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Different modalities of analgesia in open heart surgeries in Mansoura University: Randomized prospective comparative study

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Abstract---Background: Opioid usage in cardiac surgery is considered to be the corner stone in management. Inadequate pain control after cardiac surgery complicates patient recovery and increases the load on healthcare services. Multimodal analgesia can be used to achieve better analgesic effect and improves patient outcome. Material and methods: A total of 90 patients undergoing cardiac surgery with median sternotomy were randomly allocated equally into three groups intraoperatively where first group received continuous infusion of high dose opioids, second group received boluses of low dose opioids and third group received multimodal non opioid analgesics including dexmedetomidine, ketamine and magnesium sulphate. All patients received the same post-operative analgesic regimen consists of morphine patient controlled analgesia (PCA). Results: Patients in multimodal non opioid group had more stable hemodynamics intra and postoperatively. Also, patients in multimodal group had lower pain scores extubation, earlier extubation, shorter ICU stay, earlier mobilization and earlier return of bowel movements compared to patients of both groups received intraoperative higher opioid doses.

Conclusion: Combination of Dexmedetomidine, ketamine and magnesium for intraoperative analgesia offered an effective analgesic profile, more stable hemodynamics, faster extubation time, shorter ICU stay, earlier mobilization and earlier return of bowel movements with more sedated patients in the immediate postoperative period in patients undergoing open heart surgery.

Keywords---Opioid sparing, cardiac surgery, postoperative pain, multimodal analgesia, dexmedetomidine, ketamine, magnesium sulphate, analgesia.

Introduction

Pain after cardiac surgery is one of the major problems and remains one of the most controversial issues (1). Inadequate pain control after cardiac surgery increases the incidence of development of many complications. The most dangerous is respiratory system dysfunction (2). The sympathetic response to pain rises myocardial oxygen consumption leading to arrhythmia and myocardial injury (3). Multimodal opioid sparing analgesic techniques has become frequently used for achievement of a more efficient pain management (4). These techniques include many drugs including dexmedetomidine, low-dose ketamine and magnesium sulphate (5).

Material and Methods

This prospective randomized comparative study was conducted on 90 patients - based on sample size calculation which result in 24 patients with expected drop out so the result was 30 patients in each group - undergoing cardiac procedures that required cardiopulmonary bypass and median sternotomy at Cardiothoracic & Vascular Surgical Center, Mansoura University Hospitals over 24 months starting from January 2020 to January 2022. Written informed and verbal consents were obtained from all patients prior to enrolment in this study. A pilot study was done to optimize the drugs' doses.

Inclusion criteria were; Adult patients of either gender, aged above 18 years with American Society of Anesthesiologists (ASA) physical status II & III, body mass index less than 40 kg/m² scheduled for any cardiac procedure with median sternotomy that required cardiopulmonary bypass. Exclusion criteria were; patients with pulmonary dysfunction or chronic obstructive pulmonary diseases, acute or unstable angina, previous cardio-thoracic surgery, emergency surgery, left ventricular ejection fraction less than 40%, dysrhythmia or pacemaker, uncontrolled diabetes (HbA1c > 7), hyper-magnesemia, patients with major hepatic or renal dysfunction were excluded from the study. Also, need for re-exploration due to any reason or development of neurological deficit were excluded from the completion of the study.

Eligible 90 patients were randomly allocated to one of three equal groups each contains 30 patients, they were randomized according to computer-generated randomization sequence: Either high opioid based group (group H), Low opioid

based group (group L) and Multi modal non-opioid group (group N). The day before surgery, the patients were visited by an anesthesiologist and both informed and verbal consents were obtained from them after explanation of the type of surgery, anesthetic method. Also, visual analogue scale (VAS) criteria and the chart were discussed in details with the patients to become familiar with VAS assessment after the surgery and how to express the severity of pain using the chart.

Before induction of anesthesia, All patients received ringer acetate infusion at a rate of 2-4 ml/kg containing tranexamic acid 10 mg/kg, 2 mg midazolam to alleviate anxiety during arterial cannulation, the patients received antibiotic and proton pump inhibitor before start of surgery. Before induction of anesthesia, basic monitoring equipment were attached to the patient (five leads electrocardiogram (ECG) with ST segment analysis, pulse oximetry and non-invasive blood pressure. Peripheral intravenous cannula 18 G was inserted. After doing modified Allen's test, a radial artery cannula (20 G) was inserted under local anesthesia starting in non-dominant hand for invasive blood pressure monitoring and arterial blood gases (ABG) sampling throughout the surgery.

Anesthetic induction protocol was the same in the three groups. All patients were be pre-oxygenated with 100% oxygen for 3 minutes. Induction was achieved by administration of Midazolam 3 mg, Fentanyl 2-3 µg/kg, Propofol at a sleeping dose titrated ranging from 50-100 mg according to its effect on invasive blood pressure and atracurium at a dose of 0.5 mg/kg to facilitate endotracheal intubation, then the patients were mechanically ventilated with volume control mode at a tidal volume 4-6 ml/kg and respiratory rate around 14 aiming to maintain End-tidal CO₂ around 35 mmHg and PEEP 5 cmH₂O and FiO₂ 40%.

Internal jugular vein was cannulated using ultrasound (Vivid T8 GE® convex probe) by central venous catheter 7 Fr for infusion of vasoactive drugs. Cannulation of the external jugular vein was done using 16 G cannula for fluid and blood transfusion. Fluid administration will be maintained by Ringer's acetate. Blood transfusion cutoff when hemoglobin reaches less than 8 gm/dl or Hct less than 25%.

Transesophageal Echocardiography probe was (Vivid T8 GE® TEE probe) inserted and basal complete examination was done (assessing the valves function and area, chamber sizes, ejection fraction (EF %), fractional shortening (FS %), pulmonary artery pressure and regional wall motion abnormalities (RWMA). Maintenance of anesthesia was achieved by isoflurane with concentration 0.5-1.5 % with FiO₂ 40%. During cardiopulmonary bypass anesthesia was maintained by continuous infusion of Propofol at a rate of 2 mg/kg/hr. and Attracurium at a rate of 10 µg/kg/min.

The patients were randomly allocated to one of three equal groups (Figure 1) using closed sealed envelope method by one of the anesthetists not included in the study, Each group contains 30 patients where they received the following protocol intraoperative until tracheal extubation:

Group H (High Opioid Group): The patients received fentanyl infusion at a rate of 1 µg/kg/h and fentanyl bolus 20-40 µg according to patient hemodynamics with tachycardia or hypertension (Tachycardia: increase of heart rate >20% of baseline or hypertension: increase of mean blood pressure >20% of baseline), *Group L (Low Opioid Group):* The patients received fentanyl bolus 20-40 µg and propofol 20 mg at the time of surgical stimulation and according to patient hemodynamics (repeated as required) and *Group N (Multi Modal Non-Opioid Group):* The patients received infusions of dexmedetomidine 0.2 µg/kg/h, ketamine 120 µg/kg/hr, and magnesium sulfate 5 mg/kg/h. after induction till tracheal extubation.

