Major in Hospital Complications and Duration of Hospital Stay in a Comparative Study between a Multimodal Analgesia Regimen Versus IV Morphine Analgesia after Open-Cardiac Surgeries

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ABSTRACT

Background: Pain after surgery decreases the quality of life and has also been reported as being the main source of concern for cardiac surgery patients. It was stated that patients with higher anxiety and depression levels after operation have higher requirements of analgesics for postoperative pain. Reduction of pain and anxiety after cardiac surgery is valuable for the healing process and improvement of the overall experience.

Objective: To determine if the multimodal regimen of dexamethasone, gabapentin, ibuprofen, ketorolac, and paracetamol was with less complications following open-cardiac surgeries compared to IV morphine.

Patients and Methods: Sixty patients were scheduled for sternotomy elective open-heart surgeries. The patients were randomized to one of two groups (ratio 1:1) utilizing sealed envelopes by the study coordinator.30 patients in each group. This prospective, randomized, and a controlled clinical trial was performed at Sohag University Hospital.

Results: Patients in the multimodal group suffered fewer major in-hospital complications than in the morphine group. Acute coronary syndrome had occurred in (one versus zero) patients with a percentage of (3.3%) in the morphine group. Cardiac tamponade had occurred in (two versus one) patients with a percentage of (6.7%) in the morphine group and was with a percentage of (3.3%) in the multimodal group with (p-value) of (0.554). The duration of hospital stays was with M± SD of (7±1.72) days among the multimodal group versus (11±1.6) days in the morphine group, with (a p-value) of (<0.001).

Conclusions: Patients in the multimodal group suffered less major in-hospital complications than in the morphine group after cardiac surgeries.

Keywords: Multimodal analgesia, Open-heart surgeries, Morphine.

INTRODUCTION

Cardiac surgery with extracorporeal circulation is a very strong physical stressor. The specificity of this type of surgical treatment results in a significant load on the mental mechanisms of adjustment. Also, the cardiac surgical procedure is associated with a sense of considerable threat, and exaggeration of the risks and postoperative suffering stimulates anxiety reactions [(1)].

Intraoperative surgery and the start of cardiopulmonary bypass (CPB) cause extensive secretion of stress reaction hormones (epinephrine, norepinephrine, etc.) that continue to the immediate postoperative period and may lead to myocardial ischemia in this period [(2, 3)].

After surgery, myocardial damage might be provoked by cardiac sympathetic nerve reactions which disrupt the stability among the coronary blood stream and myocardial oxygen demand [(4)].

Sympathetic stimulation causes tachycardia, an increase in stroke volume, cardiac work, and myocardial oxygen consumption. In susceptible individuals, this leads to an increased risk of ischemia, or even myocardial infarction. The patient restricts physical activity out of fear of pain, which is followed by venous stasis, subsequent platelet aggregation, possible venous thrombosis, and venous thromboembolism (VTE) [(5)].

Therefore, during the postoperative period, sufficient analgesia may potentially reduce morbidity and improve quality of life. Adequately, managed acute pain lowers the myocardial oxygen demand and decreases the incidence of ischemic episodes[(5)].

There are many different causes of postoperative pain after cardiac surgery such as incisions, trauma, immobility, chest tubes left in after surgery, invasive equipment, and nursing and medical interventions. Pain after surgery decreases the quality of life of patients and affects their comfort level. Pain has also been reported to be one of the main sources of concern for cardiac surgery patients[(6)].

Postoperative treatment of pain following cardiac surgery has historically been focused on opioid analgesics. Opiates, however, have some unpleasant side effects related to the dosage [(7)]. In the last two decades, following non-cardiac surgery, evidence-based multimodal opiate sparing analgesia has become increasingly common. The renewed interest in pain management and recent attempts to quickly monitor patients have also stimulated the interest in using this technique in postoperative pain control during heart surgery [(8)].

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PATIENTS AND METHOD

This prospective, randomized, and controlled clinical study was performed on 60 patients scheduled for elective open-heart surgeries with sternotomy at Sohag University Hospital. They were be randomly allocated into two equal groups, 30 patients each at Sohag Cardiothoracic Department.

