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Comparison of Fentanyl Versus Morphine-Ketamine-Lidocaine Infusion for Postoperative Pain Following Coronary Artery Bypass Grafting (CABG): A Randomized Clinical Trial

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Abstract

Aim: This study aimed to compare the effectiveness and safety of fentanyl infusion with a combination of morphine, ketamine, and lidocaine (multimodal analgesia) for postoperative pain management in patients undergoing coronary artery bypass grafting (CABG).

Study Design: This randomized clinical trial was conducted from 2024 to 2025 and included 74 patients undergoing elective CABG at the study hospital. Patients received either fentanyl (500 µg/100 mL) or a combination of morphine (20 mg), ketamine (20 mg), and lidocaine (200 mg) diluted to 100 mL, administered as an infusion at 4 mL/h for the first 24 postoperative hours. Pain was assessed using the Visual Analog Scale (VAS) at 1, 4, 8, 12, 16, 20, and 24 hours after surgery. Additional recorded parameters included hemodynamic variables, respiratory depression, and the need for rescue analgesia.

Results: Patients receiving fentanyl infusion demonstrated a statistically significant greater reduction in pain scores at 4 and 8 hours postoperatively compared to those receiving the multimodal regimen. However, at the remaining assessment times (1, 12, 16, 20, and 24 hours), no significant differences in pain intensity were observed. Over the full 24-hour period, both regimens provided comparable analgesia. Additionally, no significant differences were found between the groups regarding adverse effects or the need for rescue analgesia.

Conclusions: Fentanyl infusion demonstrated greater efficacy in early postoperative pain control compared to the multimodal regimen; however, this benefit was of short duration. Over the first 24 hours following surgery, both strategies showed comparable efficacy and safety; therefore, both may be considered viable options for post-CABG analgesia.

Keywords: Coronary artery bypass, fentanyl, ketamine, lidocaine, morphine, pain management.

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Introduction

Coronary artery bypass grafting (CABG) utilizes grafts from the saphenous vein and other vessels to reroute blood flow around obstructed coronary arteries, thereby improving blood flow to the heart.[1] For patients with severe myocardial ischemia, CABG significantly enhances both quality of life and survival rates.[2] Effective pain management in CABG patients is essential, as adequate pain control facilitates earlier mobilization, improves postoperative cardiac performance, and reduces the risk of postoperative complications.[3]

Pain serves as the body's warning and protective mechanism against potential harmful injury.[4] Continuous intravenous infusion of analgesia via pain pumps offers an innovative solution for improved pain management compared to other infusion techniques. This approach allows for more precise dosage control, provides optimal pain control, and minimizes the need for systemic opioids, thereby reducing associated risks and enhancing patient safety.[5] Opioids, particularly morphine, are commonly used for pain management during and after surgery, as well as for severe postoperative or cancer-related pain. Morphine carries a known risk of addiction and is therefore more tightly regulated than fentanyl. Fentanyl misuse, however, can result in fatal outcomes.[6] Unlike morphine, fentanyl is less likely to cause long-term dependence and is primarily used for potent pain relief.[7] This synthetic opioid is often administered alongside morphine for pain management in advanced cancer patients and during the perioperative period. Fentanyl is 50 to 100 times more potent than morphine and provides powerful pain relief.[8]

Comparative studies demonstrate some variability depending on clinical context. Some studies suggest that morphine may provide superior analgesia compared to fentanyl in the postoperative period.[9] Conversely, in opioid-dependent patients experiencing acute trauma or undergoing surgery, fentanyl produces more rapid refractory analgesia than morphine, while both drugs demonstrate comparable long-term efficacy. These findings highlight the importance of individualized pain management strategies.[10] The dissociative anesthetic ketamine has a broad range of clinical applications. In addition to its anesthetic properties, it provides analgesia and immobilization while preserving respiratory function.[11] Lidocaine, a local anesthetic and antiarrhythmic agent, blocks sodium channels in nerve cell membranes to inhibit nerve impulse transmission and provide analgesia, thereby facilitating pain relief.[12]

