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**Original Article**

# Oral vs intravenous acetaminophen as a constituent of multimodal analgesia after coronary artery bypass graft surgery: A randomized, blinded trial

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ABSTRACT

**Background & Aim:** This trial aimed to compare the pain relief and side effects of Oral Acetaminophen (OA) and Intravenous Acetaminophen (IVA) after CABG surgery.
**Methods & Materials**: This parallel-group, triple-blinded, randomized trial was conducted on 113 CABG patients from September 2017 through February 2018. The samples were selected through blocked randomization and allocated into two groups using computer-generated. The participants administered 1gr oral (OA group, n=57) or intravenous Acetaminophen (IVA group, n=56) every 6h for the first 24h following surgery; also, pain controlled in both group with Morphine multimodal analgesia strategy. Pain intensity measurement by VAS was followed after extubating the endotracheal tube at the 0, 1, 6, 12, 18 and 24 hours during the rest and deep breathing. The Morphine consumption and the incidence of nausea and vomiting in the first 24h were assessed. Data were analyzed using SPSS software and Chi-square, t-test, mixed ANOVA and ANCOVA test.
**Results:** The pain score in the IVA group was found to be statistically significantly lower than the OA group at rest (P<0.001) and during deep breathing (P<0.001) in the first 24h. There was no statistically significant difference between groups regarding the cumulative Morphine consumption (P=0.056). The use of IVA was associated with a reduction in frequencies of nausea and vomiting incidents (P=0.029).
**Conclusion:** Administration of IVA for the management of postoperative pain in CABG patients significantly reduced pain score and incidence of nausea and vomiting compared to OA. Any reduction in cumulative Morphine consumption did not accompany the lower pain.

## Introduction

One of the progressive treatments for coronary artery disease patients is Coronary Artery Bypass Graft (CABG) surgery (1). A majority of patients after CABG surgery suffer from pain in their length of hospitalization, and over fifty percent report mild to intense pain (2). This pain associated with a sternotomy, chest tubes, eventual leg vein incision and thoracic back pain (3). Also, relieving pain is associated with a patient's recovery after cardiac surgery because patients are necessary to carry out some postoperative activities, like out-of-bed ambulation, incentive spirometry and deep breathing to bring up fast recovery and early hospital discharge (4). The use of centrally acting narcotics is the foundation of post-operative pain management; although, their adverse effects have increasing interest constituent of multimodal analgesic protocols (2). Some anesthetist has adopted multimodal strategies to assistance address these factors and improve patient satisfaction. Furthermore, to regular narcotic-based regimens, several other

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factors can help in reducing narcotic requirements (5).

Acetaminophen has generally used analgesic treatments due to its good tolerance and great safety profile, as well as an addition to multimodal analgesia strategies. It was also found to be safe and effective for reducing pain and opioids consumption (5). Studies have shown that Acetaminophen can be administered through different routes to control post-operative pain (6,7). Geoffrey et al. demonstrated there were no differences in side effects such as nausea, Itching, dizziness and drowsiness among Oral Acetaminophen (OA) and Intravenous Acetaminophen (IVA) (8). Although traditionally Acetaminophen has been administered orally, an intravenous preparation has most recently become accessible (8). OA is commonly used as a first cure of acute pain since of its high therapeutic index. IVA has rapidly and a greater peak plasma concentration (9). However, it is not clear whether IVA has clinical advantages, such as pain relief or less Morphine consumption, over OA. Although IVA might not suggest a real benefit over the OA in patients who can tolerate oral intake, it may be more useful in patients who stay intubated after surgery or those who develop delayed gastric emptying or postoperative nausea and vomiting (9).

Also, disagreement exists regarding the compatibility of these forms for use in some settings, like acute care or postoperative (10). The IVA after cardiac surgery provides useful analgesia (9) and reduces Morphine consumption than the placebo group (11). However, the most effective route of administration is inconsistent amongst the numerous study. Patterson et al. observed that IVA is not inferior to OA for postoperative analgesia in CABG patients (6). These results were similar to some studies (12,13). In Patterson's study, the IVA group received fewer opioids than the OA group (6) but Wasserman et al. demonstrated that Morphine consumption was less in the OA group than the IVA group on postoperative in patients with open colectomies (14).