Criteria for inclusion: Age > 18 years, any sternotomy-related cardiac operations.
Criteria for exclusion: peripheral neuropathy, neurological disorder, psychological diseases, history of GI bleeding, persistent pain (i.e. back pain, cancer, arthritis), serum creatinine >150 mmol/l, a hepatic disease with elevated liver enzymes (SGPT and SGOT increased to 1.5 times the overall normal value), allergy to opioid or drugs of research misuse.

Preparation of the patients: Pre-anesthetic checkup and pre-anesthetic tests such as full blood count, Bleeding time, prothrombin time, concentration, and activated partial thromboplastin time, liver and kidney function tests, random blood sugar and activated hemoglobin1c, ECG, Echocardiography, Cardiac catheterization, Coronary angiography, and Carotid doppler were carried out in all patients.
Monitoring of the patients: It requires monitoring of five leads electrocardiography (ECG), a 20-gauge radial intraarterial cannula for invasive monitoring of blood pressure, central venous pressure (CVP) via the internal jugular vein, pulse oximetry, non-invasive monitoring of blood pressure, and nasopharyngeal temperature monitoring.

There are two groups in the study:
Group M: multimodal analgesia (dexamethasone, ketorolac, gabapentin, ibuprofen, and paracetamol) was administered to patients.
Group C: morphine IV was administered to patients.
Analgesic protocol (intervention):
Preoperatively: the following were given to patients:

- One hour before surgery, 3 mg of midazolam IV was given to patients of both groups
- Two hours before surgery, 300 mg of gabapentin by mouth was given to patients in (Group M).

Group M (Multimodal): the following were given to patients:

- 300 mg of Gabapentin by mouth, 2hours before surgery.
- 30 mg of ketorolac and 8 mg of dexamethasone IV, along with 1 g of paracetamol IV. in the ICU before patient extubation.
- One hour after extubation of patients, 300 mg of Gabapentin by mouth,1 g of paracetamol IV.
- 300 mg of gabapentin daily every 12 hours orally, 400 mg of ibuprofen orally, and 1 g of paracetamol daily IV every 6 hours, from the first to the fourth postoperative day.

Group C (IV Morphine): the following were given to patients:

- Upon arrival at the ICU, 5 mg of morphine IV bolus was authorized for further administrations of up to a total of 25 mg.
- 2.5mg of IV morphine daily every 6 hours from the first to the third postoperative day,
- 1.25 mg of IV morphine daily every 6 hours on the fourth postoperative day,

In both groups: the following were obtained by patients:

- For pain relief, if (VAS >6), NSAIDs such as Ibuprofen 400mg oral or ketorolac 30mg IV were permitted to be given to patients by the attending nurse, and morphine was given as an injection of 2.5-5 mg IV if NSAIDs was ineffective.
- 4 mg ondansetron IV, and/or 10 mg of metoclopramide IV daily every 8 hours, 40 mg pantoprazole once daily, and 1 g of magnesium oxide once daily rectally to alleviate relief of nausea and constipation,

Data collection

Demographic data including age, sex, weight, NYHA class, medical illness such as DM, HT, Peripheral arterial disease, Severe COPD, and Previous MI, and or IHD in the last 3months. Detection of the cardiac complications as myocardial infarction by ECG evaluation, echocardiography, cardiac enzymes measurement, and coronary angiography. Detection of other complications such as cerebral (stroke, bleeding), GIT bleeding, and sternal complications such as infection and dehiscence. Detection of the duration of hospital stay in days.

Ethical consideration:
The patients participated in this work after approval by the ethical and research committee of Sohag Faculty of Medicine and written informed consent from each patient before participation.
Statistical analysis: Before further statistical analysis, the data were tested for normality using the Kolmogorov-Smirnov test and for homogeneity variances. Number and percent (N, %) described categorical variables, where the mean and standard deviation (Mean, SD) described continuous variables. Chi-square was used to compare categorical variables with t-test was used to compare continuous variables. A two-tailed $p < 0.05$ is statistically significant. All with the IBM SPSS 20.0 program was used to conduct all the analyses. P-value of >0.05 is non-significant.

RESULTS

Age, sex, weight, height, and BMI were compared and presented in **(table 1)** as mean ± standard deviation (M±SD), showed that there was a statistically significant difference in values in age, weight, and BMI and there was no statistically significant difference in sex and height values between the two groups.