Vasopressor, inotropes, atropine and dilators were given when required guided by patients' hemodynamics and TEE findings according to our algorithm. During cardiopulmonary bypass, Anesthesia was maintained by continuous infusion of Propofol at a rate of 2-4 mg/kg/hr. and Attracurium at a rate of 10 µg/kg/min. The patients were cooled by heat exchanger of the CPB machine to keep the patients' temperature between 32-34°C degree. The perfusion pressure was maintained between 50-80 mmHg by non-pulsatile flow rate ranging from 2.5 - 5 L/min/m². Hypotension during the cardiopulmonary bypass was treated by increasing the flow rate and if not corrected an incremental doses of vasopressor was given with correction of anemia or ABG abnormalities.

Weaning from Cardiopulmonary bypass was achieved after completion of grafts/valve repair or replacement, Resumption of mechanical ventilation was done, gradual filling of the heart and gradual weaning from cardiopulmonary bypass was achieved when the patient reached stable hemodynamics. The choice of adequate vasopressor/inotrope was done aided by TEE examination using Trans gastric (TG) basal short axis view at 0° to assess volume status, contractility and regional wall motion abnormalities (RWMA).

Post-Cardiopulmonary bypass; Complete TEE examination was done (assessing the valves function and area, chamber sizes, ejection fraction (EF), fractional shortening (FS), pulmonary artery pressure and regional wall motion abnormalities (RWMA). the patient is completely weaned from the CPB provided that the patient had stable hemodynamics. Heparin was antagonized by protamine sulphate at a dose of 1-1.3 mg for each 100 units of heparin. ABG analysis was done to correct any electrolyte or acid base disturbance. Blood and fresh frozen plasma were also given when needed according to our center protocol.

When adequate hemostasis was reached, the drainage tubes were inserted, the sternum was wired followed by closure of muscle, subcutaneous tissue and skin. After the surgery, intubated patients were transferred to the cardiothoracic surgical intensive care unit where they were fully monitored. Patients were extubated after a gradual weaning from mechanical ventilation when the patient had meets criteria of extubation including: hemodynamic stability with no signs of low cardiac output syndrome or ischemia and without significant inotropic support, normal temperature, absence of active bleeding with normal ACT, acceptable muscular power assessed by limb movements and spontaneous ventilation sufficient to maintain arterial oxygen saturation over 95% with 50% FiO₂ and end-tidal carbon dioxide under 50 mmHg and a fully awake patient

(with GCS 15) capable of following simple commands as opening eyes (6).

The patient postoperative monitoring continued in highly specialized ICU with hemodynamics monitoring including ECG with continuous ST segment analysis, pulse oximetry, invasive blood pressure monitoring, frequent ABG and ACT, chest x ray and close monitoring for chest tubes drainage for the whole ICU stay till discharge.

Postoperative pain management protocol included the same technique for the three group; after 30 minutes of tracheal extubation, all the patients in the 3 groups received standard analgesia (i.v. paracetamol 1 gm every 8 hours and i.v. ketorolac 30 mg every 12 hours) and morphine patient controlled analgesia (Disposable PCA) using Accufuser plus® (Figure 12) bolus dose = 0.5 ml, lockout interval = 15 minutes, with 5 ml/hr background continues infusion. Vasopressor, inotropes, atropine and dilators were given and continued when required guided by patients' hemodynamics according to our algorithm, Ondansetron 4 mg i.v. was given to patients in all three groups if nausea and vomiting are present up to three times in 24 hours.

Study measurements

Demographic data includes age, gender, body mass index, presence of medical disease as: HTN or DM. Duration of surgery and type of surgery was also recorded. The patients' hemodynamics including heart rate and invasive mean arterial pressure and oxygen saturation (SaO₂) was recorded at baseline before anesthesia induction, immediate after intubation, at skin incision, at sternotomy and every 15 minutes in the first hour then every 30 minutes in the pre-bypass period then after 15 mins in the first hour then every 30 mins after weaning from CPB till the end of surgery and then every six hours in the surgical ICU for 24 hours.

Occurrence of intraoperative cardiac complications were also recorded in each group as hypertension, hypotension, tachycardia, bradycardia, arrhythmia, heart block and need of pacemaker. Pre bypass and post bypass TEE findings (EF & FS) were recorded. Intraoperative use of vasopressor, inotropes, atropine and dilators was recorded and vasoactive inotropic (VIS) score (7) was calculated and recorded as follows:

Vasoactive Inotropic score (VIS) = Dopamine dose (µg/kg/min)
 + Dobutamine dose (µg/kg/min)
 + 100 × Epinephrine dose (µg/kg/min)
 + 10 × Milrinone dose (µg/kg/min)
 + 10 000 × Vasopressin dose (unit/kg/min)
 + 100 × Norepinephrine dose (µg/kg/min)

Time to tracheal extubation was recorded, total opioid consumption, length of ICU stay, onset of mobilization and post-operative nausea and vomiting. The pain at rest will be assessed at 30 minutes after tracheal extubation (primary outcome) and at 6, 12, and 24 h after tracheal extubation (secondary outcomes) using a 100-mm visual analogue scale. Sedation level will be assessed at the same time with pain scoring using the modified Ramsay sedation score.

Statistical analysis

Sample size was calculated by using G* power 3.0.10 statistical software program 2019 version. Power analysis was based on a pilot study using high opioid group; the mean $\pm$ SD of VAS at rest 30 minutes after extubation was 50 ± 20 mm. Assuming $\alpha = 0.05$ and $\beta = 0.1$ (90% power) and using the Analysis of variance (ANOVA) for 3 groups, **24 patients** were required in each group to detect a 10-mm reduction in the mean VAS at rest 30 minutes after extubation, which was considered the minimal clinically significant effect. To allow for dropouts, **30 patients** were assigned to each group.

The statistical analysis will be performed using IBM SPSS software (version 25)(2019). Continuous “quantitative” variables tested for normality using the Shapiro-Wilk test. Normally distributed data will be presented as mean $\pm$ SD and compared using the analysis of variance (ANOVA) test. Non-normally distributed data will be presented as median (range) and compared using the Kruskal-Wallis test. Categorical variables will be presented as number (percentage) and compared using the Chi-square or Fisher’s exact test as appropriate. The results will be presented as mean $\pm$ SD, median (range) or number and % of patients as appropriate. We will use the Bonferroni correction for multiple testing and P value < 0.0167 will be considered statistically significant. Significant if the p value is ≤ 0.05 . Highly significant if the p value < 0.001 .

Results

Basic demographic data of the studied groups regarding age , sex, body mass index (BMI) (kg/m^2) and presence of medical disease (HTN & DM) were presented in (Table 1) with no significant statistical difference between all groups. There was no significant statistical difference between all groups regarding surgical data including duration and type of surgery as presented in (Table 1).

The heart rate showed no significant statistical difference between all groups at baseline and tracheal intubation readings. However heart rate were statistically significant lower in Group N compared to Group H and in Group H compared to Group L at skin incision, sternotomy, 15 mins, 30 mins and 1 hour pre bypass period. There was no significant statistical difference between all groups at 15 mins, 30 mins and 1 hour post bypass period. Heart rate were significantly lower in Group N compared to Group L 30 mins post-operative with no significant statistical difference between all groups at 6, 12 and 24 hours post-operative (Table 2).