The development of pain pumps has significantly enhanced pain management strategies. This study aimed to assess the effectiveness of fentanyl infusion compared to a postoperative analgesic regimen consisting of morphine, ketamine, and lidocaine for pain control in patients undergoing CABG. Pain intensity during the first 24 hours after surgery was evaluated using the Visual Analog Scale (VAS). Cardiovascular and respiratory side effects, the need for rescue analgesia, and overall pain control were assessed to determine the degree of pain control achieved.

Materials and Methods

Study Design and Participants

This randomized clinical trial included patients eligible for CABG who were referred to the hospital between 2024 and 2025. The primary endpoint was the comparison of mean pain intensity scores, measured by the VAS, between the two groups at 1, 4, 8, 12, 16, 20, and 24 hours after initiation of the intervention. Secondary endpoints included comparisons of mean arterial pressure (MAP), incidence of respiratory depression, and the need for additional analgesic administration between the two groups. Additional secondary outcomes were duration of mechanical ventilation (defined as the time from intensive care unit [ICU] admission to successful extubation), ICU length of stay, and total hospital length of stay.

The sample size was calculated using the following formula:

$$n = (2 \times (z\_(1-\alpha/2) + z\_(1-\beta))^2 \delta^2) \; / \; d^2$$

Based on data from a previous study, and assuming a test power of 80% and a confidence level of 95%, the calculated sample size was 70 patients (35 per group).[12] To account for potential attrition, a 10% increase was applied, resulting in 37 patients in each group.

Patients were randomly allocated to one of the two study groups using a computer-generated randomization sequence. Allocation concealment was ensured using sealed, opaque envelopes, which were opened only at the time of intervention. The attending anesthesiologists and nursing staff responsible for managing the pumps were not blinded to group assignments. However, the patients and the anesthesiology resident responsible for collect-

ing postoperative data (VAS scores and hemodynamic parameters) were blinded to the group assignments.

Age, gender, and body mass index were collected as part of the demographic data through structured interviews with the patients. A checklist was used for data collection and documentation of clinical parameters, including the cardiac pump time and the intubation grade. Blood pressure measurements, pain intensity assessed using the Visual Analog Scale, the presence or absence of pain, timing and loading doses of administered analgesics during the pre-study period and at 1, 4, 8, 12, 16, 20, and 24 hours post-intervention were recorded for both groups. The occurrence of postoperative respiratory depression was also documented.

Inclusion and Exclusion Criteria

Patients aged 30 to 80 years who were undergoing elective CABG surgery and were classified as anesthesia class II and III were included. Eligible patients had an ejection fraction of ≥40% and had not received analgesics within 6 hours prior to surgery. Patients with a history of kidney, liver, gastrointestinal, or pulmonary failure; diabetes mellitus; neurological disorders associated with pain insensitivity; or alcohol or drug dependence were excluded. All participants provided written informed consent prior to enrollment. Exclusion criteria included patients who became critically ill after surgery and required additional medical treatment or ICU admission; those with excessive postoperative bleeding requiring reoperation; patients who developed progressive heart failure requiring high-dose inotropic support; patients undergoing emergency surgery; those undergoing concomitant valve surgery with CABG; patients with allergies to the study drugs; patients who experienced seizures or hemodynamic instability or required a balloon pump support after drugs administration; and patients who did not provide consent.

Research Method

After obtaining approval from the Hormozgan University of Medical Sciences Research Ethics Committee (Approval Number: IR.HUMS.REC.1402.393, Date: 24.01.2024), and registering the study with the Iranian Clinical Trial Registration Center (IRCT20231227060539N1), the research was conducted in accordance with the Declaration of Helsinki. The study methodology was explained to eligible patients, and permission for participation was obtained. Clinical records of patients awaiting CABG surgery were accessed through the Clinical Information System. Patients selected for sampling met the study's inclusion criteria. The study methodology was explained to them, and written informed consent was obtained. Relevant demographic variables, including age, gender, and body mass index, were collected through interviews. Patients underwent anesthesia assessment one day prior to surgery.