Table (1): Demographic data

Demographic data.	Multimodal (n=30)		Morphine(n=30)		P-value
	No.	%	No.	%	
Age in years	39.2±14.31		48.57±14.54		0.015*
Sex					
Male	13	43.3	19	63.3	0.121
Female	17	56.7	11	36.7	
Weight in kg	64.43±16.51		72.77±12.37		0.031*
Height in cm	1.64±0.12		1.65±0.09		0.770
BMI	23.57±3.56		26.81±4.52		0.003**

* Statistically significant difference ($p<0.05$),
**Highly statistically significant difference ($p<0.01$).

Comorbidities

Diagnosis, procedure, NYHA class, medical diseases as diabetes, hypertension COPD, asthma, recent ACS, hypercholesterolemia, liver disease, peripheral arterial diseases, investigations as coronary angiography and carotid Doppler, AF, PHT, and Lt VEF from echocardiography were compared and presented in **(table 2)** as mean ± standard deviation (M±SD) showed statistically significant differences in values in diagnosis, procedure, diabetes, hypertension, coronary angiography, and PHT but other items showed no statistically significant differences**.**

Table (2): Comorbidities

Comorbidities	Multimodal (n=30)		Morphine (n=30)		P-value
	No.	%	No.	%	
NYHA class					
Dyspnea at extraordinary work	3	10.0	1	3.3	
Dyspnea at ordinary work	18	60.0	12	40.0	0.097
Dyspnea at less ordinary work	9	30.0	17	56.7	
Diagnosis					
RHD valve lesion	26	86.7	17	56.7	0.017*
CHD.ASD	2	6.7	2	6.7	
Redo nonfunctioning valve	1	3.3	0	0.0	
Ischemia and vessel lesion	1	3.3	10	33.3	
Procedure					
Valve replacement	25	83.3	13	43.3	0.007**
ASD.VSD repair	2	6.7	2	6.7	
Valve replacement	1	3.3	0	0.0	
CABG	1	3.3	10	33.3	
Valve repair	1	3.3	4	13.3	
DM					
No	28	93.3	19	63.3	0.005**
Yes	2	6.7	11	36.7	
HT					
No	24	80.0	11	36.7	0.001**
Yes	6	20.0	19	63.3	
Hypercholesterolemia					
No	30	100.0	30	100.0	

Comorbidities	Multimodal (n=30)		Morphine (n=30)		P-value
	No.	%	No.	%	
Severe COPD					
No	29	96.7	30	100.0	0.313
Yes	1	3.3	0	0.0	
Asthma					
No	29	96.7	29	96.7	1.000
Yes	1	3.3	1	3.3	
Liver disease					
No	29	96.7	30	100.0	0.313
Yes	1	3.3	0	0.0	
Peripheral arterial disease					
No	30	100.0	30	100.0	-
Recent ACS					
No	30	100.0	30	100.0	-
AF					
No	21	70.0	18	60.0	0.417
Yes	9	30.0	12	40.0	
Coronary angiography					
Free	30	100.0	3	10.0	<0.001**
Ischemia.2.3.4 vessels	0	0.0	27	90.0	
Carotid Doppler					
No	30	100.0	30	100.0	-
PHT					
Mean ±SD	57.1±27.46		43.17±17.32		0.022*
LT V EF					
Mean ±SD	61.5±7.83		59.97±5.7		0.389

Data are expressed as **mean ± standard deviation.**
(P-value) was calculated by **independent-samples t-test and Chi-square**.
A statistically significant difference ($p<0.05$)
**Highly statistically significant difference ($p<0.01$)

Detection of the cardiac complications by ECG and echocardiography

Acute coronary syndrome had occurred in one patient with a percentage (3.3%) of cases in the morphine group after (30 days) postoperative and was treated with nitrates, oxygen, and morphine. Arrhythmia had occurred in one patient in both groups with a percentage (3.3%) of cases after (three weeks) postoperative. Cardiac tamponade had occurred in (2 patients) with a percentage (6.7%) of cases in the morphine group after ten days postoperative and had occurred in (one patient) with a percentage (3.3%) of cases in the multimodal group after one week postoperative that was managed by pericardiocentesis with a (p-value) of (0.554).

Cardiac complications were presented in (table 3).