The mean arterial blood pressure showed no significant statistical difference between all groups except at 1 hour pre bypass period where mean arterial blood pressure were lower in Group N (79.83 ± 11.84) compared to Group L (86.83 ± 11.65) (Table 3). Visual analogue score (VAS) was significant statistically lower in Group N (2 “0-8”) (5 “0-6”) compared to Group H (4 “0-10”) (6 “4-7”) and Group L (5 “2-9”) (6 “4-8”) at 30 minutes and 60 minutes respectively after tracheal extubation. Also, VAS was significantly lower in Group H (4 “0-10”) (6 “4-7”) compared to Group L 2 (5 “2-9”) (6 “4-8”) at 30 minutes and 60 minutes respectively after tracheal extubation (Table 4).

Sedation score were significant statistically higher in Group N (1.93 ± 0.25) compared to Group H (1.53 ± 0.51) and Group L (1.10 ± 0.31) at 30 mins after tracheal extubation. Also, sedation score was significant statistically higher in Group H (1.53 ± 0.51) compared to Group L (1.10 ± 0.31) at 30 mins after tracheal extubation (Table 5). Ejection fraction and fractional shortening showed no significant statistical difference between all groups as regard pre-operative TTE, pre bypass TEE and post bypass TEE respectively (Table 6).

Intraoperative recorded data showed that atropine requirement was significant statistically higher in Group N (8 “26.7%”) compared to both Group H (2 “6.7%”) and 2 (1 “3.3%”) respectively, opioid used were significant statistical higher in Group H compared to Group L and 3. Group N consumed the least opioid among all three groups where Group N (3 ± 0.26), Group H (13.28 ± 0.98) and Group L (7.30 ± 0.71) mcg/kg. Vasoactive inotropic score showed no significant statistical difference between all three groups (Table 7).

As regard intraoperative complications Group N showed significant statistical incidence of bradycardia in Group N (7 “23.3%”) compared to Group H (1 “3.3%”) and 2 (1 “3.3%”). Also, incidence of tachycardia was higher in Group H (15 “50%”) and 2 (15 “50%”) compared to Group N (0 “0%”). There was no significant statistical difference in the incidence of hypertension or hypotension between studied groups (Table 7).

Postoperative data showed significant statistical difference in extubation times where extubation time (hours) was earlier in Group N compared (3.03 ± 0.96) compared to Group H (4.53 ± 0.86) and Group L (4.43 ± 0.86), shorter ICU stay (days) in Group N (1.70 ± 0.56) compared to Group H (2.53 ± 0.57) and Group L (2.53 ± 0.63), earlier return of bowel movements (hours) in Group N (10.87 ± 2.15) compared to Group H (11.73 ± 1.01) and Group L (11.87 ± 0.73) and earlier mobilization (hours) in Group N (9.67 ± 2.68) compared to Group H (11.17 ± 2.12) and Group L (11.17 ± 2.13) (Table 8).

Discussion

Postoperative pain is usually significant after cardiac surgeries which in turn complicates and delays postoperative recovery. The unique characteristic of cardiac surgical pain is that it includes several sites of pain, early hemodynamic instability, and longer duration of postoperative recovery (8).

The impending complications associated with acute postoperative pain are predominantly challenging for all patients especially patients whom undergone cardiac surgery who are already hemodynamically fragile remarkably in the first hours after surgery (3). Poorly controlled postoperative pain leads to insufficient respiratory effort leading to atelectasis and hypoxia, retention of sputum, increased risk of acute bronchitis and pneumonia which are linked with increased need for prolonged postoperative ventilatory support and consequently prolonged intensive care unit (ICU), and hospital stay (9).

With the emergence of “Fast Track” concept, the use multimodal pain management had greatly increased. Multimodal analgesia entails using multiple agents and techniques that each target a different pain pathway. Multimodal analgesia protocols hope to design a synergy to improve pain control and decrease opioid requirement. By using lower doses of each individual agent and decrease the occurrence of side effects (10).

In the present study we used three techniques including traditional high opioid dose, low opioid dose and multimodal non-opioid technique including Dexmedetomidine, Ketamine and Magnesium sulphate to compare between them on the patient outcome during and after cardiac surgery including pain control and patient's hemodynamics.

The study included 90 Adult patients of either gender, aged above 18 years with American Society of Anesthesiologists (ASA) physical status II & III, body mass index less than 40 kg/m² scheduled for any cardiac procedure with median sternotomy that required cardiopulmonary bypass over a period of 24 months. Patients were divided into three groups: Group H (high opioid), Group L (low opioid) and Group N (multimodal non opioid group).

The study evaluated hemodynamics of the patients intra and post operatively. As regard the heart rate group N showed highly significant ($P \leq 0.001$) lower heart rate readings comparing group N to group H and group L and lower heart rate readings comparing group H to group L after intubation till establishment of cardiopulmonary bypass with no significance in the post bypass period and heart rate were significantly lower in group N compared to group L 30 mins post-operative.

As Regard mean arterial blood pressure readings it was lower clinically in group N compared to both groups, but it showed no significant statistical difference between all groups except at 1 hour pre bypass period where mean arterial blood pressure were significantly lower ($P \leq 0.05$) in group N compared to group L with no significant statistical difference between all groups in post bypass and postoperative period.

The lower heart rate in Group H may be due to higher opioid doses compared to Group L. The decrease in heart rate and blood pressure in Group N may be explained by dexmedetomidine mechanism of action which inhibit norepinephrine release by activating alpha 2- adrenoceptor in the CNS in the locus ceruleus and spinal cord so it decreases and prevent pain signal transmission inducing sedation, analgesia and sympatholytic effect (11). Although Ketamine causes sympathetic stimulation and causes increase in heart rate and blood pressure (12). Ketamine had no evident effect on heart rate and blood pressure in our study as its effect was modulated by dexmedetomidine. Use of magnesium sulphate potentiate the effect on hemodynamics through the inhibitory effects of magnesium on the release of catecholamine (13).

Dexmedetomidine prompts sympatholysis which decreases heart rate and mean arterial blood pressure through activation of presynaptic α_2 -adrenoceptors in the central nervous system. At higher concentrations, activation of α_2 -adrenoceptors

in vascular smooth muscle, leads to an increase in blood pressure and reduction of heart rate (14).

Absent Ketamine stimulatory effect on cardiovascular system may be explained by sympatholytic effect of dexmedetomidine which prevent ketamine from its cardio pressor effect (which act mainly by central sympathetic stimulation and inhibition of catecholamine uptake in neuronal nerve endings leading to increase heart rate and blood pressure with preservation of cardiac output) (15). This direct myocardial depressant effects of ketamine may be due to inhibition of calcium transients which are unmasked by sympathetic blockade due to dexmedetomidine administration (16).

Heart rate and blood pressure readings revealed no significant difference between both groups in post-bypass period and this may be explained by usage of inotropic drugs, vasopressors and atropine during and after weaning from heart-lung machine to target heart rate ranging from 80-100 beats/min and MAP above 60 mmHg.

