

The Effects of Conventional and Balanced Anesthesia Protocols on Intraoperative Hemodynamic Parameters and Postoperative Recovery in Cardiac Surgery: Observational Study

Kardiyak Cerrahide Konvansiyonel ve Dengeli Anestezi Yönetimlerinin İntraoperatif Hemodinamik Parametreler ve Postoperatif Derlenme Üzerine Etkileri: Gözlemsel Çalışma

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ABSTRACT Objective: Fast-track and balanced anesthesia protocols have been developed in years, in cardiac surgery. Conventional high-dose fentanyl and midazolam techniques lost their popularity because of several known side effects. The primary aim of this study is; to compare traditional and balanced anesthesia protocols in terms of postoperative pain and sedation scales and early extubation criterias. The secondary aim is to observe the effects of these two different anesthesia protocols on intraoperative hemodynamics. **Material and Methods:** Conventional anesthesia group patients were administered 10 µg kg⁻¹ fentanyl, 0.15 mg kg⁻¹ midazolam as anesthesia induction; 3 µg kg⁻¹ fentanyl and 0.01-0.05 mg kg⁻¹ midazolam as anesthesia maintenance. Balanced anesthesia group patients were administered propofol 2 mg kg⁻¹, ketamine 1 mg kg⁻¹ as anesthesia induction; continuous infusion of remifentanyl and sevoflurane as anesthesia maintenance. Patients were evaluated in terms of intraoperative hemodynamic parameters. In addition; pain, sedation, and extubation criteria were evaluated at postoperative 2nd hour. **Results:** Forty-nine adult patients who underwent coronary surgery were analyzed. Intraoperative hemodynamics were similar in both groups. However, the rates of total nitroglycerine and ephedrine doses were found to be significantly higher in the group conventional (p<0.001, p=0.013). In addition, postoperative sedation scores and the rate of patients who didnot meet extubation criteria were higher in the conventional group (p<0.001). **Conclusion:** Our balanced anesthesia management protocol seems to provide intraoperative hemodynamic stability, in addition, better postoperative recovery in coronary surgery patients.

ÖZET Amaç: Kalp cerrahisinde yıllar içinde hızlı ve dengeli anestezi protokolleri geliştirilmiştir. Konvansiyonel yüksek doz fentanil ve midazolam teknikleri, bilinen birçok yan etkileri nedeniyle popülerliğini yitirmiştir. Bu çalışmanın birincil amacı, geleneksel ve dengeli anestezi protokollerini intraoperatif hemodinami ve postoperatif klinik sonuçlar açısından karşılaştırılmasıdır. İkincil amacı ise bu iki farklı anestezi protokolünün intraoperatif hemodinamikler üzerine etkisinin gözlenmesidir. **Gereç ve Yöntemler:** Konvansiyonel anestezi grubundaki hastalara anestezi induksiyonu olarak 10 µg kg⁻¹ fentanil, 0,15 mg kg⁻¹ midazolam; anestezi idamesi olarak 3 µg kg⁻¹ fentanil ve 0,01-0,05 mg kg⁻¹ midazolam uygulandı. Dengeli anestezi grubundaki hastalara anestezi induksiyonu olarak propofol 2 mg kg⁻¹, ketamin 1 mg kg⁻¹; anestezi idamesi olarak remifentanil infüzyonu ve sevofluran uygulandı. Hastalar intraoperatif hemodinamik parametreler açısından değerlendirildi. Ek olarak, ağrı, sedasyon ve ekstübasyon kriterleri postoperatif 2. saatte değerlendirildi. **Bulgular:** Koroner cerrahi uygulanan 49 erişkin hasta analiz edildi. İntraoperatif hemodinami her iki grupta da benzerdi. Ancak kullanılan toplam nitrogliserin ve efedrin doz oranları konvansiyonel grupta anlamlı olarak yüksek bulundu (p<0,001, p=0,013). Ayrıca postoperatif sedasyon skorları ve ekstübasyon kriterlerini karşılamayan hasta oranı konvansiyonel grupta daha yüksekti (p<0,001). **Sonuç:** Dengeli anestezi yönetim protokolümüzün, koroner cerrahi hastalarında daha iyi intraoperatif hemodinamik stabilitenin, bunun yanında daha iyi postoperatif iyileşme sağladığı sonucuna vardık.