Table (3): Cardiac complications

Cardiac complication	Multimodal (n=30)		Morphine (n=30)		P-value
	No.	%	No.	%	
Cardiogenic shock, heart failure					
No	30	100	30	100	-
Acute coronary syndrome					
No	30	100	29	96.7	0.313
Yes	0	0	1	3.3	
Arrhythmia, treatment by drugs					
No	29	96.7	29	96.7	1.000
Yes	1	3.3	1	3.3	
Cardiac tamponade, pericardiocentesis					
No	29	96.7	28	93.3	0.554
Yes	1	3.3	2	6.7	

(P-value) calculated by **Chi-square**

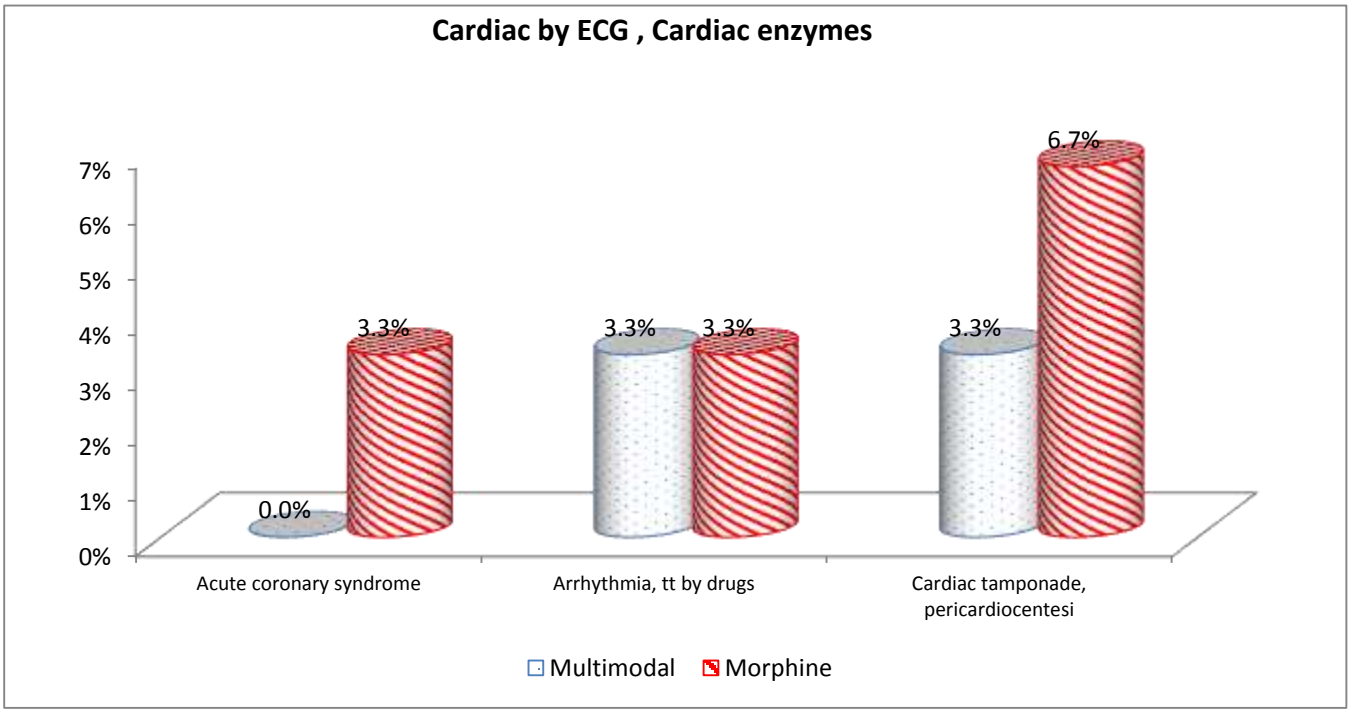

Figure (1): **Cardiac complications**

Cerebral, GIT, Sternal, and thromboembolic complication

The sternal infection had occurred in one patient in the multimodal group with a percentage (3.3%) of cases after three weeks postoperative that was treated by debridement and repeated dressing. Other complications had not occurred in both groups.

Cerebral, GIT, Sternal, and thromboembolic complications were presented in (table 4)

Showed no statistically significant differences in values between both groups except in the sternal complications but the p-value was not reached significant values with a (p-value) of (0.313).