Regarding Visual analogue score (VAS), the study revealed significant lower VAS score at 30 minutes, 6 hours after extubation in group N ($P < 0.001$) compared to group H and group L and showed lower VAS in group H ($P < 0.001$) compared to group L with no significant difference in pain score after 12 and 24 hours.

In the first hours after the operation, the trend of pain severity was lower in group N than other groups. The pain severity reached its peak 6 hours after extubation in all groups with lower VAS in patients in whom received dexmedetomidine, ketamine and magnesium until the 6th hour after surgery. The pain severity declined in all groups after 12 and 24 hours respectively as they received the same post-operative analgesic regimen.

The study outcome is parallel with Habibi et al., who concluded that dexmedetomidine can be used as a safe and effective analgesic for decreasing the postoperative pain and analgesic requirements after cardiothoracic surgeries (17). Recent reviews found that application of multimodal analgesic regimens may show particular significance in preventing postoperative pain and provide optimal pain control with possibly less side effects when compared with a conventional opioid-based strategy (18)(19).

A study by Carollo et al., found that when Dexmedetomidine is used as an adjunct to general anesthesia, it significantly reduces post-operative pain scores and decreases opioids and inhalational anesthetic requirements with maintaining patients' hemodynamics, providing rapid and smooth recovery and early post-operative extubation (20). Another study by Hamouda et al., demonstrated that early infusion of dexmedetomidine following CABG operations was associated with a reduction of opioid uses and lower pain scores compared to opioids alone (21). Ji et al., found that using intravenous Dexmedetomidine infusion initiated after cardiopulmonary bypass and then continued for less than 24 hours postoperatively in the ICU in patients undergoing CABG improves morbidity, mortality and has good outcome on patient recovery (22).

Aiwei et al., concluded that dexmedetomidine use in cardiac surgery offers effective sedative and analgesic outcome with decreasing variability in heart rate and blood pressure and decrease incidence of tachycardia to painful stimulation. Also, it decreases prevalence of hypertension, tachycardia and analgesic requirement with no respiratory depression and early post-operative extubation (23). Another study by Peltoniemi et al., suggests use of small perioperative dose of ketamine 1-2 mg/kg/hr. reduces postoperative pain and decrease opioid requirement and post-operative nausea and vomiting (24). Also, Jouguelet-Lacoste et al., found that low-dose ketamine decreases perioperative opioid requirement by about 40% with no evident side effects or hallucinations. Also (25) found that low intravenous doses of ketamine decrease opioid requirement and reduces post-operative pain scores. These results are consistent with our findings (26).

Magnesium sulfate is another an important adjuvant drug in the conduct of anesthesia, with several beneficial clinical effects including analgesia and a low incidence of adverse events when used at recommended doses (27). In a recent randomized controlled study done by Silva et al., who used Magnesium sulfate in total intravenous anaesthesia concluded that Magnesium sulfate is a safe and effective choice for intraoperative analgesia, when opioid sparing technique is preferred (28).

In a recent review by Jannati et al., he showed two studies comparing magnesium to a placebo in CABG surgery, he stated that the patients who received magnesium had lower pain scores and less opioid consumption in the first 2 days after surgery (29). One of the most recent studies by Krakowski et al., suggests both prevention and treatment of postoperative pain after cardiac surgery should optimally include multimodal analgesics beside using regional anesthesia and multidisciplinary approach to reach the optimum control (30).

In this present study dexmedetomidine was used without loading dose to decrease its adverse effects on cardiovascular system. Studies had found that skipping or decreasing loading dose of dexmedetomidine to half, eliminates its side effect as hypotension and bradycardia without losing its desired sedative and analgesic effects (31). Dexmedetomidine infusion, even those without the loading dose, is an effective adjuvant which offers an effective analgesic effect. It can reduce opioid consumption without unfavorable hemodynamic effects in cardiac surgery patients (21).

All the patients in the three groups received the same postoperative analgesic regimen with standard simple analgesics including paracetamol and NSAIDs and Morphine PCA. The pain scores after 6 hours became similar and these results are similar to results by Motamed et al., who found that morphine PCA remains an excellent technique resulting in a high level of patient satisfaction as a component of multimodal analgesic regimen for acute postoperative pain control (32).

The use of patient-controlled analgesia pumps has shown to decrease total opioid consumption with increased patient satisfaction more efficiently than conventional parenteral analgesics. Essentially, in the post-operative ICU setting

where these pumps are most commonly used without increased incidence of adverse events (33). Unfortunately, Regional anesthesia -which offers a superior analgesic effect- use is limited in cardiac surgery due to fear of complications with full heparinization. This thought is confirmed by a recent review done by Jaing et al., who reviewed different types of regional anesthesia can be done in cardiac surgery and concluded that Regional techniques do not offer significant analgesia as part of the multimodal pain management protocol beside its concerns and possible adverse effects (34). Sedation level of the patients assessed by Modified Ramsay sedation score showed that patients in group N had higher level of sedation at 30 and 60 minutes ($P \leq 0.001$) after extubation compared to both groups.

The sedative effect produced by Dexmedetomidine mimic natural sleeping. Though Dexmedetomidine highly sedative, the patients didn't lose their awareness, so they can answer still questions related to pain and sedation scoring relaxed and comfortable state (29). These findings are similar to our results where the patients in group N were sedated compared to group H and group L but they responded well to pain scoring questions and were calm in the first hours following surgery till weaning from mechanical ventilation.

The sedation offered by dexmedetomidine didn't affect extubation time and maintain patient hemodynamics after surgery as the patient remains calm with stable hemodynamics during and following extubation. Postoperative data showed significant statistical difference where patients in multimodal non opioid group had earlier extubation time, shorter ICU stay and faster onset of mobilization and the three groups had the same incidence of postoperative nausea and vomiting.

Dexmedetomidine does not cause respiratory system depression. It preserves respiratory drive intact, so that at clinically effective doses, sedation with continuous IV dexmedetomidine infusion does not delay weaning from mechanical and extubation (35). And these findings are similar to our study. Mogahd et al., compared Ketamine-Dexmedetomidine versus Ketamine-Propofol in Patients after CABG surgery, they found that Ket-Dex combination in cardiac surgery offered shorter duration of post-operative mechanical ventilation with less total fentanyl dose requirement compared to the other group similar to our findings (Mogahd et al. , 2017).

Duration of ICU stay, return of bowel movements were significant statistical lower in group N ($P \leq 0.001$) ($P \leq 0.05$) compared to group H and L respectively. These findings correlates with a study by Williams et al., who found that the usage of intraoperative Dexmedetomidine in cardiac surgery decrease the length ICU and hospital stay and incidence of ileus and reintubation (37). A retrospective analysis on patients undergoing CABG concluded that a multimodal analgesia protocol shows that it reduces opioid use, intubation time, and decreased ICU and hospital length of stay compared to standard analgesic protocols (38).

