synthesis with no effect on thromboxane A2. Prostacyclin is a potent inhibitor of platelet aggregation; its selective blockade by COX-2 inhibitors may upset thrombosis homeostasis and cause adverse cardiovascular events. Ketorolac, on the other hand, potently blocks platelet aggregation through thromboxane A2 inhibition (23, 25). This may be beneficial in patients with aspirin resistance to prevent CABG graft failure. The duration of this antiplatelet effect can last up to 24 hours after a single dose. Additionally, antiplatelet effects of ketorolac may offset the risk of hemorrhage in postoperative patients who may be hypercoagulable following exactly off-pump CABG surgery (17).

The authors previously reported the results of a randomized trial that found that oral naproxen is effective as an adjunct for the optimization of pain control and lung recovery after CABG, without increasing the risk of postoperative complications. In contrast to naproxen, intravenous ketorolac can be provided earlier in the postoperative period before the resumption of oral intake. Ketorolac provides an

analgesic effect similar to that of fentanyl, but with a lower incidence of postoperative nausea and somnolence, and leads to an earlier return of bowel function.(15)With these advantages over opioids, ketorolac administration ultimately may shorten hospital length of stay.

Paracetamol has been studied in many surgical settings such as functional endoscopic sinus surgery, cholecystectomy, hysterectomy, and orthopedic surgeries with variable favorable results (26, 27). Direction of acetaminophen via a nasogastric tube or rectally after surgery is insufficient to accomplish an antipyretic plasma concentration (10 mg/ml); this was probably mainly because of late gastric emptying after anesthesia and surgery (13, 28) In a study conducted by Cattabriga et al., they found that, in patients undertaking cardiac surgery, intravenous paracetamol in combination with tramadol delivers effective pain control(29) (30).

Paracetamol have resulted in hypotension in critically ill patients although this effect could be explained as an allergic phenomenon (31). The remaining prostaglandin inhibitors seem to exert less marked cardiac depressant effect; in fact, the haemodynamic safety of other NSAIDs such as diclofenac and ketorolac used at antipyretic doses and analgesic doses has been reported in several studies (29).

The hemodynamic effects of NSAIDs used for postoperative pain control in patients undergoing major vascular surgery have been reported in a few studies (32, 33) .Although exogenous administration of prostaglandins has marked hemodynamic repercussions, exogenous inhibition of prostaglandin synthesis has little hemodynamic effect. This could reflect a balance between the reduction in synthesis of prostaglandins with vasodilator and vasoconstrictor actions, with a neutral overall effect. However, NSAIDs must be used cautiously in clinical situations in which prostaglandins have been shown to have advantageous therapeutic effects, such as circulatory insufficiency, shock, myocardial ischemia, coronary spasm and systemic and pulmonary hypertension; in addition, NSAIDs may antagonize the effect of antihypertensive medication. In the present study, such patients were excluded and therefore no evaluation of hemodynamic stability when the drugs were present were made.

Our study found no association between use of 0.5 mg/kg ketorolac and mortality, MI, or clinically important hemorrhage. These results, however, are limited by unexpected differences in the baseline characteristics of number of on-pump CABG patients and STS risk scores. On-pump CABG means a patient placed on cardiopulmonary bypass throughout surgery (34). The STS risk score is intended for all patients who undergo CABG surgery and helps as a prognosticator of post-operative mortality.(35)

Limitations

This study has several limitations. First; sample size was small second; this study was single-centered. We recommended future trial with large sample size, multi-center and long duration of follow-up.

Conclusion

In conclusion, ketorolac and Paracetamol produced marked postoperative pain relief after cardiac surgery and the analgesic effects of these compounds were not associated with a clinically significant impairment in hemodynamic function and mortality, MI, or clinically significant bleeding in postoperative CABG patients.

Abbreviations

CABG
coronary artery bypass graft; VAS:visual analogue pain scale; NSAIDs:nonsteroidal anti-inflammatory drugs; PGs:prostaglandins; COX-2:cyclooxygenase-2; NMDA:N-methyl-D-aspartate; ICU:Intensive care unit; MI:Myocardial infarction

Declarations

Ethical Approval and Consent to participate: The local Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, approved all of the procedures of this study. (IR.AJUMS.REC.1395.510). The RCT code of this study was: IRCT2016122631573N1

Consent for publication: Authors provide formal written Consent to Publish before publication

Availability of supporting data :All data were retrieved from the institutional database and are available from the corresponding author upon reasonable request

Competing interests: The authors report no conflict of interest

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Authors' contributions: Fatemeh Javaherforooshzadeh and Hasan Abdalbeygi collected data and drafted the manuscript. Hasan Abdalbeygi provided study materials and patients' information. Farahzad Janatmakan and Behnam Gholizadeh conceived of the study and participated in its design. All authors read and approved the final manuscript.