Table (4): Cerebral, GIT, Sternal and Thromboembolic complication

Complication	Multimodal		Morphine		P-value
	No.	%	No.	%	
Cerebral, TIA, or stroke					
No	30	100.0	30	100.0	-
Thromboembolic					
No	30	100.0	30	100.0	-
GIT bleeding					
No	30	100.0	30	100.0	-
Sternal infection or dehiscence					
No	29	96.7	30	100.0	0.313
Yes	1	3.3	0	0.0	

(P-value) calculated by **Chi-square**

Duration of hospital stay in days was presented in (table 5).

Showed statistically significant differences in values between both groups (lower in the multimodal group) in the duration of hospital stay in days, was with (M±SD) of (7±1.72) in the multimodal and was with (Mean ±SD) of (11±1.6) in the morphine group with a (p-value) of (<0.001).

Table (5): Duration of hospital stay in days

	Multimodal (n=30)		Morphine (n=30)		P-value
	No.	%	No.	%	
Hospital stays in days					
Mean ±SD	7±1.72		11±1.6		<0.001**

DISCUSSION

In our study, the mean age of the patients was (39.2±14.31) and (48.57±14.54) in **(group M)** and **(group C)** respectively with a significant difference. The sex distribution of the study population showed that there were (13) males and (17) females in the multimodal group compared to (19) males and (11) females in the morphine group. Although there was some difference in the sex distribution between both groups this was not significant. Regarding the BMI, it showed a mean BMI of (23.57±3.56) among the multimodal group compared to (26.81±4.52) in the morphine group with a statistically significant difference. In contrast to our study, the study was done by **Rafiq *et al.*** [9] who compared a multimodal regimen consisting of dexamethasone, gabapentin, ibuprofen, ketorolac, and paracetamol against a traditional opiate-based regimen (morphine and paracetamol) on (180) patients after open cardiac surgeries, They found that there were no significant differences between both groups as regards age (62-64 ± 12), sex, and BMI but with much older age population compared to our study.

Regarding, detection of cardiac complications by ECG, cardiac enzymes, and echocardiography**,** we found that there were no statistically significant differences in values between both groups. Acute coronary syndrome had occurred in one patient with a percentage of (3.3%) in the morphine group. Arrhythmia had occurred in one patient in both groups with a percentage of (3.3%). Cardiac tamponade had occurred in two patients with a percentage of (6.7%) in the morphine group and had occurred in one patient with a percentage of (3.3%) in the multimodal group with (p-value) of (0.554).

This in agreement with the study done by **Markham *et al.*** [10] showed that the ERAS group had fewer cardiac complications than the control group such as arrhythmia and pericarditis.

Another similar study by **Qazi *et al.*** [11] showed that short-term use of NSAIDs (ibuprofen) might be safe as regards cardiac complications. They also, showed that there was no significant difference between the groups in the rates of postoperative myocardial infarction with a (P-value of >0.05).

In contrast, the study was done by **Rafiq *et al.*** [9] showed that there was no significant difference between the two study groups as regards the cardiac complications, Arrhythmia (AF) had occurred in both groups with a percentage of (45.5%) in the morphine group versus a percentage of (40.25%) in the multimodal group. Pericardial effusion had occurred in both groups with a percentage of (4.05%) in the

morphine group versus a percentage of (1.3%) in the multimodal group. Ketorolac and ibuprofen are the NSAIDs utilized in multimodal regimens, these are both non-selective NSAIDs, and their results do not support the occurrence of more cardiovascular events in this group [(9)]. Although their result showed that the multimodal group had less cardiac complications than the morphine group, this huge percentage might be due to the big sample size (182 patients).

Regarding cerebral, GIT, sternal, and thromboembolic complications in our study, we found no statistically significant differences in values between both groups except in the sternal complications but the p-value was not reached significant values with (a p-value of 0.313).

This is coinciding with the study of **Rafiq *et al.*** [(9)] who found that there was no statistically significant difference in values between the two groups. But patients in the morphine group suffered more thromboembolic complications in crude numbers with a percentage of (4.05%) than in the multimodal group.

A recently published retrospective database study raised the concern of NSAIDs as a whole being associated with increased deaths and recurrent MIs in a population with previous MI (not a surgical population). Interestingly the authors found that ibuprofen usage below (7 days), was not associated with increased death and MI [(12)].