Prior to surgery, angiotensin-converting enzyme inhibitors (ACEI) therapy was temporarily discontinued. Upon arrival in the operating room, patients were positioned on the operating table, and routine monitoring was initiated. This included application of a noninvasive blood pressure (NIBP) cuff, cardiopulmonary monitoring leads, and pulse oximetry. Baseline hemodynamic parameters—systolic blood pressure, diastolic blood pressures, and mean arterial pressure—were recorded. Subsequently, the left (non-dominant) radial artery was infiltrated with 2% lidocaine, after which the pulse was augmented to facilitate insertion of an angio-cannula for blood pressure monitoring (size 20). The angio-cannula was connected to a blood pressure monitor to obtain and record the required parameters. Subsequently, the patient underwent induction of general anesthesia with etomidate (0.2 mg/kg), cisatracurium (0.2 mg/kg), and fentanyl (10 μg/kg), after which the surgical procedure was commenced. Fixed drug doses were used in this study to enable a more accurate comparison of the efficacy and safety of the drug regimens by eliminating confounding variables related to dose adjustment. The selected doses were determined based on standard clinical protocols and previous studies.

Each patient received equal volumes of serum and the same type of fluid therapy during surgery. In addition, identical types and dosages of propofol, atracurium, and sufentanil infusions were administered for maintenance of anesthesia. Intraoperative blood loss was assessed by the surgical team and anesthesiologist based on the volume in suction canisters and the weight of used surgical swabs. All patients received standardized crystalloid fluid therapy according to institutional protocols to maintain hemodynamic stability, with the aim of administering a comparable volume per kilogram of body weight.

After surgery, patients were transferred to the ICU for close monitoring and were subsequently categorized into two groups: the fentanyl pain pump group (500 µg/10 mL, Caspian Tamin Co., Iran) and the combination group (morphine 10 mg/1 mL ampule, Daroo Pakhsh Co., Iran;

ketamine 500 mg/10 mL ampoule, Rotexmed Co., Germany; and lidocaine 2%, 100 mg/5 mL, Caspian Tamin Co., Iran). In the first group, the pain pump was set up for continuous intravenous (IV) infusion of fentanyl (500 micrograms) diluted in 100 cc of distilled water and administered at a preset rate of 4 cc/h. In the second (combination) group, ketamine (20 mg), lidocaine (200 mg), and morphine (20 mg) were diluted in 100 cc of distilled water and administered via a pain pump. The selected doses were based on previous studies investigating similar postoperative pain management approaches.[13,14] Although establishing an exact clinically relevant equianalgesic comparison between fentanyl monotherapy and a multimodal combination regimen is challenging, the doses chosen for each approach were consistent with those reported to provide adequate clinical pain control.

Blood pressure values and pain intensity scores based on the VAS criteria were recorded at 1, 4, 8, 12, 16, 20, and 24 hours after the intervention by the anesthesia resident. If the VAS score was greater than 3, the patient received 2.5 mg of intravenous methadone as rescue analgesia. Methadone was selected due to its long half-life, proven efficacy in the postoperative period, and availability in the hospital formulary. The collected data were statistically analyzed and compared between the two groups. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram detailing patient enrollment, allocation, follow-up, and analysis is presented in Figure 1.

Statistical Analysis

Statistical analysis and data processing were performed using SPSS version 27.0 (IBM Corporation, Armonk, New York, USA). Descriptive statistics, including mean, variance, and standard deviation, were calculated. Data normality was assessed using the Kolmogorov-Smirnov test. Quantitative data are presented as mean ± standard deviation, and qualitative data as frequency and percentage. Depending on data distribution, comparisons between groups were performed using the independent t-test or the Mann-Whitney test. A p-value of less than 0.05 was considered statistically significant.

