The Effect of Paracetamol on the Patient-Controlled Pain After Coronary Artery Bypass Surgery: A Randomized Clinical Trial Study

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Background: Pain is one of the patients' common problems, and usual morbidity after coronary artery bypass graft (CABG). This study aimed to assess the effect of Paracetamol and fentanyl in reducing post-CABG pain.

Methods: This double-blind randomized clinical trial was conducted on 160 patients undergoing elective CABG (80 in group F (Fentanyl) and 80 in group P (Paracetamol)), at the cardiac surgery department of hospitals affiliated with Zahedan University of Medical Sciences. In group F, 50μg of Fentanyl (intravenous (IV)) was injected followed by a solution of 10 μg/cc at a rate of 4 cc/hr. For patients in group P, 15 mg/kg of Paracetamol (IV) was administered followed by a solution of 25 μg/cc at a rate of 4 cc/hr. Patients have been infused with the named drugs within the first 24 hours after the operation. Pain severity was assessed by the visual pain score (VAS) tool at baseline, and two, four, eight, twelve, and twenty-four hours after the surgery.

Results: The mean of pain score in 12 (P=0.002) and 24 (P<0.0001) hours after surgery in group P was significantly less than that of group F. The mean heart rate in patients receiving Paracetamol was significantly (P = 0.005) less than that of patients receiving Fentanyl for 4 hours after surgery. The mean of increasing creatinine postoperatively in two groups was significant. The mean of increasing AST and ALT postoperatively in group P was significant with no case of liver function impairment.

Conclusion: It seems Paracetamol is a good choice for reducing post-CABG pain with no significant complication, although further and more comprehensive research is needed.

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Introduction
Pain is one of the patients’ common problems, and usual morbidity after coronary artery bypass graft (CABG), and its incidence is about 28% to 56% (1-6). This clinical morbidity in post CABG patients can be very important because of their negative effect on a wide range of next complications such as inadequate expectoration, atelectasis, pneumonia, deep vein
thrombosis (DVT) caused by decreased mobility, or even pulmonary thromboembolism, postoperative pulmonary complications (PPCs), such as pneumonia and acute respiratory failure, and myocardial infarction (7-9).

Physicians use different methods to control the patients’ pain, including oral or preemptive administration, parenteral, bupivacaine infusion, epidural, peripheral neural block, and patient-controlled analgesia (10-15).

Currently, opioid analgesics are used broadly as a post-CABG pain control drug. Nevertheless, the use of opiates especially in patients at high risk of pulmonary complications can increase the risk of respiratory depression; besides that, other unwanted side effects such as nausea, vomiting, constipation, pruritus, mental dysfunction, and opioid-induced hyperalgesia is apparent in the use of this drug group (16-18).

On the other hand, studies have shown that the use of non-opioid analgesics such as Paracetamol and NSAIDs by providing “multimodal” or “balanced” analgesia can reduce the dose of opioid needed and, as a result, reduce its complications (19-20).

Intravenous (IV) Paracetamol is a relatively new drug that has been used in Europe and the United States for about ten years ago. An important advantage of this form of drug versus its oral and rectal forms is that its high availability, for instance 1 gram of IV formulation of this drug has about twice plasma concentration compared to other forms, resulting in better CNS penetration. Furthermore, according to former studies, the use of Paracetamol can reduce the need for opioids to reduce postoperative pain (21-24).

Considering the above-mentioned points and limited studies in Iran in this topic, this study aimed to assess the effect of Paracetamol analgesia in comparison with fentanyl in reducing post- coronary artery bypass graft (CABG) pain.

Methods
This double-blind randomized clinical trial was conducted on patients undergoing elective CABG surgery at the cardiac surgery department of hospitals affiliated with Zahedan University of Medical Sciences.

All procedures were performed following Declaration of Helsinki. Ethical approval was obtained from the ethics board at Zahedan University of Medical Sciences (IR.ZAUMS.REC.1394.238) and the registration code at the Iranian Registry of Clinical Trials is IRCT2016121131351N1. All participants were requested to sign the informed consent.

The study included patients undergoing elective CABG with preoperative ejection fraction (EF) more than 30%, class I-III of American Society of Anesthesiologists (ASA), no concurrent involvement of the heart valves, and no need for intra-aortic pump during surgery.