Patrono *et al.* [(13)] speculated that the lower incidence of thromboembolic complications in the multimodal group in the study of **Rafiq *et al.*** [(14)], was due to the antithrombotic effect of the NSAIDs

The antithrombotic effect of the NSAIDs may even be more important after cardiac surgery, as cardiac surgery has been shown to induce hypercoagulability and that hypercoagulability is associated with an increased incidence of thromboembolic complications and death after cardiac surgery. This is speculative and future studies must elucidate this point [(14)].

Also, the study of **Qazi *et al.*** [(11)] found that short-term use of NSAIDs (ibuprofen) might be safe as regards GIT and sternal complications. Also, they found that there was no significant difference between the groups in the rates of the GIT bleeding and the sternal complication with a (P-value of >0.05)**.**

Moreover, the study of **Javaherforooshzadeh *et al.*** [(15)] showed that there was no significant difference between the two groups in terms of the hospital mortality rate such as MI, CVA, and TIA with a (P-value of > 0.05).

In contrast, the study of **Nussmeier *et al.*** [(16)] that involved (10 days) of treatment and (30 days) of follow-up, the study was done on (1671 patients) after CABG surgery. The patients received intravenous parecoxib for at least (3 days), followed by oral valdecoxib through (day 10); intravenous placebo followed by oral valdecoxib; or placebo for (10 days), postoperative analgesia was by intrathecal or epidural opioids. They showed a significantly higher incidence of combined thromboembolic events among patients receiving parecoxib and valdecoxib than among patients receiving placebo. This might be due to preexisting generalized atherosclerotic disease, exposure to the additional risks of cardiopulmonary bypass, or both. Certainly, platelet activation resulting from shear stresses might occur in patients with atherosclerotic vessels and increase sternal infection with a (p-value of 0.04). Because the COX 2 enzyme mediates prostaglandin synthesis, inhibiting this enzyme might impede reparative inflammatory responses.

Imantalab *et al.* [(17)] suggested that preventing some adverse effects with effective pain management results in patient satisfaction. As adverse effects are generally unpleasant for patients, it can be assumed that the absence of them reinforces positive experiences

The optimal medication for pain management after cardiac surgery should be considered individually with each case to produce the best possible experience for the patient [(18)].

Added to that analgesic therapy and especially the need for opioids should be frequently evaluated. Paracetamol, reportedly causing none of the side effects of opioids or NSAIDs could especially be researched and developed more as postoperative analgesia [(19)].

As regards the duration of hospital stay, our study showed highly statistically significant differences in values between both groups (lower in the multimodal group), with a mean of (7±1.72) days among the multimodal group versus (11±1.6) days in the morphine group, with (a p-value) of (<0.001) as regards the duration of hospital stay.

Many studies showed differences in hospital stays between multimodal analgesic groups and opioid groups with variable statistical significances in the form of lower hospital stay period in the multimodal groups however, neither of them reached our results in this concern which might be explained by the number of drugs, doses and time of administration in our study. The study of **Rafiq *et al.*** [(9)] showed that the duration of hospital stay was insignificantly lower in the multimodal group versus the morphine group with a mean (7.4 days±3.3) days among the multimodal group versus (8.2±4.6) days in the morphine group with (a p-value) of (<0.257).

Altun *et al.* [(20)] found that the length of hospital stay was longer in the placebo group versus the (tramadol + paracetamol) combination due to the high dose of opioids, the total morphine consumption, and the additional morphine requirements in the placebo group.

Also, the study of **Markham *et al.* (10)** showed that the length of hospital stay was shorter in the ERAS versus the placebo group but the p-value not reached significance (0.23).

Moreover, the study of **Özmen *et al.* (21)** showed that there were no statistically significant differences between the groups in terms of the length of hospital stay with a (p-value of >0.05).

And similar to the study of **Immer *et al.* (22)** found that a shorter hospitalization was in the NSAIDs groups with a mean of (7.3 ±1.6 days) versus in the tramadol group with a mean of (8.6 ±1.7 days) and with a (p-value) of (0.57).

CONCLUSION

A multimodal treatment consisting of dexamethasone, gabapentin, ibuprofen, and paracetamol safe in patients undergoing open-heart surgery than a regimen consisting of IV morphine. Also, patients in the multimodal group suffered less major in-hospital complications. The duration of hospital stays was lower in the multimodal group than in the morphine group. Based on the data, the authors concluded that by using non-opioid pain control approaches, generally improved patient experiences were obtained.

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