Results

Seventy-four patients were included in the study, with 37 patients in each group (fentanyl pump vs. morphine, ketamine, and lidocaine combination). No significant differences were observed between the groups in demographic and baseline clinical variables, including age (p=0.677), sex (p=0.814), body mass index, and cardiac pump duration (p=0.098) (Table 1).

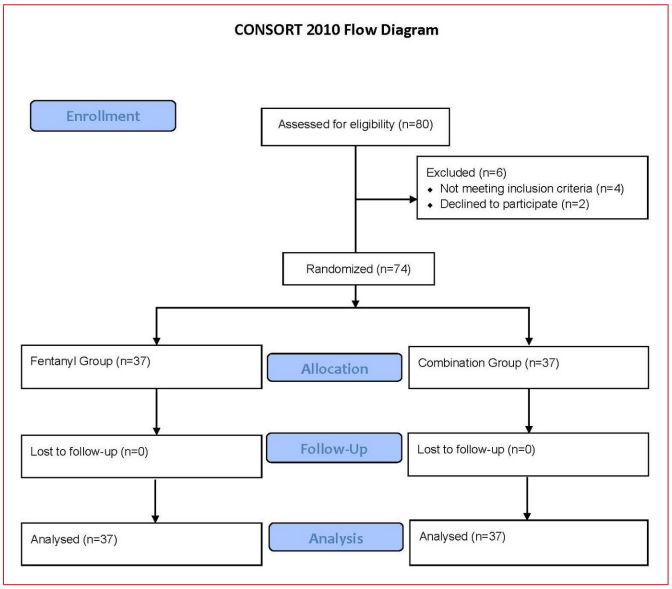

Figure 1. CONSORT flow diagram of patient enrollment, randomization, allocation, and analysis.

Caption: Study flow diagram according to the CONSORT guidelines. Both groups were followed for 24 hours after coronary artery bypass graft (CABG) surgery. Pain intensity and hemodynamic parameters were recorded at intensive care unit (ICU) admission and at 1, 4, 8, 12, 16, 20, and 24 hours post-intervention.

Primary Endpoint: Pain Intensity

No differences in pain intensity, measured using the Visual Analog Scale were observed between the fentanyl and combination groups at any time point: 1 hour (p=0.662), 4 hours (p=0.256), 8 hours (p=0.070), 12 hours (p=0.767), 16 hours (p=0.947), 20 hours (p=0.672), and 24 hours (p=0.498) (Table 2). However, within-group analysis over time showed that the fentanyl group demonstrated a significant reduction in VAS pain scores at 4 hours (p=0.015) and 8 hours (p=0.032) post-intervention compared with 1 hour post-intervention (Table 3). No statistically significant between-group differences were observed at the remaining time points (p>0.05) (Table 4).

Secondary Endpoints

Across the entire assessment period, no statistically significant differences in mean arterial pressure were observed between groups at any measurement time point: pre-intervention (p=0.186), 1 hour (p=0.513), 4 hours (p=0.777), 8 hours (p=0.834), 12 hours (p=0.402), 16 hours (p=0.228), 20 hours (p=0.314), and 24 hours post-intervention (p=0.777) (Table 5).

Table 1. Baseline demographic and clinical characteristics of patients in the two groups

Parameter	Group				p
	Fentanyl group		Combination group		
	Frequency	Percent	Frequency	Percent	
Sex					
Female	15	40.5	16	43.2	0.814*
Male	22	59.5	21	56.8	
Intubation grade					
1	6	16.2	7	18.9	
2	28	75.7	29	78.4	0.699**
3	3	8.1	1	2.7	
Parameter	**Mean**	**SD**	**Mean**	**SD**	**p**
Age (years)	61.02	11.53	60.01	9.49	0.677***
BMI (kg/m²)	23.84	3.50	24.30	3.48	0.573***
Pumping duration (min)	118.59	23.18	127.48	22.41	0.098***