Keywords: Cardiac anesthesia; fentanyl; midazolam; propofol; remifentanyl

Anahtar Kelimeler: Kardiyak anestezi; fentanil; midazolam; propofol; remifentanil

Because the compromised circulatory system is less tolerant of depression, anesthesia induction in patients with heart disease is generally problematic.

Attenuating sympathetic activity to noxious stimuli such as laryngoscopy, intubation, and the surgical incision is one of the primary goals of cardiac

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anesthesia. Vasodilation due to anesthetic drugs and hypotension caused by cardiac depression should be avoided. No single anesthetic agent is suitable for all cardiac patients, and many drug combinations have been used to maintain hemodynamic stability.¹

Besides hemodynamic stability, anesthesia protocols aim to carefully manage the depth of intraoperative anesthesia, intra-postoperative pain management, as well as postoperative recovery.

The technique used in previous years for induction of anesthesia in cardiac surgery is the "high-dose opioid" technique, based on the induction of anesthesia with high-dose opioid+midazolam and periodic administration of the same drugs. However, opioids' known side effects in the perioperative period have reduced the popularity of high-dose opioid protocols; such as respiratory depression, prolonged intubation, decreased bowel movements, nausea, vomiting, hyperalgesia, addiction potential, prolonged intensive care unit (ICU) and hospital stays. In addition, midazolam has been shown to cause a high rate of postoperative delirium, and prolonged ICU stays in cardiac surgery patients.²

Fast track and balanced anesthesia protocols have been developed in years for all these reasons. The balanced anesthesia methods are provided with a sedative-hypnotic agent with a low side-effect profile, as well as opioids with a short duration of action and volatile anesthetics. Various combinations of propofol, ketamine, dexmedetomidine, remifentanyl, lidocaine, and magnesium have been used frequently in managing anesthesia and analgesia in cardiac surgery in recent years, and their beneficial effects have been proven.³⁻⁶

The primary aim of this study is to compare traditional and balanced anesthesia protocols in terms of postoperative pain and sedation scales and early extubation criteria. The secondary aim is to observe the effects of these 2 different anesthesia protocols on intraoperative hemodynamics.

MATERIAL AND METHODS

This prospective observational study was approved by Ankara City Hospital No 1 Clinical Researches Ethics Committee (date: May 26, 2021, no: E1-21-

1624) and written informed consent was obtained from each subject. The study was conducted in accordance with the principles of the Declaration of Helsinki. Adult patients who underwent coronary surgery with cardiopulmonary bypass (CPB) were included in the study. Exclusion criteria were as follows: cardiac surgeries other than isolated coronary surgeries, emergency surgeries, reoperations, a history of ejection fraction under 40%, neurological and psychiatric disorders, uncontrolled hypertension, or uncontrolled diabetes mellitus, as well as the patient's age being under 18 years. After recording demographical data and comorbidities, all patients were monitored in operating rooms with pulse oximetry, 5-channel electrocardiography, and invasive artery pressure. A bispectral index (BIS™, Covidien, MN, ABD) sensor was placed on forehead.

After preoxygenation, conventional anesthesia group patients (group conventional) were administered 10 µg kg⁻¹ fentanyl, 0.15 mg kg⁻¹ midazolam intravenously (IV) as anesthesia induction. During the maintenance of anesthesia, 3 µg kg⁻¹ fentanyl and 0.01-0.05 mg kg⁻¹ midazolam were administered intermittently to keep the BIS between 40-50. Postoperative analgesia was provided with 1 mg kg⁻¹ paracetamol IV and 1 mg kg⁻¹ tramadol IV every 8 hours, and 1 mg kg⁻¹ fentanyl IV was used as rescue analgesic.