Notwithstanding, the benefits offered by each rout should as well take into account related risks and disadvantages (10). The costs of treatment are also of major concern. Based on a literature review in 2014, IVA costs 35 times more than that of OA (15). When assessing a more expensive new drug therapy, like IVA, it appears reasonable to assign whether the new drug therapy is better to the standard treatment, in this case, OA. These factors must be considered in medicinal decision-making. It is now unclear whether IVA is more effective and has fewer side effects compared to OA after CABG surgery. The purpose of this research was to compare analgesic effects, morphine consumption, and the incidence of nausea and vomiting post-CABG for IVA and OA. We hypothesized that IVA reduced postoperative pain, morphine requirement and rate of nausea and vomiting post-CABG in comparison with OA.

## Methods

This single-center, parallel-group, triple-blinded, randomized trial was carried out from September 2017 through February 2018. This trial was registered with the Iranian Registry of Clinical Trials (IRCT2016022026217N2). Ethical approval of this research (No: LUMS.REC.1394.41) was obtained from the Ethics Committee of the Lorestan University of Medical Sciences, Khorramabad, Iran. Participants first provided informed consent about the aims and process of the study. Patients' aged 18-65 undergoing CABG surgery with a median sternotomy, with the internal thoracic arteries grafts and saphenous vein harvesting, were eligible for trial inclusion. Patients with a preoperative left ventricle ejection fraction ≤ 35%; Body Mass Index (BMI) > 30 kg/m$^2$; serum bilirubin > 1.8 mg/dl; alanine amino-transferase or aspartate amino-transferase>1.5; serum creatinine>2.0 mg/dl; any coagulopathy, Persian-language limitations, reoperation for any reason and participants impotent to collaborate for pain intensity measurement were omitted from the study. Each patient had a history of

sensitivity to study medications, was not included in the study. If during the study, the participant had hypersensitivity or toxicity, the study medications was discontinued and symptomatic treatment or antidote therapy was used.

Participants were selected sequentially, and the statistician allocated subjects into two groups using computer-generated randomization (blocks of size 6 and 8, 1:1 ratio). Participants in the IVA group received intravenous Acetaminophen (TYLOPHEN®, Exir, Borujerd, Iran) 1 gr and oral placebo; while group OA received oral Acetaminophen (ACETAMIN®, Tehrandarou, Tehran, Iran) 1 gr along with matched volume intravenous normal saline. All participants received a standardized anesthesia protocol in the operations room and drug doses were computed based on the patients' weight. Post-operation, patients were transferred to the cardiothoracic intensive care.

The first dose of Acetaminophen was administered as soon as they were awake and endotracheal tube extubated, and able to swallow, followed by a repetition dose each six hours up to the first 24 hours. Furthermore, in the cardiothoracic intensive care, patients were beginning intravenous Morphine regimen by patient-controlled analgesia as 1-2 mg bolus dose and 20 minutes lockout interval. Rescue analgesia was 2mg intravenous Morphine boluses if inefficiently pain controlled. Anti-emetic drugs were used prophylactically and if necessary for patients in both groups. Study medicines were prepared by the trained nurse who was not blind to the allocation and was administered by another nurse. Each participant was coded confidentially and codes remained with the trained nurse until the end of the analysis. The statistician, nurse who administered drugs and collect data and case subjects were blinded to allocation groups.

Self-assessment by the patient was evaluated post-CABG pain. A Visual Analog Scale (VAS) was used for the evaluation of pain intensity from zero (no pain) to ten (most severe pain imaginable). Participants were introduced with the VAS preoperatively. Pain intensity measurement was followed after extubating endotracheal tube at the first, sixth, 12*th*, 18*th*, and 24*th* hours during the rest and deep breathing. The amount of cumulative Morphine consumption and the occurrence of nausea and vomiting in the first 24 hours was measured and documented.

The sample size was calculated according to a similar investigation done by Pettersson et al. (6). Based on their report, the mean Morphine consumption was 17.4 ± 7.9 mg in the IVA group and 22.1 ± 8.6 mg in the OA group. Power analysis was performed using $\alpha$=0.05, $\beta$=0.2, $S_1$=7.9, $S_2$=8.6, $\mu_1$=17.4 and $\mu_2$=22.1. Therefore, we computed a sample size at a minimum of 50 patients in each arm. However, considering probable attrition of 20%, 60 individuals for each arm were determined.