Abbreviations: BMI: Body mass index; CPB: Cardiopulmonary bypass. Data are presented as mean±standard deviation (SD) or n (%). P>0.05 for all comparisons. *Chi-square test; **Fisher's exact test; ***Independent samples t-test

Table 2. Comparison of Visual Analog Scale (VAS) scores between groups

Time Point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	Mean difference	p
1 hour	5.08±1.73	4.86±2.32	0.21	0.662
4 hours	4.67±1.71	5.18±2.18	0.51	0.256
8 hours	4.64±1.75	5.43±1.90	0.78	0.070
12 hours	4.67±1.65	4.78±1.47	0.10	0.767
16 hours	4.62±1.75	4.64±1.71	0.02	0.947
20 hours	4.45±1.65	4.62±1.62	0.16	0.672
24 hours	4.48±1.64	4.24±1.42	0.24	0.498

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. p<0.05 was considered statistically significant.

Changes in MAP from baseline were also analyzed at each time point and showed no significant intergroup differences at 1 hour (p=0.134), 4 hours (p=0.187), 8 hours (p=0.213), 12 hours (p=0.511), 16 hours (p=0.609), 20 hours (p=0.610), and 24 hours (p=0.192) post-intervention (Fig. 2). Similarly, when comparing MAP changes relative to the 1-hour post-intervention time point, no significant differences were observed at 4 hours (p=0.723), 8 hours (p=0.660), 12 hours (p=0.124), 16 hours (p=0.086), 20 hours (p=0.163), and 24 hours (p=0.768) (Fig. 2). Further analyses of MAP changes using other reference time points (4, 8, 12, 16, and 20 hours) also revealed no significant intergroup differences (all p>0.05) (Table 5).

The incidence of respiratory depression was low and comparable between groups (p=0.691). Among affected patients, 10.8% (4/37) were in the fentanyl group and 8.1% (3/37) were in the combination group.

The requirement for rescue opioids (methadone) was similar between groups (p=0.639), with 59.5% (22/37) of patients in the fentanyl group and 54.1% (20/37) in the combination group requiring additional analgesia.

Analysis of postoperative recovery parameters revealed no significant between-group differences. The mean duration of mechanical ventilation was 8.2±2.1 hours in the fentanyl group and 7.9±1.8 hours in the combination

Table 3. Comparison of the mean change in Visual Analog Scale (VAS) score from baseline (one hour post-intervention) at subsequent time points between groups

Time point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	Mean difference	*p*
1 hour				
4 hours	-0.40±1.30	0.32±1.20	0.72	0.015
8 hours	-0.43±1.64	0.56±2.24	1.00	0.032
12 hours	-0.40±1.57	-0.08±2.26	0.32	0.477
16 hours	-0.45±2.00	-0.21±2.43	0.24	0.641
20 hours	-0.62±2.12	-0.24±2.80	0.37	0.515
24 hours	-0.59±1.70	-0.62±2.44	0.02	0.956
4 hours				
8 hours	-0.02±1.48	0.24±1.70	0.27	0.469
12 hours	0.01±1.88	-0.40±2.00	0.40	0.373
16 hours	-0.05±2.18	-0.54±2.20	0.48	0.344
20 hours	-0.21±1.94	-0.56±2.40	0.35	0.492
24 hours	-0.18±1.98	-0.94±2.14	0.75	0.120

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. $p<0.05$ was considered statistically significant.