After preoxygenation, balanced anesthesia group patients (group balanced) were administered propofol 2 mg kg⁻¹ IV, ketamine 1 mg kg⁻¹ IV as anesthesia induction. In the maintenance of anesthesia, continuous IV infusion of remifentanyl (infusion rate; 0.25 to 0.5 mcg kg⁻¹ min⁻¹) and inhalational sevoflurane [1-3%, as keeping minimum alveolar concentration (MAC) 1)] was administered to maintain BIS 40-50. Postoperative analgesia was provided with 1 mg kg⁻¹ paracetamol IV and 1 mg kg⁻¹ tramadol IV every 8 hours, 1 mg kg⁻¹ fentanyl IV was used as rescue analgesic. In the course of CPB, a sevoflurane vaporizer was designed for the CPB pump. End-tidal volatile anesthetic concentration and MAC values were obtained from the oxygenator outlet, which were connected to the monitor and ventilator.

Ventilation is performed with 7-8 mL kg⁻¹ tidal volume adjusted for ideal body weight with a mixture

of O₂/air (FiO₂ 0.5) and 5 cm H₂O positive end expiratory pressure in all patients. The respiratory rate was set to keep an end-tidal CO₂ pressure between 35-45 mmHg. Arterial oxygen pressure was optimized at 100-200 mmHg. Hemoglobin concentrations were kept above 7.5 g dL⁻¹ during the operation and above 8.5 g dL⁻¹ after the operation. CPB was performed with a target flow of 2.2-2.4 L min⁻¹ per m² and in moderate hypothermia (30-32 °C). Crystalloid cardioplegia (Plegisol®, Hospira Inc, USA) was used and maintained using 1:4 ratio mixed blood cardioplegia at 20 min intervals. After decannulation, heparin was reversed by protamine. The CPB was terminated, and sternum was closed after bleeding control. Administration of anesthetics was stopped upon completion of the surgical procedure.

Nitroglycerin infusion was started (initial dose 0.1 mcg/kd/min) if the blood pressure of the patients increased above 100 mmHg in the intraoperative period and the BIS values were 40 or less. The total dose of nitroglycerin administered to the patients in the intraoperative period was recorded. Ephedrine was administered before and during CPB when the mean arterial pressure fell below 60 mmHg (in bolus doses of 5 mg). The total ephedrine dose administered to the patients during this period was recorded. Considering low cardiac output syndrome after CPB, inotropic agents were given as infusion (dopamine, dobutamine) instead of ephedrine. Patients who needed inotropic support were also recorded.

Hemodynamic parameters [systolic and diastolic arterial pressures (SAP, DAP), heart rate (HR)], lactate and BIS values were recorded at five intraoperative time points: T1- before anesthesia induction as basal measurements, T2- 5 minutes after endotracheal intubation, T3- right before sternotomy, T4- 10th minutes of CPB, T5- after sternum closure. In addition, all intraoperatively administered medicines were recorded.

Patients were evaluated in terms of pain, sedation, and extubation criteria at the postoperative 2nd hour. No anesthetic drug was administered to the patients during this period. The pain was evaluated with visual analog scale (VAS) score, which consists of a line with the endpoints “0- no pain at all” and

“10-pain as bad as it could be”. The patients were asked to point their pain levels on the chart. Sedation was evaluated with a Modified Ramsay Sedation (MRS) score, which consists of six levels of sedation from “1-anxious and agitated” to “6-no response”. Extubation criteria were defined as; patients obey simple commands and can lift head, hemodynamically stable, PaO₂>80 mmHg at FiO₂ 0.5, spontaneous smooth ventilation for 20 minutes (respiratory rate 10-18 min⁻¹, tidal volume>8 mL kg⁻¹), bleeding<200 mL within last 30 minutes.

STATISTICAL ANALYSIS

Based on previous studies on the field, a sample size of 23 patients per group (power=0.80, alfa=0.05) would be sufficient, when 1% standard deviation difference is considered significant.