We used SPSS software (V.22) for all statistical analyses. Qualitative data are shown as number and percentage; quantitative data are shown as a mean and standard deviation. The Kolmogorov-Smirnov test evaluated the normality of the variable. Descriptive statistics were used to organize and summarize demographic data. The differences in patient essential and demographic characteristics between IVA and OA groups were compared using independent two-sample t-test and chi-square test. The mixed ANOVA was employed to compare the VAS score at different time points as well as intraoperative Fentanyl dose were considered as confounders. The differences in VAS score at each time point between two groups were compared using an independent two-sample t-test. A P-value < 0.05 was considered statistically significant for all tests.

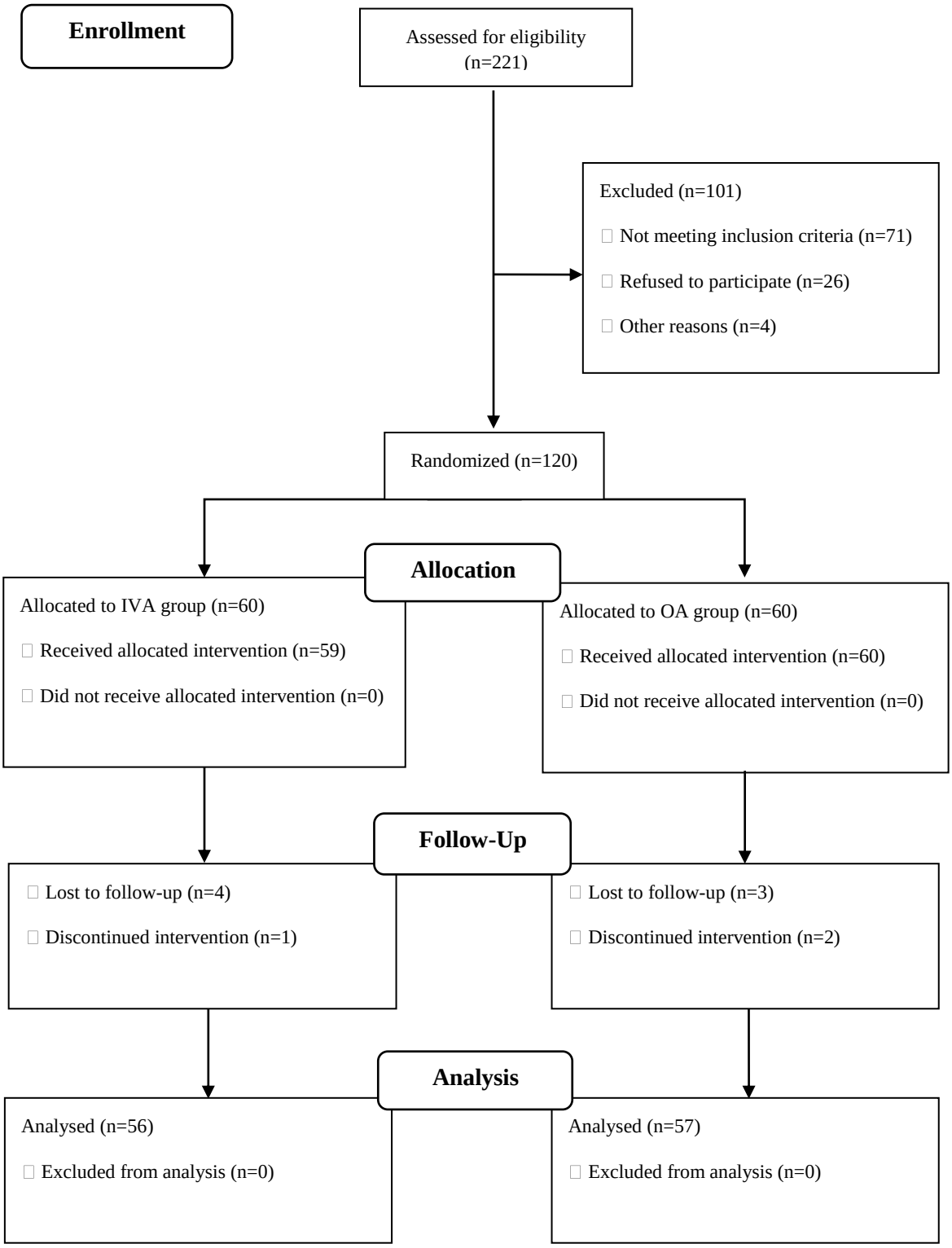


**Figure 1.** Consort flow diagram of the study

## Results

A total of 120 participants were enrolled in two groups (60 participants in each group). Four subjects in the IVA group and three subjects in the OA group withdrawn after enrollment and were therefore excluded from analyses. In the IVA group, participants were excluded for the following causes: an allergic reaction (one participant), reoperation because of excessive bleeding (two participants) and protocol infringement (one participant). In the OA group, participants were excluded for the following