Table 4. Comparison of the mean change in Visual Analog Scale (VAS) score from the 4-hour post-intervention time point at subsequent time points between groups

Time point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	Mean difference	*p*
8 hours				
12 hours	0.02±1.70	-0.64±1.60	0.67	0.083
16 hours	-0.02±2.24	-0.78±1.95	0.75	0.127
20 hours	-0.18±1.98	-0.81±1.88	0.62	0.171
24 hours	-0.16±1.87	-1.18±2.07	1.02	0.059
12 hours				
16 hours	-0.05±1.97	-0.13±1.00	0.08	0.824
20 hours	-0.21±1.43	-0.16±1.25	0.05	0.864
24 hours	-0.18±1.44	-0.54±1.53	0.35	0.315
16 hours				
20 hours	-0.16±1.93	-0.02±1.62	0.13	0.764
24 hours	-0.13±1.73	-0.40±1.95	0.27	0.531
20 hours				
24 hours	0.02±1.36	-0.37±1.36	0.40	0.205

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. $p<0.05$ was considered statistically significant.

group (p=0.513). The length of ICU stay was 5.1±1.3 days versus 4.9±1.2 days, respectively (p=0.494). The total hospital stay was 7.3±1.5 days versus 7.1±1.4 days (p=0.556). Since there was little difference in the time required for these parameters between the two groups, it may be concluded that both analgesic techniques provide similar pain control without adversely affecting postoperative recovery.

Table 5. Mean arterial pressure (MAP) values at different time points

Time point	Fentanyl group (Mean±SD)	Combination group (Mean±SD)	*p*
Baseline (ICU)	100.75±12.23	105.40±15.66	0.186
1 hour	87.48±10.61	85.92±9.77	0.513
4 hours	88.83±8.97	88.10±12.79	0.777
8 hours	87.36±9.55	86.88±9.97	0.834
12 hours	86.78±10.00	88.91±11.72	0.402
16 hours	83.08±8.08	85.81±10.99	0.228
20 hours	84.86±10.14	87.38±11.20	0.314
24 hours	86.32±10.32	85.60±11.42	0.777

Statistical analysis: Independent samples t-test for continuous variables; Chi-square test for categorical variables. Abbreviations: SD: Standard deviation; VAS: Visual Analog Scale; MAP: Mean arterial pressure. $p<0.05$ was considered statistically significant.

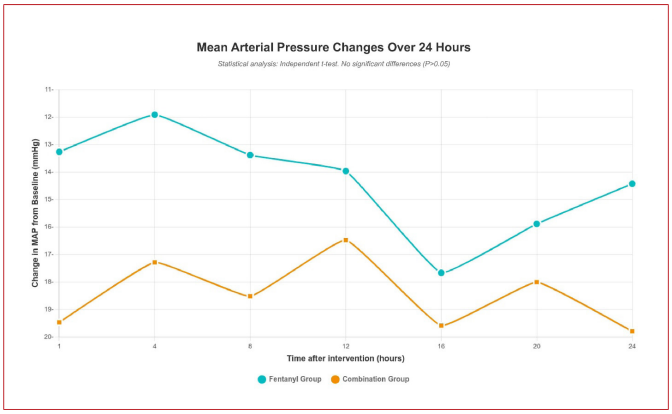

Figure 2. Mean arterial pressure changes: fentanyl vs. combination therapy over 24 hours.

Caption: Comparison of mean arterial pressure (MAP) changes from baseline between the fentanyl (cyan) and combination therapy (orange) groups over the 24-hour post-intervention period. Both groups demonstrated sustained reductions in MAP, with no statistically significant differences observed between groups (p>0.05, independent samples t-test).

Discussion

The results of this study demonstrated that during the early postoperative period (4 and 8 hours), fentanyl produced significantly greater pain reduction compared to the multimodal regimen (combination of morphine, ketamine, and lidocaine) ($p<0.05$). However, this superiority was not sustained at later time points (12, 16, 20, and 24 hours), where no statistically significant differences were observed between the two groups. These findings suggest that although fentanyl provides rapid pain relief, concerns remain regarding the duration of its analgesic effect. Incorporating a multimodal pain relief strategy may reduce overall pain burden. This approach may require less fentanyl during the recovery period while maintaining adequate long-term pain control. This is particularly relevant in the clinical setting when considering postoperative pain management strategies following CABG surgery.