Statistical analyses were performed using SPSS 25.0 program (SPSS Inc., Chicago, IL, USA). Statistical analysis data were presented as mean±standard deviation, median (interquartile range), and n (%). The conformity of the variables to the normal distribution was analyzed using the analytical method (Shapiro-Wilk test, df<50). Independent groups t-test (Student t-test) was used for normally distributed data, and Mann-Whitney U test was used for data not normally distributed. Chi-square test was used in the evaluation of categorical data. Whether there was a statistically significant difference between repeated measurements within the groups was evaluated with repeated measurements ANOVA. The Greenhouse-Geisser correction was used when the sphericity assumption was not met. The results were evaluated at the 95% confidence interval, and the significance was at the p<0.05 level.

RESULTS

A total of 55 adult patients who underwent elective isolated coronary surgery at our tertiary cardiac center were included and 49 of them were analyzed. Prolonged mechanical ventilation related to surgical complications (postoperative graft thrombosis, low cardiac output syndrome, bleeding, etc.) was observed in 6 patients and therefore they were excluded from the analysis.

Demographic data including age, gender, body mass index, Euroscore II values, and clinical characteristics including the presence of preoperative comorbidities were similar in both groups (Table 1). There was no difference between the groups in terms of cross-clamp, CPB, and operation durations, inotropic agents requirements, total fluid intake, and urine output rates ($p>0.05$) (Table 2). However, the rates of total nitroglycerine and ephedrine doses were found to be significantly higher in the conventional group ($p<0.001$, $p=0.013$).

The number of patients who met the extubation criteria at the 2nd postoperative hour was found to be significantly higher in the group balanced, and similarly, the duration of extubation and intensive care stay was shorter in the balanced group ($p<0.001$, $p<0.001$, $p=0.007$). MRS scale was found to be significantly higher in the conventional group ($p<0.001$). The VAS scores were similar in two groups ($p>0.05$) (Table 2).

SAP, DAP, HR, BIS, and lactate measurements performed in the 5 intraoperative periods

TABLE 1: Demographical data of the study population.

	Group conventional (n=24)	Group balanced (n=25)	p value
Age (years)	60.04±9.5	60.12±9.6	0.977*
Body mass index	26.93±2.9	28.44±3.3	0.105*
Male gender	19 (79.2)	20 (80.0)	0.942†
Hypertension	20 (83.3)	16 (64.0)	0.125†
Chronic obstructive pulmonary disease	0 (0.0)	2 (8.0)	0.157†
Diabetes mellitus	11 (45.8)	10 (40.0)	0.680†
Chronic renal failure	2 (8.3)	1 (4.0)	0.527†
Ejection fraction %	55.00 (50.0-56.5)	56.00 (52.0-58.0)	0.221‡
Euroscore II	1.140 (0.88-1.70)	0.880 (0.74-1.47)	0.190‡

*Independent samples t-test, mean±standard deviation; †Chi-square test, n (%); ‡Mann-Whitney U test, median (interquartile range).

TABLE 2: Perioperative variables.

	Group conventional (n=24)	Group balanced (n=25)	p value
Intraoperative variables			
Cross clamping duration (min)	67.79±24.75	70.64±26.11	0.697*
CPB duration (min)	107.25±44.99	103.92±31.37	0.764*
Operation duration (min)	310.00±39.78	290.40±35.09	0.073*
Patients who had dopamine infusion during operation	9 (37.5)	7 (28.0)	0.478†
Patients who had dobutamine infusion during operation	2 (8.3)	0 (0.0)	0.141†
Nitroglycerin (total dose for per patient, mg)	7.00 (4.0-12.5)	0.80 (0.1-2.0)	<0.001‡
Ephedrine (total dose for per patient, mg)	50.00 (40.0-100.0)	30.00 (20.0-40.0)	0.013‡
Total iv fluid	1500.0 (1400.0-2000.0)	1500.0 (1000.0-2000.0)	0.575‡
Total urine output	950.0 (800.0-1550.0)	850.0 (700.0-1500.0)	0.637‡
Postoperative variables			
Patients who met extubation criterias at postoperative 2 nd hour	6 (30.0)	22 (88.0)	<0.001†
Modified Ramsay sedation score at postoperative 2 nd hour	4.00 (4.0-4.0)	3.00 (2.0-4.0)	<0.001‡
Visual analog pain score at postoperative 2 nd hour	2.00 (1.0-2.0)	3.00 (1.0-4.0)	0.110‡
Mechanical ventilation duration (hours)	8.00 (6.0-8.0)	5.00 (4.0-5.0)	<0.001‡
Intensive care unite stays (hours)	21.00 (20.0-26.0)	18.00 (18.0-22.0)	0.007‡