Ickeringill et al., found that an infusion of Dexmedetomidine at as dose of 0.4 $\mu\text{g.kg}^{-1}$ per hour during the operation decrease the duration of post-operative mechanical ventilation and decrease opioid need and associated with shorter ICU stay (39). Atropine requirement was significantly higher ($P \leq 0.05$) in group N

compared to group H and L with the tendency toward bradycardia which results from use of Dexmedetomidine. The incidence of tachycardia was higher ($P \leq 0.001$) in group H and L compared to group N as Dex-Ket-Mg combination offers a more stable hemodynamics.

These findings are similar to a study done by Gong et al., who concluded that use of Dexmedetomidine in adult and pediatric cardiac surgery was found to decrease heart rate, blood pressure, occurrence of tachycardia and arrhythmias in both adult and pediatric patients with increased risk of bradycardia (40). Vasoactive inotropic score showed no significance between the studied groups with no significant difference in cardiac function by comparing ejection fraction and fractional shortening of the patients between basal TTE and intraoperative TEE measurements with no related evidence of new onset myocardial ischemia in the studied groups despite the theoretical concerns against α -2 adrenoceptor agonists as Dexmedetomidine may lead to vasoconstrictive effect and hypotensive action which may cause ischemic effect (41). These findings are in contrast to a study who found that intraoperative dexmedetomidine administration during general anesthesia leads to a sustained increase of blood pressure and a worsening of ventricular function in patients with diastolic dysfunction (42).

Conclusion

Combination of Dexmedetomidine, ketamine and magnesium for intraoperative analgesia offered an effective analgesic effect, prevent intraoperative and immediate postoperative hemodynamic swings which are very vital for patients undergoing cardiac surgery, faster extubation time, shorter ICU stay, earlier mobilization and earlier return of bowel movements with more sedated patients in the immediate postoperative period.

Declarations

Conflicts of interest

The authors declare no competing interests.

Ethical approval

Ethical approval was obtained from Institutional Research Board with code number (MD.19.11.255).

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon request.

Registration of research studies

ClinicalTrials.gov number: NCT04223219.

Disclosure of interest

The authors report no financial or non-financial conflicts of interest in this work.

Consent for publication

Written informed consent was taken from all patients before enrollment in this study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

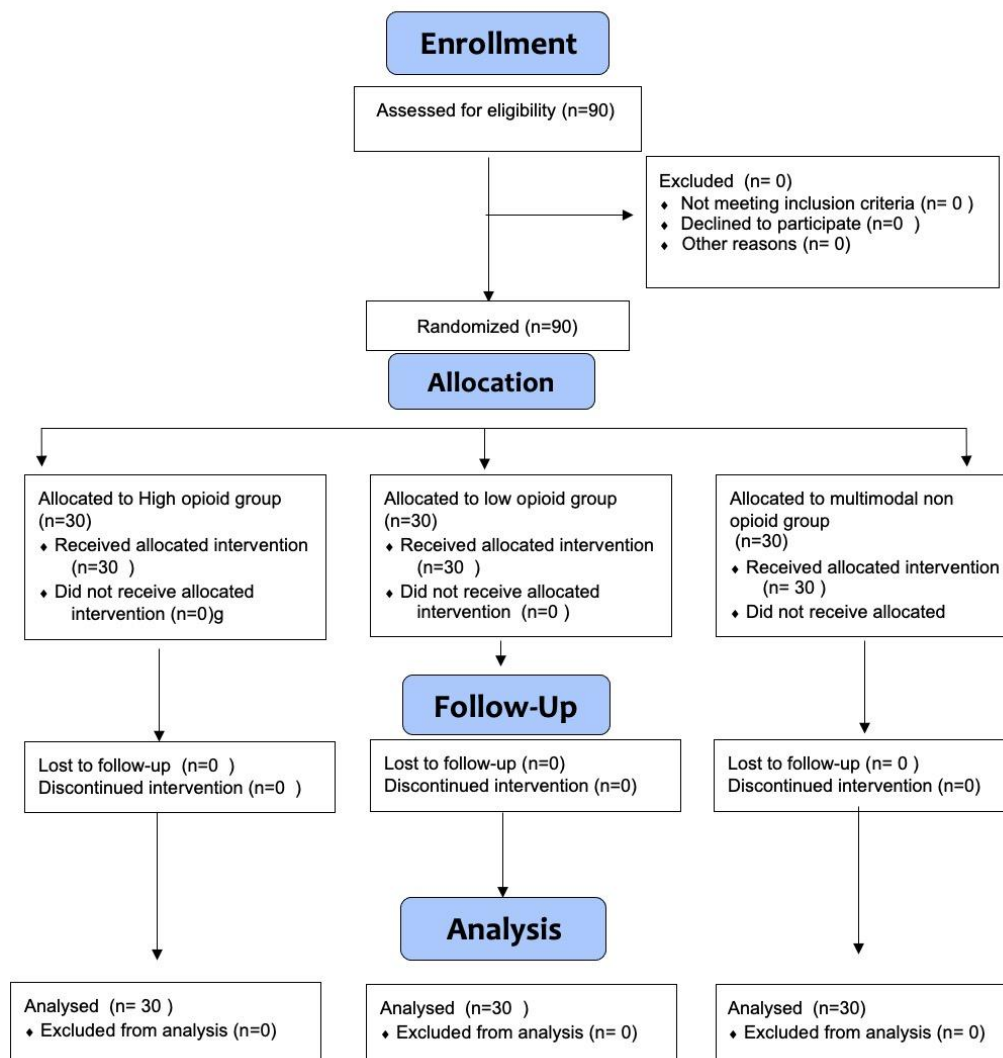
1. Imantalab V, Mirmansouri A, Mohammadzadeh Jouryabi A, Naderi Nabi B, Kanani G, Nassiri Sheikhan N, et al. Comparing the Effectiveness of Patient Control Analgesia Pump and Bolus Morphine in Controlling Pain After Cardiopulmonary Bypass Graft Surgery. *Anesthesiol pain Med*. 2017 Oct;7(5):e12756. 10.5812/aapm.12756
2. Zubrzycki M, Liebold A, Skrabal C, Reinelt H, Ziegler M, Perdas E, et al. Assessment and pathophysiology of pain in cardiac surgery. *J Pain Res*. 2018 Aug;Volume 11:1599–611. 10.2147/JPR.S162067
3. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res*. 2017 Sep;Volume 10:2287–98. 10.2147/JPR.S144066
4. Chandrakantan A, Glass PSA. Multimodal therapies for postoperative nausea and vomiting, and pain. *Br J Anaesth*. 2011 Dec;107:i27–40. 10.1093/bja/aer358
5. Sultana A, Torres D, Schumann R. Special indications for Opioid Free Anaesthesia and Analgesia, patient and procedure related: Including obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, opioid addiction and cancer surgery. *Best Pract Res Clin Anaesthesiol*. 2017 Dec;31(4):547–60. 10.1016/j.bpa.2017.11.002
6. Borracci RA, Ochoa G, Ingino CA, Lebus JM, Grimaldi S V., Gambetta MX. Routine operation theatre extubation after cardiac surgery in the elderly. *Interact Cardiovasc Thorac Surg*. 2016 May 1;22(5):627–32. 10.1093/icvts/ivv409
7. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass*. *Pediatr Crit Care Med*. 2010 Mar;11(2):234–8. 10.1097/PCC.0b013e3181b806fc
8. Barr LF, Boss MJ, Mazzeffi MA, Taylor BS, Salenger R. Postoperative Multimodal Analgesia in Cardiac Surgery. *Crit Care Clin*. 2020 Oct;36(4):631–51. 10.1016/j.ccc.2020.06.003
9. Amodeo G, Bugada D, Franchi S, Moschetti G, Grimaldi S, Panerai A, et al. Immune function after major surgical interventions: the effect of postoperative pain treatment. *J Pain Res*. 2018 Jul;Volume 11:1297–305. 10.2147/JPR.S158230
10. Mauermann E, Ruppen W, Bandschapp O. Different protocols used today to achieve total opioid-free general anesthesia without locoregional blocks. *Best Pract Res Clin Anaesthesiol*. 2017 Dec;31(4):533–45. 10.1016/j.bpa.2017.11.003
11. Gertler, Brown, Mitchell and S. Dexmedetomidine: A novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)*. 2001;14(1):13.
12. Aroni F, Iacovidou N, Dontas I, Pourzitaki C, Xanthos T. Pharmacological