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Figures

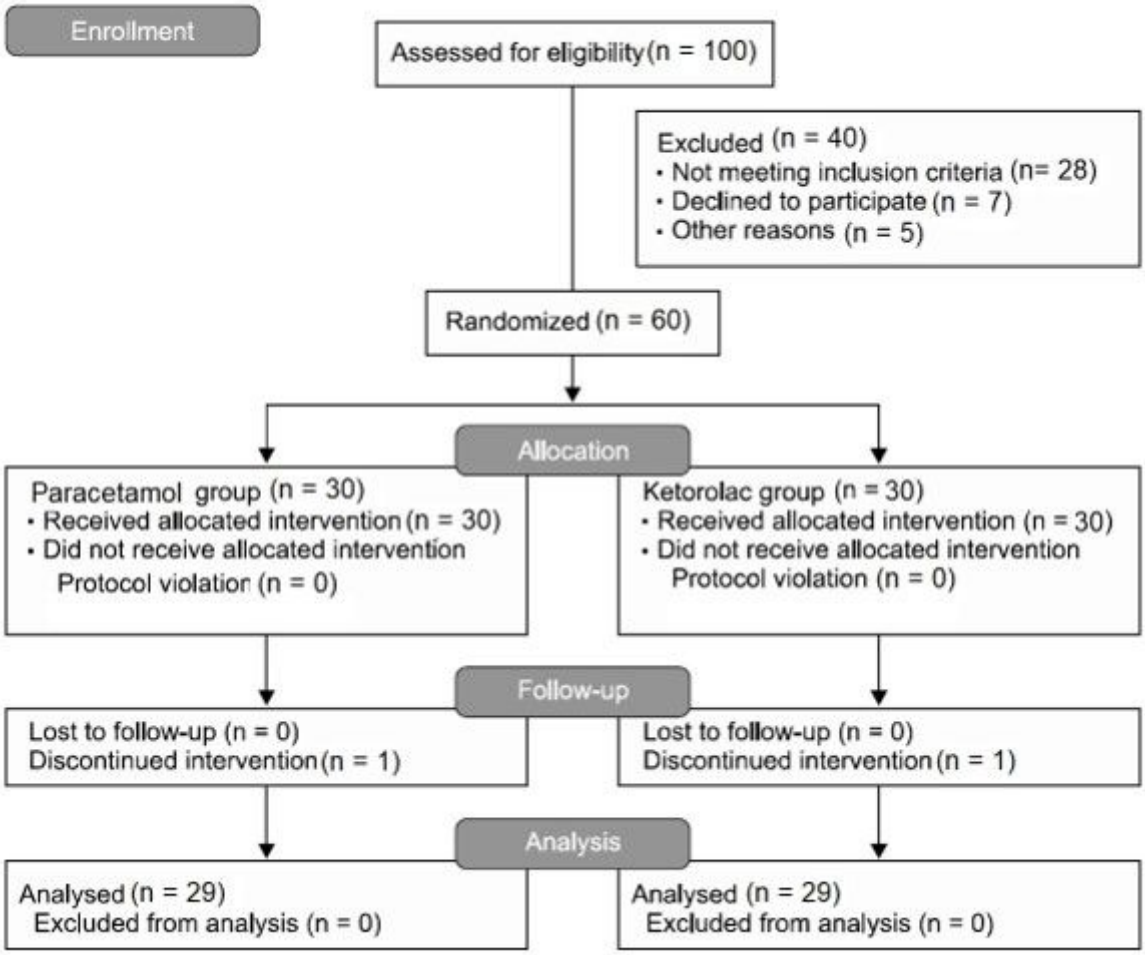

Figure 1

The consort flow chart

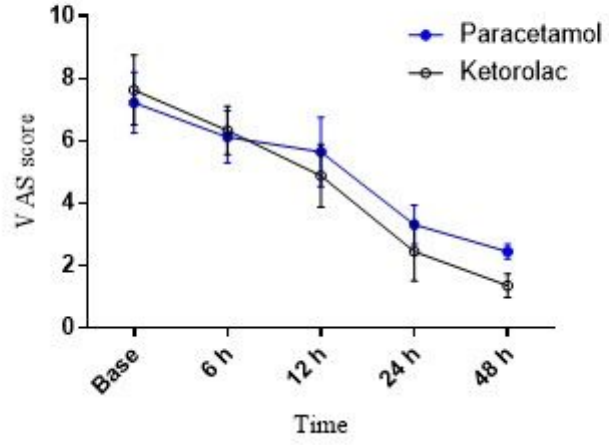

Figure 2

VAS score after operation. There was significant VAS score declines in both groups ($P < 0.05$).