Patients with a history of susceptibility to the drugs of the study, uncontrolled systemic disease such as unstable diabetes, alcohol, and drug addiction, history of mental illness and depression, history of asthma or other allergic reactions, sternum or rib fractures during the operation, pre-operative increased in liver enzymes more than twice the normal level, other causes of chest pain except for coronary artery disease, pre-operative EF < 30%, neurological symptoms, and any abnormalities in preoperative alertness were excluded.

The participants and outcome assessors (the trained nurse) were blind to the study groups. Sample size was determined based on 80% of power and 95% of confidence level; and significance level (α) was assumed to be 0.05. The highest number was selected for sample size.

Block randomization method was done with online website (www.sealedenvelope.com/simple-randomiser/v1/lists). The corresponding author generated the random allocation sequence, enrolled participants, and assigned participants to interventions: 80 patients in group F (Fentanyl) and 80 patients in group P (Paracetamol).

Patients in group F received Fentanyl (intravenous (IV)), Caspian tamin Pharmaceutical Co., Iran), 50 μg as a bolus dose followed by a solution of 10 μg/cc at a rate of 4 cc/hr up to the first 24 hours after the surgery.

Patients in group P received Paracetamol, (IV, Fresenius Kabi Deutschland Pharmaceutical Co., Germany), 15 mg/kg of Paracetamol (IV) was administered as a bolus dose followed by a solution of 25 μg/cc at a rate of 4 cc/hr up to the first 24 hours after the surgery.

As primary outcomes, pain severity was assessed by the visual pain score (VAS) tool at baseline, and two, four, eight, twelve, and twenty-four hours after the surgery.

Secondary outcomes included mean arterial blood pressure (MAP), heart rate, and arterial oxygen saturation percentage (SaO2) (performed by pulse oximetry). They are the most prognostic outcomes for patients undergoing CABG and were evaluated at baseline, two, four, eight, twelve, and twenty-four hours after the surgery.

In addition, the complications of the drugs such as itching, nausea, vomiting, respiratory depression (RR <8) were assessed by patient asking and physical examination 24 after the drug initiation. Also, renal dysfunction (creatinine > 2mg/dL), and liver function impairment (Liver Function
Test (LFT) more than twice as normal) were evaluated through blood sampling 24 after the drug initiation.

All data were analyzed by SPSS software version 24 at the end of the study and statistically analyzed by a significant level of 0.05. A Chi-square test was performed to evaluate differences in the distribution of the categorical variables. Mann-Whitney and Wilcoxon tests were performed to evaluate differences in the mean of the continuous variables.

**Results**

Over study period, 176 patients, who were eligible for the study, were identified. Six patients were excluded due to Emergency CABG and 10 patients declined to participate; the remainder 160 patients were randomly assigned to the control and the intervention groups (Figure 1).

THE PATIENTS’ MEAN AGE IN GROUP P WAS 56.60±6.18 YEARS, AND IN GROUP F WAS 58.73±8.13 YEARS OLD, WHICH THIS DIFFERENCE WASN’T STATISTICALLY SIGNIFICANT IN THE TWO GROUPS (P-value=0.06). IN GROUP P, 36 PATIENTS (45%) WERE FEMALE AND 44 PATIENTS (55%) WERE MALE; AND IN GROUP F, 40 PATIENTS (50%) WERE WOMEN AND 40 PATIENTS (50%) WERE MEN, WHICH THIS DIFFERENCE WASN’T STATISTICALLY SIGNIFICANT IN THE TWO GROUPS (P=0.52) (Table 1).

**Figure 1.** CONSORT Flow Diagram

**Table 1.** Demographic and clinical characteristics of patients.

| Variables | Group P | Group F | P-value |
|-----------|---------|---------|---------|
| Age       | 56.60±6.18 | 58.73±8.13 | 0.060   |
| Female    | 36 (45%)  | 44 (55%) | 0.520   |
| Male      | 44 (55%)  | 40 (50%) |         |
According to Figure 2, the mean of pain during transfer to ICU, and 2, 4, and 8 hours after surgery in group P was less than that of group F, but the Mann-Whitney test did not show a significant difference. However, the mean of pain in 12 (P = 0.002) and 24 (P < 0.0001) hours after surgery in group P was significantly less than that of group F.