- aspects and potential new clinical applications of ketamine: Reevaluation of an old drug. *J Clin Pharmacol*. 2009;49(8):957–64.
13. Herroeder S, Schönherr ME, De Hert SG, Hollmann MW. Magnesium-essentials for anesthesiologists [Internet]. Vol. 114, *Anesthesiology*. 2011. p. 971–93. 10.1097/ALN.0b013e318210483d
 14. Castillo RL, Ibacache M, Cortínez I, Carrasco-Pozo C, Fariás JG, Carrasco RA, et al. Dexmedetomidine Improves Cardiovascular and Ventilatory Outcomes in Critically Ill Patients: Basic and Clinical Approaches. *Front Pharmacol*. 2020 Feb 28;10. 10.3389/fphar.2019.01641
 15. Noppers I, Olofsen E, Niesters M, Aarts L, Mooren R, Dahan A et al. Effect of rifampicin on S-ketamine and S-norketamine plasma concentrations in healthy volunteers after intravenous S-ketamine administration. *Anesthesiology*. 2011;114(48):1435–45.
 16. Domino EF. Taming the Ketamine Tiger. *Anesthesiology*. 2010;113:678–86.
 17. Habibi V, Kiabi FH, Sharifi H. The Effect of Dexmedetomidine on the Acute Pain After Cardiothoracic Surgeries: A Systematic Review. *Brazilian J Cardiovasc Surg*. 2018;33(4):404–17. 10.21470/1678-9741-2017-0253
 18. Bignami E, Castella A, Pota V, Saglietti F, Scognamiglio A, Trumello C, et al. Perioperative pain management in cardiac surgery: a systematic review. *Minerva Anesthesiol*. 2018 Apr;84(4). 10.23736/S0375-9393.17.12142-5
 19. Del Rio JM, (Jake) Abernathy J, Taylor MA, Habib RH, Fernandez FG, Bollen BA, et al. The Adult Cardiac Anesthesiology Section of STS Adult Cardiac Surgery Database: 2020 Update on Quality and Outcomes. *J Cardiothorac Vasc Anesth*. 2021 Jan;35(1):22–34. 10.1053/j.jvca.2020.08.005
 20. Carollo DS, Nossaman BD RU. Dexmedetomidine: A review of clinical applications. *Curr Opin Anaesthesiol* 2008;21457–61. 2008;21:457–61.
 21. Hamouda T, Ismail M, Ibrahim TH, Ewila H, Elmahrouk A. Role of dexmedetomidine infusion after coronary artery bypass grafting. *Cardiothorac Surg*. 2020 Dec 22;28(1):4. 10.1186/s43057-019-0014-8
 22. Ji F, Li Z, Young N, Moore P LH. Perioperative dexmedetomidine improves mortality in patients undergoing coronary artery bypass surgery. *J Cardiothorac Vasc Anesth*. 2014;28:267–73.
 23. Aiwei Li, Vivian Man Ying Yuen SGD& PCLK. Pharmacokinetics and pharmacodynamics of dexmedetomidine. *Drug Dev Ind Pharm*. 2016;1–11.
 24. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clin Pharmacokinet*. 2016;55(9):1059–77.
 25. Grathwohl KW. Does Ketamine Improve Postoperative Analgesia? More Questions Than Answers. *Pain Med*. 2011 Aug 1;12(8):1135–6. 10.1111/j.1526-4637.2011.01199.x
 26. Jouguelet-Lacoste J, La Colla L, Schilling D CJ. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med*. 2015;16(99):383–403.
 27. Cavalcanti IL, De Lima FLT, Da Silva MJS, Da Cruz Filho RA, Braga ELC, Verçosa N. Use profile of magnesium sulfate in anesthesia in Brazil. *Front Pharmacol*. 2019;10(APR):1–8.
 28. Silva Filho SE, Sandes CS, Vieira JE, Cavalcanti IL. Analgesic effect of magnesium sulfate during total intravenous anesthesia: randomized clinical study. *Brazilian J Anesthesiol*. 2021 Sep;71(5):550–7. 10.1016/j.bjane.2021.02.008

29. Jannati M, Attar A. Analgesia and sedation post-coronary artery bypass graft surgery: A review of the literature. *Ther Clin Risk Manag.* 2019;15:773–81.
30. Krakowski JC, Hallman MJ, Smeltz AM. Persistent Pain After Cardiac Surgery: Prevention and Management. *Semin Cardiothorac Vasc Anesth.* 2021 Dec 20;25(4):289–300. 10.1177/10892532211041320
31. Grewal A. Dexmedetomidine: New avenues. *J Anaesthesiol Clin Pharmacol.* 2011;27(3):297–302.
32. Motamed C. Clinical Update on Patient-Controlled Analgesia for Acute Postoperative Pain. *Pharmacy.* 2022 Jan 27;10(1):22. 10.3390/pharmacy10010022
33. Papa L, Maguire L, Bender M, Boyd M, Patel S, Samcam I. Patient controlled analgesia for the management of acute pain in the emergency department: A systematic review. *Am J Emerg Med.* 2022 Jan;51:228–38. 10.1016/j.ajem.2021.10.042
34. Jiang T, Ting A, Leclerc M, Calkins K, Huang J. Regional Anesthesia in Cardiac Surgery: A Review of the Literature. *Cureus.* 2021 Oct 15; 10.7759/cureus.18808
35. Liu H, Ji F, Peng K, Applegate RL, Fleming N. Sedation After Cardiac Surgery. *Anesth Analg.* 2017 Apr;124(4):1061–70. 10.1213/ANE.0000000000001588
36. Mogahd M, Mahran M, Shafik M, Foad Elbaradi G. Safety and Efficacy of Ketamine-dexmedetomidine versus Ketamine-propofol Combinations for Sedation in Patients after Coronary Artery Bypass Graft Surgery. *Ann Card Anaesth.* 2017;20(2):182–7.
37. Williams JB, McConnell G, Allender JE, Woltz P, Kane K, Smith PK, et al. One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. *J Thorac Cardiovasc Surg.* 2019 May;157(5):1881–8. 10.1016/j.jtcvs.2018.10.164
38. Markham T, Wegner R, Hernandez N, Lee JW, Choi W, Eltzschig HK, et al. Assessment of a multimodal analgesia protocol to allow the implementation of enhanced recovery after cardiac surgery: Retrospective analysis of patient outcomes. *J Clin Anesth.* 2019 May;54:76–80. 10.1016/j.jclinane.2018.10.035
39. M Ickeringill, Y Shehabi, H Adamson UR. Dexmedetomidine infusion without loading dose in surgical patients requiring mechanical ventilation: haemodynamic effects and efficacy. *Anaesth Intensive Care.* 2004;32(6):741–5.
40. Gong Z, Ma L, Zhong YL, Li J, Lv J, Xie YB. Myocardial protective effects of dexmedetomidine in patients undergoing cardiac surgery: A meta-analysis and systematic review. *Exp Ther Med.* 2017 May;13(5):2355–61. 10.3892/etm.2017.4227
41. Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. *Anesthesiology.* 2000 Nov;93(5):1345–9.
42. Lee SH, Na S, Kim N, Ban MG, Shin SE, Oh YJ. The Effects of Dexmedetomidine on Myocardial Function Assessed by Tissue Doppler Echocardiography During General Anesthesia in Patients With Diastolic Dysfunction. *Medicine (Baltimore).* 2016 Feb;95(6):e2805. 10.1097/MD.0000000000002805