causes: reoperation because of excessive bleeding (one participant) and to be nothing by mouth (NPO) because of frequent vomiting (two participants) (Fig. 1). Table 1 presents participants baseline and demographic characteristics. The age, gender, BMI, medical history, duration of intubation, duration of cross-clamping of the thoracic aorta and cardiopulmonary bypass were similar between groups. There was a difference between groups as intraoperative fentanyl consumption (Table 1).

There were no significant differences in the baseline pain intensity scores among the study groups at rest (4.83±2.12 vs. 5.07±1.89, P=0.543) (Table 2) and during deep breathing (5.32±2.21 vs. 5.61±1.83, P=0.446) (Table 3). Participants in the IVA group while resting significantly had fewer pains at the time point of 1h (3.53±1.95 vs. 4.73±2.34, P=0.004), 6h (3.73±2.38 vs. 4.22±2.46, P=0.028) and 12h (3.26±2.04 vs. 4.14±2.01, P=0.024) after extubating the endotracheal tube (Table 2). As well as the IVA group during a deep breath significantly had fewer pains at the time point of 1h (4.33±2.27 vs. 5.56±2.41, P=0.007), 6h (4.21±2.09 vs. 5.28±2.21, P=0.010) and 12h (3.94±2.30 vs. 4.78±2.17, P=0.048) after extubating the endotracheal tube (Table 3). The VAS scores reduced in equal groups pass the time, and the difference was not significant at the time point of 18h and 24 h after extubating the endotracheal tube (Table 2, 3). There was a significant difference in pain scores between two groups at rest (P<0.001) and deep breathing (P<0.001) during 24 hours after controlling for the confounding effect of intraoperative fentanyl consumption (Table 2, 3). There was no interaction between intervention and time during the rest (P=0.383) and deep breathing (P=0.724).

After adjust of fentanyl there is a difference in pain severity between groups at rest and during a deep breathing (Fig 2, 3).