*Independent samples t-test, mean±standard deviation; †Chi-square test, n (%); ‡Mann-Whitney U test, median (interquartile range); CPB: Cardiopulmonary bypass.

did not show any significant difference between the two groups (p=0.071, 0.086, 0.065, 0.451, 0.592, respectively) (Table 3) (Figure 1).

DISCUSSION

In this prospective, observational study comparing “midazolam and high dose fentanyl-based”

TABLE 3: Hemodynamic variables, BIS levels and lactate levels for intraoperative five timepoints.

	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	p*
	T1 SAP	T2 SAP	T3 SAP	T4 SAP	T5 SAP	
Group conventional	183.08±27.1	120.96±10.1	132.00±22.7	60.58±15.4	107.50±14.4	0.071
Group balanced	168.96±26.6	120.32±20.2	112.78±18.4	60.92±12.7	96.26±13.2	
	T1 DAP	T2 DAP	T3 DAP	T4 DAP	T5 DAP	
Group conventional	81.75±11.2	64.54±5.8	68.75±11.7	53.08±11.4	58.42±11.7	0.086
Group balanced	76.21±8.2	64.20±11.5	62.61±9.1	52.35±10.9	50.35±6.2	
	T1 HR	T2 HR	T3 HR	T4 HR	T5 HR	
Group conventional	83.37±8.7	76.37±13.1	76.17±11.7	-	98.33±15.8	0.065
Group balanced	77.00±14.1	78.09±11.6	68.52±15.2	-	88.04±12.3	
	T1 BIS	T2 BIS	T4 BIS	T4 BIS	T5 BIS	
Group conventional	93.44±5.9	41.28±14.9	48.72±8.4	43.50±7.0	43.75±6.2	0.451
Group balanced	94.70±3.9	41.88±20.0	46.87±10.8	48.04±12.4	44.32±10.2	
	T1 lactate	T2 lactate	T3 lactate	T4 lactate	T5 lactate	
Group conventional	-	1.04±0.3	-	2.82±0.8	3.09±1.1	0.593
Group balanced	-	1.31±0.6	-	3.13±1.1	3.10±1.2	

*Repeated ANOVA test; BIS: Bispectral index; SD: Standard deviation; SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; HR: Heart rate.