The faster onset of fentanyl can be attributed to its high potency (50-100 times that of morphine), rapid onset of action (1-2 minutes), and efficient penetration of the blood-brain barrier. In contrast, the multimodal regimen, which combines agents with different mechanisms of action (morphine with a slower onset, ketamine as an N-methyl-D-aspartate [NMDA] antagonist, and lidocaine as a local anesthetic), requires more time for synergistic effects to develop, which may become apparent in the later postoperative hours.[7]

Based on the results of the present study, although pain reduction in the early hours after injection was significantly greater in patients receiving the fentanyl pump compared to those receiving the combination of morphine, lidocaine, and ketamine, no statistically significant difference in pain intensity was observed between the groups over time. Additionally, the need for supplemental analgesic injections did not differ significantly between the two groups. This study is the first to compare the effectiveness of fentanyl with the simultaneous combination of morphine, lidocaine, and ketamine for pain relief. Previous studies have reported mixed findings regarding the effectiveness of different analgesics in the early postoperative period. One study reported that lidocaine provided better pain relief than morphine and ketamine at 20 minutes postoperatively; however, after 40 minutes, the differences were no longer statistically

significant. These findings are consistent with the present study, suggesting that although some drugs may provide more pronounced initial pain relief, this advantage may diminish over time.[15] In a study of patients undergoing CABG surgery, the three opioids (morphine, fentanyl, and remifentanil) were compared for postoperative pain control, and no statistically significant difference in VAS pain scores was observed among the groups.[16] Similarly, another study comparing morphine with non-opioids after cardiac surgery found no difference in pain scores between the two groups during the first 48 postoperative hours.[17] However, a separate study evaluating an intravenous remifentanil pain pump versus a morphine pump after coronary artery surgery demonstrated that pain intensity scores at 12 and 24 hours postoperatively were significantly lower in the remifentanil group than in the morphine group.[18] A systematic review comparing different opioid regimens for postoperative pain concluded that although short-term differences in analgesic onset may exist, most opioid regimens provide comparable pain relief over 24 hours, supporting our findings of transient early differences.[19] In our study, although pain intensity was significantly lower during the early postoperative hours (4 and 8 hours after surgery) in patients receiving fentanyl, no significant difference was observed between the two groups at 24 hours postoperatively. Similarly, there was no significant difference between the groups in the need for additional analgesics. A 2019 study comparing different analgesic modalities in cardiac surgery also reported no significant differences in overall pain scores or opioid requirements among various analgesic protocols, which aligns with our long-term findings.[20] However, one comparative study evaluating analgesia after CABG surgery with fentanyl and morphine reported that VAS scores and analgesic consumption were lower in patients treated with morphine.[21] Overall, the finding of the present study that there was no significant difference in the need for additional analgesics between the two groups is consistent with other studies showing that different analgesic combinations do not result in significantly different requirements for supplementary pain management over time.[22,23] The results of this study contribute to the ongoing debate regarding optimal pain management strategies in postoperative CABG care. The initial efficacy of fentanyl compared with the combination of morphine, lidocaine, and ketamine highlights its potential usefulness in acute settings where rapid pain control is essential. However, the diminishing differences over time emphasize that, although immediate pain relief is important, sustained pain management strategies are equally critical to ensure patient comfort and satisfaction. Furthermore, the findings suggest that relying solely on potent opioids such as fentanyl may not be sufficient for comprehensive postoperative pain management. Combining multimodal analgesia using agents such as lidocaine and ketamine alongside opioids such as morphine may be beneficial in reducing overall opioid consumption while effectively managing pain over longer periods.