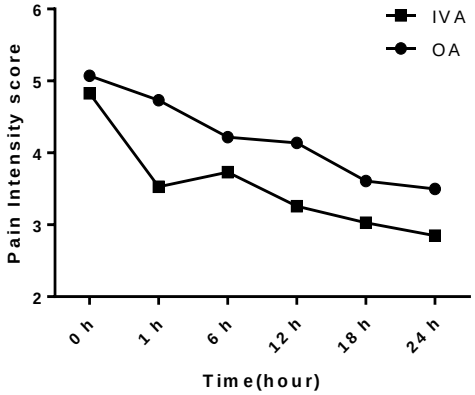


**Figure 2.** Pain difference between the two groups at rest after adjusting for Fentanyl use

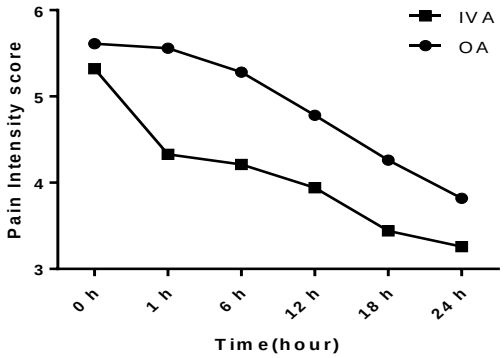


**Figure 3.** Pain difference between the two groups during deep breathing after adjusting for Fentanyl use

The cumulative consumption of Morphine during 24 h postoperatively was 15.17±9.9 mg in IVA group and 18.77±10.64 mg in the OA group (mean difference: -3.60 (95% CI, -0.2327 to 7.4327); P=0.056). Four participants in OA group demanded rescue analgesia with Morphine however in IVA group, no rescue analgesia was needed. Participants in IVA group significantly had fewer indications of nausea and vomiting (n=12 vs. n=23, P=0.029). In the IVA group anti-emetic consumption regardless of the prophylactic doses was less than in the OA group however the difference was not significant (n=9 vs n=16, P=0.124).

**Table 1.** Comparison of baseline and demographic characteristics among the study groups

| Variables | IVA group | OA group | P value |
|---|---|---|---|
| **Age**(years) | 54.66 ±2.14 | 53 ±2.39 | **0.318*** |
| **Gender** | | | |
| Female | 17(30) | 22(38.6) | **0.356**** |
| Male | 39(70) | 35(61.4) | |
| **BMI** | 24.6±5.2 | 23.9±2.4 | **0.251*** |
| **Medical history** | | | |
| Hypertension | 25(45) | 19(33) | **0.217**** |
| Diabetes mellitus | 12(21.4) | 16(28) | **0.413**** |
| **duration of intubation** (h) | 15.3±3.4 | 15.3±3.4 | **0.909*** |
| **duration of CBP time** (min) | 75.2±21.1 | 71.9±20.1 | **0.312*** |
| **Aortic cross-clamping time** (min) | 44/1±16/5 | 43/1±14/2 | **0.681*** |
| **Intraoperative fentanyl dose** (mg) | 1021±230 | 890±512 | **0.005*** |

* Independent t-test ** Chi-square test

**Table 2.** Comparison of pain intensity scores at rest among the study groups in differences time

| Time point | Pain intensity scores | | P value* | P value** |
|---|---|---|---|---|
| | Oral Acetaminophen (Mean±SD) | Intravenous Acetaminophen (Mean±SD) | | |
| **0 h** | 5.07±1.89 | 4.83±2.12 | 0.543 | |
| **1 h** | 4.73±2.34 | 3.53±1.95 | 0.004 | |
| **6 h** | 4.22±2.46 | 3.73±2.38 | 0.028 | |
| **12 h** | 4.14±2.01 | 3.26±2.04 | 0.024 | 0.001 |
| **18 h** | 3.61±1.99 | 3.03±1.90 | 0.118 | |
| **24 h** | 3.50±2.13 | 2.85±1.91 | 0.091 | |
| **P value**[b] | <0.001 | <0.001 | | |

* P values were from independent t-test

** P values were from mixed ANOVA after adjusting fentanyl use

**Table 3.** Comparison of pain intensity scores during a deep breath among the study groups at differences time

| Time point | Pain intensity scores | | P value* | P value** |
|---|---|---|---|---|
| | Oral Acetaminophen (Mean±SD) | Intravenous Acetaminophen (Mean±SD) | | |
| **0 h** | 5.61±1.83 | 5.32±2.21 | 0.446 | |
| **1 h** | 5.56±2.41 | 4.33±2.27 | 0.007 | |
| **6 h** | 5.28±2.21 | 4.21±2.09 | 0.010 | <0.001 |
| **12 h** | 4.78±2.17 | 3.94±2.30 | 0.048 | |
| **18 h** | 4.26±2.26 | 3.44±2.15 | 0.052 | |
| **24 h** | 3.82±2.29 | 3.26±2.10 | 0.181 | |
| **P value**[b] | <0.001 | <0.001 | | |

* P values were from independent t-test

** P values were from mixed ANOVA after adjusting for Fentanyl use

## Discussion

The results of the current randomized, triple-blind clinical trial study demonstrate pain is a lower level at rest and during the deep breathing in the 24 hours after CABG, when IVA was administered, compared with OA. Participants in the IVA group at rest and during the deep breathing significantly had fewer pains at the time point of 1h, 6h and 12h, while pain scores at time point 0h, 18h and 24h following extubating the endotracheal tub were similar between groups.