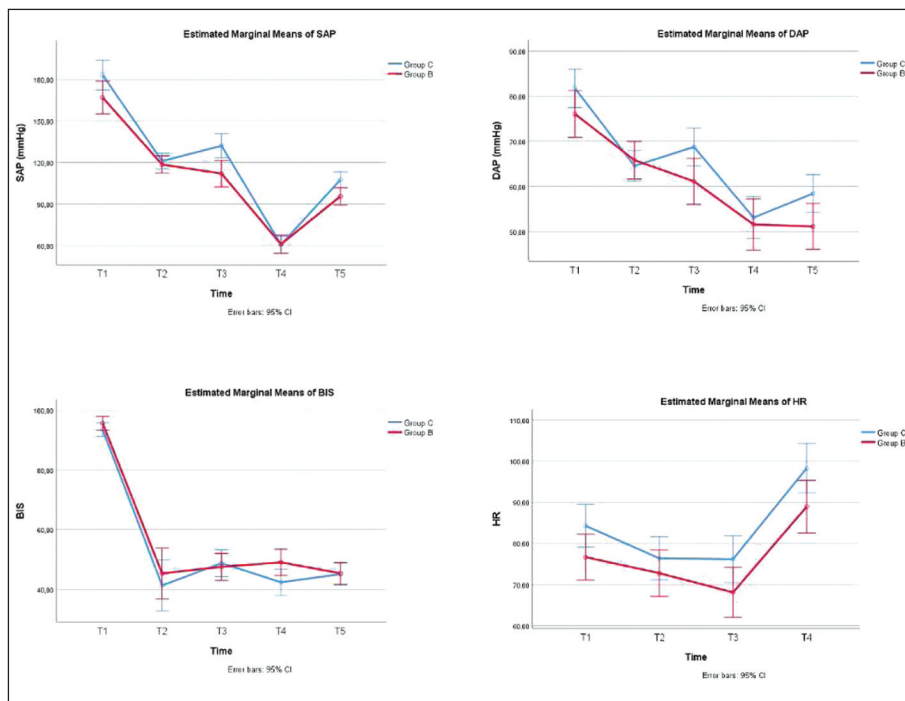


FIGURE 1: Blood pressure, HR, and BIS values at intraoperative five time points. HR: Heart rate; BIS: Bispectral index; SAP: Systolic arterial pressures; DAP: Diastolic arterial pressures; CI: Confidence interval.

conventional anesthesia management with balanced anesthesia, which is provided with “propofol-ketamine induction followed by sevoflurane and remifentanyl infusion”, we found that balanced anesthesia management provided faster postoperative recovery and caused less use of hemodynamic drugs (ephedrine and nitroglycerine).

High-dose opioid-based anesthetic regimens were defended for years since studies confirmed their ability to allow hemodynamic stability even in patients with limited cardiac reserves.⁷ Present-day cardiac anesthesia continues to rely heavily on opioids. However, its known side effects, especially prolonged mechanical ventilation, have led to the unpopularity of opioid-based anesthesia. Besides high-dose opioids, midazolam also is an agent that is currently avoided in cardiac surgery practice. After long years of use, it has come to the fore with an important side effect defined in recent years: “postoperative delirium”.^{2,8} It is said that 57% of patients are affected by delirium and this causes longer ICU and hospital stays after cardiac surgery.⁸

With an increasing demand for intensive cardiovascular and ventilatory support during the immediate postoperative period, the “fast-tracking cardiac anesthesia” term has emerged. This aims of early endotracheal extubation and shortened length of ICU and hospital stays with following cost reduction.⁷ The use of multimodal analgesia and opioid reduction policies were included in the recommendations recently presented by the Enhanced Recovery After Surgery (ERAS) Cardiac Society.⁹ Selecting ultra-short acting and titrable opioids as remifentanyl, is an important aspect of patient recovery. In addition, ketamine has been shown to be useful in reducing intraoperative opioid consumptions.¹⁰ Short-acting hypnotic drugs, ultra-short acting opioids, and inhalational anesthetics count as the components of fast-track cardiac anesthesia.

Although there is no standard technique of fast-track cardiac anesthesia, propofol seems to become an accepted agent.^{6,11} It is superior to benzodiazepines in multiple ways. Its effect begins quickly, it provides high-quality amnesia, facilitates airway manipulations and faster spontaneous ventilation

return. Propofol is a strong antiemetic, and it has anti-inflammatory and antioxidant properties. Besides, delirium is not a side effect. However, it may cause hypotension resulting from decreased systemic vascular resistance and cardiac contractility. In patients undergoing cardiac surgery, the application of subanesthetic doses of ketamine in combination with propofol was shown to result in hemodynamic stability.⁶ Ketamine is a sympathomimetic agent, which increases blood pressure and cardiac output, and it has been used in anesthesia practice for years with its hypnotic and strong analgesic effects. Its use in cardiac surgery has come to the fore in recent years, with its strong analgesic effects as well as suppression of the inflammatory response caused by CPB.¹²⁻¹⁴ In addition to the positive effects of ketamine on hemodynamic stability and inflammatory response, it has also been shown to have positive effects on postoperative delirium, unlike midazolam.⁴ Besides, ketamine is shown to be associated with neuroprotection and preemptive analgesia, so it appears as an important part of opioid free anesthesia and ERAS protocols.