Figures

Figure 1: Consort flow diagram of the studied groups



Tables

Table (1)

Basic demographic, clinical data and surgical data of the cases in the study groups. Data are expressed as mean $\pm$ SD and number %

Variable	Group H (n=30)	Group L (n=30)	Group N (n=30)	P- value	P1	P2	P3
Age (years)	50.87 $\pm$ 9.52	50.57 $\pm$ 7.08	50.93 $\pm$ 8.87	0.948	0.990	0.999	0.985
Sex							
Male	16 (53.3%)	16 (53.3%)	15 (50%)	0.965			
Female	14 (46.7%)	14 (46.7%)	15 (50%)				
BMI (kg/m ²)	29.10 $\pm$ 3.40	29.76 $\pm$ 3.88	29.98 $\pm$ 2.82	0.582	0.734	0.578	0.966
Medical disease							
DM	17 (56.7 %)	12 (40%)	13 (43.3%)	0.392			
HTN	23 (76.7%)	20 (66.7%)	16 (53.3%)	0.162			
Surgery	7.73 $\pm$ 0.72	7.72 $\pm$ 0.98	7.33 $\pm$ 0.71	0.889	0.990	0.999	0.985
Duration							
Surgery							
type							
CABG	15 (50%)	14 (46.7%)	13 (43.3%)	0.655			
Valve	15 (50%)	16 (53.3%)	17 (56.7%)				
replacement							

*P value $\leq$ 0.05 is significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

CABG: Coronary artery bypass graft surgery

Table (2)
Heart rate (beat/min.) of the cases in the study groups at different times. Data are expressed as mean $\pm$ SD

	Heart rate (beat/min)	Group H (n=30)	Group L (n=30)	Group N (n=30)	P- value	P1	P2	P3
Intraoperative	Basal	83.27 $\pm$ 8.92	83.77 $\pm$ 9.64	83.40 $\pm$ 9.55	0.977	0.977	0.998	0.987
	At intubation	82.47 $\pm$ 8.43	82.87 $\pm$ 10.53	82.50 $\pm$ 9.64	0.984	0.986	0.999	0.988
	At Skin incision	80.30 $\pm$ 9.65	81.23 $\pm$ 11.99	68.43 $\pm$ 8.76**	0.001	0.933	<0.001	<0.001
	At Sternotomy	80.10 $\pm$ 11.18	83.77 $\pm$ 12.44	66.73 $\pm$ 9.37**	0.001	0.408	<0.001	<0.001
	15 mins	78.87 $\pm$ 11.25	82.93 $\pm$ 14.64	66.80 $\pm$ 8.03 **	0.001	0.369	<0.001	<0.001
	30 mins	79.03 $\pm$ 10.90	85.30 $\pm$ 14.68	67.77 $\pm$ 8.85**	0.001	0.102	0.001	<0.001
	1 hour	80.60 $\pm$ 11.89	82.63 $\pm$ 12.78	66.07 $\pm$14.35**	0.001	0.818	<0.001	<0.001
	15 mins	96.90 $\pm$ 9.82	95.37 $\pm$ 11	94.60 $\pm$ 11	0.695	0.842	0.680	0.958
	30 mins	97.10 $\pm$ 7.84	96.67 $\pm$ 9.96	96.57 $\pm$ 10.74	0.974	0.983	0.975	0.999
	1 hour	96.40 $\pm$ 7.08	96.27 $\pm$ 9.91	96.37 $\pm$ 9.60	0.998	0.998	0.999	0.999
Post-operative	30 mins	93.83 $\pm$ 6.98	95.10 $\pm$ 10.77	88.67 $\pm$ 9.33*	0.019	0.854	0.080	0.021
	6 hours	87.20 $\pm$ 7.87	87.37 $\pm$ 7.92	84.33 $\pm$ 10.51	0.333	0.997	0.425	0.384
	12 hours	84.23 $\pm$ 8.63	84.90 $\pm$ 9.17	80.87 $\pm$ 8.75	0.173	0.954	0.309	0.188
	24 hours	80.33 $\pm$ 9.81	81.13 $\pm$ 6.95	79.33 $\pm$ 7.58	0.697	0.924	0.885	0.673

*P value $\leq$ 0.05 is significant

**P value $\leq$ 0.001 is highly significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

Mins : minutes

Table (3)
Mean arterial blood pressure (MAP) (mmHg) of the cases in the study groups at different times. Data are expressed in mean $\pm$ SD

MAP (mmHg)		Group H (n=30)	Group L (n=30)	Group N (n=30)	P- value	P1	P2	P3	
Intraoperative	Basal	92.17 ± 11.67	92.87 ± 13.08	92.47 ± 12.51	0.976	0.675	0.995	0.991	
	At intubation	87.33 ± 8.65	88.50 ± 10.34	87.47 ± 12.83	0.900	0.907	0.999	0.926	
	At Skin incision	88.93 ± 11.68	87.57 ± 11.94	82.93 ± 8.93	0.089	0.879	0.091	0.234	
	At Sternotomy	86.53 ± 9.42	88.63 ± 15.05	81.87 ± 9.57	0.076	0.765	0.272	0.068	
	Pre bypass	15 min	84.70 ± 9.48	86.13 ± 11.68	82.67 ± 11.28	0.465	0.866	0.749	0.435
		30 min	82.97 ± 9.52	86.43 ± 11.77	82.80 ± 10.57	0.334	0.422	0.998	0.388
		1 hour	81.97 ± 10.12	86.83 ± 11.65	79.83 ± 11.84*	0.052	0.217	0.742	0.047
	Post bypass	15 min	73.80 ± 8.80	72.17 ± 7.07	69.27 ± 7.14	0.076	0.692	0.065	0.317
		30 min	79.53 ± 6.54	76.73 ± 6.27	75.80 ± 7.54	0.093	0.254	0.091	0.856
		1 hour	83.70 ± 7.54	83.07 ± 8.51	81.80 ± 6.18	0.606	0.942	0.588	0.789
Post-operative	30 min	85.23 ± 7.93	85.57 ± 8.24	85.20 ± 4.86	0.976	0.982	0.990	0.979	
	6 hours	86.20 ± 7.16	86.73 ± 7.17	86.43 ± 6.98	0.958	0.954	0.991	0.985	
	12 hours	89 ± 6.95	89.57 ± 7.54	89.37 ± 7.74	0.956	0.953	0.980	0.994	
	24 hours	93.03 ± 8.91	93 ± 8.46	93 ± 8.99	0.999	0.999	0.999	0.999	