The mean of heart rate during the transfusion to ICU, and at 2, 8, 12, and 24 hours after surgery in patients receiving Paracetamol was less than that of Fentanyl recipients, this difference was not statistically significant (P > 0.05). However, the mean heart rate in patients receiving Paracetamol was significantly (P = 0.005) less than that of patients receiving Fentanyl for 4 hours after surgery (Figure 3).

Figure 2. Comparison of the mean pain score at different times in two study groups.

Figure 3. Comparison of mean heart rate at different times in two study groups.
The mean of MAP during transference to ICU, and at hours 2, 4 and 12 after the surgery in group P was greater than F. However, the mean of MAP at 8 and 24 hours after surgery in group P was less than group F, and at all these times, the differences were not significant (P >0.05) (Figure 4).

The mean of creatinine in baseline and 24 hours after surgery in group F were 0.83±0.31 and 1.29±0.58 and in group P were 0.88±0.41 and 1.37±0.59, respectively. This increasing about creatinine in two groups was significant. The mean of ALT in baseline and 24 hours after surgery in group F were 17.31±4.62 and 18.50±6.19 and in group P were 18.00±3.69 and 19.44±5.71, respectively. The mean of AST in baseline and 24 hours after surgery in group F were 17.81±8.57 and 18.95±8.77 and in group P were 18.38±9.83 and 23.41±11.93, respectively. Although, this increasing in in group P was significant, no case of liver function impairment (LFT more than twice as normal) was detected.

Both groups were similar and statistically not different in terms of the distribution of unwanted side effects such as nausea, vomiting, respiratory depression, and renal dysfunction. It should be noted that pruritus and liver function impairment was not observed in any of the patients in the two groups.

**Discussion**

Different drugs are used to control the pain of patients after surgery, which include opioids, Paracetamol, NSAIDs, and the newer specific COX-2 inhibitors, epidural and topical anesthetic techniques, and peripheral nerve block (25). However, among various medications, the efficacy of using Paracetamol in cardiac surgery has not yet been adequately studied.

The results of this study showed that the mean value of VAS in group P was lower in comparison with F-group in all seven time-points measured, but only in 12 and 24 hours after the operation, which most of the patients separated from mechanical ventilation, this difference was significant that it was consistent with the findings of Jahangiri Fard et al., study which was done on 100 patients with elective CABG (26).

In the present study, the mean MAP and HR of patients were similar between the two groups. The mean number of RRs was significantly lower in all of the seven times measured in the F group than in the P group, which can be attributed to the potential effect of respiratory depression of Fentanyl (27); however, respiratory depression (RR <8) was not seen in the present study which these results were consistent with the results of Krishan et al., (28) study which was conducted on ten patients who received an intravenous infusion of remifentanil perioperatively for CABG.

The serum creatinine level <2 mg/dL after surgery was
observed in 24% of the patients in group P and 28% of the patients in group F, which was not significant. A part of the cause of this increase in creatinine can be attributed to AKI after CABG, due to disruption in blood flow and some degree of tissue necrosis during surgery, which is usually an unavoidable complication (29). Furthermore, in line with previous study, no case of liver dysfunction was detected in our study despite increasing in LFT level in both study groups (26).

The findings of the Apfel et al., systematic review study (30) showed that the use of single-dose Paracetamol can reduce the amount of PONV in patients at least as much as antiemetic. The mechanism of this effect is not related to the reduction in need for opioids and is a result of the reduction in pain intensity of patients (which itself is a risk factor for PONV), and metabolization to AM404 in the brain (which inhibits the reuptake of anandamide) (31).

The main limitation of this study was the small sample size. Another limitation was short follow-up time. The sources of potential bias in this study were the different pain threshold of the patients and the other was the different patients’ complication in drug usage.

Our findings revealed that Due to its relatively low side effects, Paracetamol it can be considered as suitable alternatives for morphine-restricted patients after CABG surgery.

Our study showed that Paracetamol can produce desirable analgesia with minor complications in the patients, although further and more comprehensive research is needed.

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