The findings of our present study show that there was no significant difference regarding the cumulative Morphine consumption between two groups 24h after surgery. However, indicate of vomiting and nausea were less in the IVA group than OA group 24h after surgery. Additionally, in the IVA group anti-emetic consumption regardless of the prophylactic doses was less than in the OA group; however, the difference was not significant.

The IVA group significantly had less pain than the OA group 1-24 h after starting interventions. The plausibility of this finding might be explained by the fact that Acetaminophen achieves high levels of plasma concentration and bioavailability within few hours when it is given intravenously and gradually increase the plasma concentration of oral form (16, 17). The results of our study are contradicting the findings of Brett's study that integrate pharmacokinetic with clinical efficacy consequences to establish such a relation. However, even though their results indicated higher plasma concentrations of IVA than OA, but no differences in clinical efficacy (18). Different analgesic protocols conducted in different settings for different surgeries may achieve different results.

The results of this study have demonstrated the IVA has better analgesia than OA; in the first 12 hours after extubation, at-rest, and deep-breath pain intensity in the IVA group are significantly lesser than the OA group. The pain intensity reduced in the study groups through time so that pain intensity was similar between groups at the time point of 18h and 24 h. These results are in opposition to those of Geoffrey et al. (8). Who found IVA had no benefits for postoperative analgesia in comparison to OA. We believe that these results could be since participants in this study received the Acetaminophen doses for three full days post-operatively. It was found in this study and another study (19) that IVA could be more useful for pain control in the early hours post-operation. The pain intensity progressively decreased with time, so that there was no difference in VAS score 30–72 hours post-operation in patients (19). Therefore, the administration of OA is recommended over the next and following days of surgery.

The result of this trial showed that the IVA group required 3.6 mg less of Morphine than the OA group, even if the difference did not reach statistical significance. Similar results have been shown in the study after CABG surgery, in which about 4.7 mg less of Morphine was required during a 1-24h after starting interventions with the IVA (6). Cattabriga et al., reported a significant reduction in pain but not cumulative opioid consumption after cardiac surgery (19); other trials also report improved pain scores without a reduction in opioid consumption (7, 8). Our results are consistent with those reported by Jelacic et al. recently indicated that IVA significantly reduction 24-hour postoperative opioid consumption (11). This study administered IVA immediately after anesthesia induction but before the incision, while we were administered IVA after surgery. Analgesia received preoperative motivation, may affect nociceptive receptors differently than protective or rescue analgesia and possibly result in improved relieve pain (20).

We also found in our trial that indicated of nausea and vomiting and followed by anti-emetic consumption was further recurrent in the OA group than in the IVA group. The supposition is often made that decreasing morphine consumption will result in reduced opioid-related adverse effects like nausea and vomiting (11). Another study reported that pain itself is a risk factor for nausea and vomiting after surgery. However, Patterson's study does not corroborate these findings. The results of his study showed; Morphine-sparing effect was not accompanied by any decrease in the occurrence of nausea and vomiting (6). Nasogastric delivery is not an efficient way to absorption oral drugs if the gastrointestinal function has not returned to regular.

This study had many strengths, and our strategies appear that we are sure within the validity of results. The reality that it was a

parallel-group, triple-blinded, randomized trial study empowered us to diminish the hazard of selection bias. The patients correctly adhered to the intervention; this is because minimal medication side effects were noticed in any subject. This indicates that the intervention can be used safely as a standard method.

The indicated of nausea and vomiting could be unmeasured precisely; this is because we did not use a standard instrument to measure those complications. The results of the current study cannot be generalized to chronic pain and other surgical procedures either, although the authors predict a similar outcome. Recommendations can be made about future studies in this setting. Studies should contain both efficacy and safety consequences and should evaluate several dosing to characterize well longer-time use and changes relating to the dosage forms applied in workout. The researchers suggest that a study performing a cost-analysis between IVA and OA group.

## Conclusion

The results of this study suggest that IVA is effective than OA for pain management after CABG, but no inferior to Morphine consumption. Also, the administration of IVA reduced the incidence of nausea and vomiting than OA. The IVA can be a proper treatment as part of a multimodal analgesia approach in the critical group such as CABG patients.

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## Conflict of Interest

There is no conflict of interest.

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