The results also showed no statistically significant difference in adverse effects between patients receiving fentanyl pump analgesia and those receiving a combination of morphine, lidocaine, and ketamine. Specifically, no significant differences were observed in hemodynamic parameters, including blood pressure or respiratory depression, between the two groups. Despite the sympathomimetic properties of ketamine, no significant difference in MAP was observed between groups ($p>0.05$). This stability may be attributed to the low dose of ketamine (20 mg/100 cc), the slow infusion rate, and the moderating effects of morphine and lidocaine. These findings suggest that ketamine can be administered in a controlled manner without causing hemodynamic instability.[17] This finding is consistent with several previous studies investigating the efficacy and safety profiles of these analgesics in the postoperative setting. One study comparing the clinical efficacy of fentanyl, esmolol, and lidocaine in preventing hemodynamic responses to intubation demonstrated that mean arterial blood pressure after intubation and extubation was lower in the intervention groups than in the control group. Additionally, systolic and diastolic blood pressure at the first, third, and fifth minutes after intubation and extubation were significantly lower in the esmolol group compared to the fentanyl and lidocaine groups, while no hemodynamic differences were observed among the three groups at other time points.[24] Another study comparing the effects of lidocaine and fentanyl on hemodynamic parameters reported that lidocaine was associated with a greater reduction in systolic blood pressure and an increased need for ephedrine.[25] Furthermore, a recent study (2023) comparing different analgesic combinations in cardiac surgery found no significant differences in respiratory depression or hemodynamic instability among various multimodal regimens, further supporting the safety findings of the present study.[26] A study investigating and comparing fentanyl alone with fentanyl plus lido-

caine for reducing hemodynamic responses to tracheal intubation in patients under general anesthesia reported that systolic and diastolic blood pressures before induction, 3 minutes before intubation, and at 1, 3, and 5 minutes after intubation did not differ significantly between the two groups.[27] The absence of a significant difference in blood pressure between the two groups suggests that both treatment strategies involving the use of a fentanyl pump or the combination of morphine, lidocaine, and ketamine are relatively safe with respect to hemodynamic stability. This finding is particularly important given concerns regarding opioid-induced respiratory depression. Although some studies have shown that combining ketamine with opioids can improve pain control while potentially reducing opioid requirements and related adverse effects, the present study did not demonstrate such advantages. The lack of significant differences may be attributed to factors such as drug dosage, individual patient responses, and the specific surgical setting. Consequently, the present findings support the conclusion that both fentanyl and drug combinations including morphine, lidocaine, and ketamine can be effective for postoperative pain management without significant differences in hemodynamic adverse effects. Cardiopulmonary bypass (CPB) time was longer in the multimodal group (127 vs. 118 minutes, p=0.098). Although this near-significant difference may have influenced the inflammatory response, it did not have a clinically significant impact on pain outcomes. Future studies should further evaluate CPB duration as a potential confounding variable.[28] Additionally, future research should focus on dose optimization and patient-specific factors to identify the most effective pain management protocols.[29]

Limitations

Other studies have reported limitations similar to those of the present research. For example, the study population was drawn from a single center, which may affect how the findings are applied. The use of methadone as rescue medication in both groups may have influenced the results and contributed to the reduction of observed differences between the groups at later time points. One of the main threats to the external validity of the findings is the single-center design and relatively small sample size. Furthermore, the 24-hour follow-up period does not capture the long-term efficacy and safety of the analgesic regimens. Although the study was designed to be double-blind, subjective pain assessments remain susceptible to individual bias. The absence of a placebo or non-analgesic control group, along with the potential influence of psychosocial factors, may also have affected the results. Finally, we were unable to systematically assess the full spectrum of postoperative complications due to incomplete documentation in the available medical records.

Conclusion

The results of this study demonstrate that fentanyl provides better pain relief during the early postoperative hours compared to the multimodal regimen (morphine, ketamine, and lidocaine), without increasing adverse effects. However, over the 24-hour postoperative period, no significant differences were observed between the two groups, particularly between 12 and 24 hours after surgery. These findings support the use of fentanyl as an effective option for immediate postoperative pain control following CABG surgery.

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