*P value $\leq$ 0.05 is significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

Min : minutes

Table (4)

Visual analogue score (VAS) of the cases in the study groups at different times after tracheal extubation. Data are expressed as median (range)

VAS Score	Group H (n=30)	Group2 (n=30)	Group N (n=30)	P-value	P1	P2	P3
30 minutes	4 (0-10)	5 (2-9)	2 (0-8)**	0.001	0.249	0.030*	<0.001
6 hours	6 (4-7)	6 (4-8)	5 (0-6)**	<0.001	0.551	0.001	<0.001
12 hours	4 (2-5)	4 (2-6)	3 (2-6)	0.063	0.263	0.790	0.072
24 hours	2 (0-4)	2 (0-3)	2 (0-4)	0.862	0.937	0.993	0.937

*P value ≤ 0.05 is significant

**P value ≤ 0.001 is highly significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

Table (5)
Sedation score of the cases in the study groups after tracheal extubation at different times. Data are expressed as mean $\pm$ SD.

<i>Sedation Score</i>	<i>Group H (n=30)</i>	<i>Group L (n=30)</i>	<i>Group3 (n=30)</i>	<i>P-value</i>	<i>P1</i>	<i>P2</i>	<i>P3</i>
<i>30 min</i>	<i>1.53 $\pm$ 0.51**</i>	<i>1.10 $\pm$ 0.31</i>	<i>1.93 $\pm$ 0.25**</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>
<i>6 hours</i>	<i>1</i>	<i>1</i>	<i>1</i>	<i>1</i>			
<i>12 hours</i>	<i>1</i>	<i>1</i>	<i>1</i>	<i>1</i>			
<i>24 hours</i>	<i>1</i>	<i>1</i>	<i>1</i>	<i>1</i>			

**P value ≤ 0.001 is highly significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

Min:minutes

Table (6)
Ejection fraction (EF) and Fractional shorting (FS) % of the cases in the study groups at different times. Data are expressed as mean $\pm$ SD

<i>Variables</i>		<i>Group H</i> (n=30)	<i>Group L</i> (n=30)	<i>Group3</i> (n=30)	<i>P-value</i>	<i>P1</i>	<i>P2</i>	<i>P3</i>
<i>Basal</i>	<i>EF</i>	62.07 $\pm$ 8.17	62.53 $\pm$ 5.96	62.73 $\pm$ 5.41	0.923	0.460	0.920	0.992
<i>Pre bypass</i>	<i>EF</i>	61.20 $\pm$ 7.54	61.40 $\pm$ 6.04	61.60 $\pm$ 4.77	0.969	0.991	0.966	0.991
<i>Post bypass</i>	<i>EF</i>	60.03 $\pm$ 6.46	60.77 $\pm$ 6.08	60.83 $\pm$ 4.56	0.837	0.875	0.853	0.999
<i>Basal</i>	<i>FS</i>	35.30 $\pm$ 5.25	34.60 $\pm$ 4.17	35 $\pm$ 4.05	0.835	0.821	0.964	0.937
<i>Pre bypass</i>	<i>FS</i>	34.80 $\pm$ 4.87	34.03 $\pm$ 3.76	34.33 $\pm$ 3.45	0.764	0.747	0.897	0.956
<i>Post bypass</i>	<i>FS</i>	34.87 $\pm$ 4.68	33.57 $\pm$ 3.57	33.47 $\pm$ 2.96	0.287	0.386	0.332	0.994

*P value $\leq$ 0.05 is significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

TTE: Transthoracic echo

TEE: Transesophageal echo

EF: Ejection fraction

FS: Fractional shorting

Table (7)
Intraoperative data in the study groups. Data are expressed as number %, mean $\pm$ SD and median (range)

Variables	Group H (n=30)	Group L (n=30)	Group N (n=30)	P- value	P1	P2	P3
Atropine requirement (n)	2 (6.7%)	1 (3.3%)	8 (26.7%)*	0.012			
Opioid use (mcg/kg)	13.28 $\pm$ 0.98	7.30 $\pm$ 0.71**	3 $\pm$ 0.26**	< 0.001	<0.001	<0.001	<0.001
VIS	5 (0-15)	5 (0-10)	5 (0-15)	0.900	0.997	0.959	0.987
Intraoperative complications							
Bradycardia (n)	1 (3.3%)	1 (3.3%)	7 (23.3%)*	0.012			
Tachycardia (n)	15 (50%)	15 (50%)	0 (0%)**	< 0.001			
Hypertension (n)	0 (0%)	3 (10%)	2 (6.7%)	0.227			
Hypotension (n)	1 (3.3%)	0 (0%)	2 (6.7%)	0.355			

*P value $\leq$ 0.05 is significant

**P value $\leq$ 0.001 is highly significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

VIS: vasoactive inotropic score

(n): number of cases

Table (8)
Postoperative data in the study groups. Data are expressed as mean $\pm$ SD and number %

Variables	Group H (n=30)	Group L (n=30)	Group N (n=30)	P value	P1	P2	P3
Extubation (hours)	4.53 $\pm$ 0.86	4.33 $\pm$ 0.86	3.03 $\pm$ 0.96**	<0.001	0.902	<0.001	0.001
ICU stay (Days)	2.53 $\pm$ 0.57	2.53 $\pm$ 0.63	1.70 $\pm$ 0.56 **	0.986	<0.001	<0.001	0.001
Bowel movement (hours)	11.73 $\pm$ 1.01	11.87 $\pm$ 0.73	10.87 $\pm$ 2.15*	0.017	0.931	0.055	0.022
Mobilization (hours)	11.17 $\pm$ 2.12	11.17 $\pm$ 2.13	9.67 $\pm$ 2.68*	0.019	0.998	0.038	0.038
PONV	11 (36.7%)	8 (26.7%)	5 (16.7%)	0.216			

*P value $\leq$ 0.05 is significant

**P value $\leq$ 0.001 is highly significant

P1: Significance between Group H and Group L

P2: Significance between Group H and Group N

P3: Significance between Group L and Group N

Group H: High opioid group

Group L: Low opioid group

Group N: Multimodal non opioid group

PONV: postoperative nausea and vomiting