Our balanced cardiac anesthesia protocol which includes anesthesia induction with propofol-ketamine combination and anesthesia maintenance with remifentanyl and sevoflurane seems to provide efficient fast-track anesthesia. The majority of patients (88%) have met the extubation criteria at the postoperative 2nd hour. They have also significantly shorter mechanical ventilation duration and ICU stay than the conventional group. We evaluated endotracheal extubation in 2 different ways; the time for meeting the extubation criteria and mechanical ventilation duration. The reason is the duration of mechanical ventilation is generally surgeon-dependent and many surgeons are reluctant to extubate patients in 2 hours.

Evaluation and monitoring of analgesia and sedation are the key parameters of post-anesthesia management. Inadequate control of pain and excessive sedation may cause complications such as hemodynamic instability, prolonged mechanical ventilation, and ICU stay. Intraoperative ultra-short acting opioids are suggested to provide safe and stable operating conditions but postoperative pain

management is a concern with these agents.^{15,16} However, our balanced anesthesia protocol supplemented with intraoperative remifentanyl did not cause negative effects on postoperative pain control, because postoperative 2nd-hour pain scores of patients were not significantly different in the 2 groups. We may conclude that postoperative pain management protocols seem to be efficient. We assessed the depth of postoperative residual sedation with the MRS Scale which is a common sedation monitoring tool in mechanically ventilated patients. Balanced anesthesia group patients had significantly lower sedation scores than the conventional group. Mean sedation score was “3” in the balanced anesthesia group, which means they were commonly scored as “awake, but responds to command only” while the conventional group’s mean score was “4” which means they were commonly scored as “asleep, brisk response to a light glabellar tap or loud auditory stimulus”. The overall effect of the shorter duration of mechanical ventilation and sedation caused a significantly shorter duration of ICU stays in the balanced anesthesia group of patients than the conventional anesthesia group.

The current study showed no significant differences in blood pressure and HR measurements at the 5 intraoperative 5 points. However, the total doses of nitroglycerin and ephedrine used in the intraoperative period were found to be significantly higher in the conventional group. This means that hemodynamic stability was achieved in both groups, but significantly higher amounts of ephedrine and nitroglycerine were needed to achieve hemodynamic stability in the conventional group. That is, more hemodynamic fluctuations were experienced in the conventional group, although this was not reflected in the 5 intraoperative time points. It is not surprising that anesthesia management maintained with remifentanyl infusion and sevoflurane provides more stable hemodynamics than intermittent doses of midazolam and fentanyl. In a study that evaluates propofol-ketamin combination with high dose

fentanyl technique, it is suggested that propofol-ketamin combination is associated with cardiovascular stability, reduced incidence of myocardial infarction (MI), and decreased need for inotropic agents.⁶ Our study did not show any difference in terms of postoperative inotropic agent usage or postoperative complications including MI.

CONCLUSION

Balanced anesthesia management protocol seems to provide intraoperative hemodynamic stability, in addition, better postoperative recovery in coronary surgery patients. Besides the improvement of cardiac surgical and CPB techniques, anesthetic regimens have allowed advancing safety and outcomes in cardiac surgery patients. It can be said that it’s time to say goodbye to high-dose opioid regimens used in cardiac surgery for years. A multimodal approach to anesthesia and analgesia in cardiac surgery should be applied, with short-acting agents, effectively controlling pain, overcoming side effects, advancing patient outcomes, and quality of recovery.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Eda Balci, Aslıhan Aykut, Zeliha Aslı Demir; **Design:** Eda Balci, Aslıhan Aykut, Zeliha Aslı Demir; **Control/Supervision:** Zeliha Aslı Demir; **Data Collection and/or Processing:** Eda Balci, Aslıhan Aykut; **Analysis and/or Interpretation:** Eda Balci, Aslıhan Aykut; **Literature Review:** Eda Balci; **Writing the Article:** Eda Balci, Zeliha Aslı Demir; **Critical Review:** Zeliha Aslı Demir.

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