

Effects of Intravenous Versus Inhalational Anesthesia on Red Cell Distribution Width and Mean Platelet Volume in Patients Undergoing Coronary Artery Surgery

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Koroner Arter Cerrahisi Geçiren Hastalarda İntravenöz Anestezi ve İnhalasyon Anestezisinin Kırmızı Hücre Dağılım Genişliği ve Ortalama Platelet Volümü Üzerine Etkileri

ABSTRACT

Objective: The effects of midazolam-based intravenous anesthesia (TIVA) and sevoflurane-based inhalation anesthesia (SEVO) maintenance on postoperative hematological parameters were compared in patients undergoing coronary artery surgery.

Methods: The 100 patients included in the study were divided into two groups according to the anesthesia management: All patients' anesthesia inductions were performed with 10 µg kg⁻¹ fentanyl, 0.15 mg kg⁻¹ midazolam, and 0.8 mg kg⁻¹ rocuronium. Anesthesia was maintained with total intravenous anesthesia in the TIVA group patients, while sevoflurane was used in the SEVO group patients. Demographic, clinical, operative data, red cell distribution width (RDW), and mean platelet volume (MPV) values were recorded.

Results: Except that the extubation time was shorter in the SEVO group, no difference was observed between the groups in terms of all these variables. There was a significant increase in postoperative RDW and MPV measurements in both groups. Postoperative RDW value was lower in the inhalation anesthesia group compared to the TIVA group (p=0.013).

Conclusion: In our study, RDW was found to be lower in the inhalation anesthesia group, indicating less inflammation. There was no difference in terms of postoperative complications and mortality.

Keywords: Total intravenous anesthesia, sevoflurane, RDW, MPV, cardiac anesthesia

Öz

Amaç: Koroner arter cerrahisi geçiren hastalarda, midazolam bazlı intravenöz anestezi (TIVA) ile sevofluran bazlı inhalasyon anestezisinin (SEVO) postoperatif hematolojik parametreler üzerine etkilerini incelemeyi amaçladık.

Yöntem: Çalışmamıza dahil edilen 100 hasta anestezi yönetimlerine göre iki gruba ayrıldı: Tüm hastaların anestezi induksiyonları 10 µg kg⁻¹ fentanil, 0.15 mg kg⁻¹ midazolam ve 0.8 mg kg⁻¹ rokuronyum ile gerçekleştirildi. TIVA grubu hastaların anestezi idamesi total intravenöz anestezi ile gerçekleştirilirken, SEVO grubu hastalarda sevofluran ile gerçekleştirildi. Hastaların demografik özellikleri, perioperatif verileri, kırmızı hücre dağılım genişliği (RDW) ve ortalama platelet volümü (MPV) değerleri kaydedildi.

Bulgular: SEVO grubunda ekstübasyon zamanının kısa olması dışında, iki grup arasında perioperatif veriler açısından anlamlı fark görülmedi. Her iki grupta da RDW ve MPV değerlerinde postoperatif artış anlamlı bulundu. Postoperatif RDW değerindeki artışın SEVO grubunda daha düşük olduğu görüldü (p=0.013).

Sonuç: Çalışmamızda, inflamasyon belirteci olan RDW'nin inhalasyon grubunda daha düşük olduğu bulundu. İnhalasyon ve TIVA anestezisi ile koroner arter cerrahisinde postoperatif komplikasyonlar ve mortalite açısından fark görülmedi.

Anahtar kelimeler: Total intravenöz anestezi, sevofluran, RDW, MPV, kardiyak anestezi

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INTRODUCTION

Red cell distribution width (RDW) is a measure of the heterogeneity of circulating red blood cells in size and is calculated by dividing the standard deviation of the red cell volume by the mean corpuscular volume. RDW is known to be associated with inflammatory parameters in many disorders and is used as a predictive marker for postoperative outcomes⁽¹⁾. Studies have reported that increased RDW levels are associated with poor outcomes in patients with cardiovascular diseases such as coronary artery disease, idiopathic pulmonary hypertension, and severe aortic stenosis after transcatheter aortic valve implantation⁽²⁻⁴⁾. Mean Platelet Volume (MPV) is a laboratory parameter that shows active and large platelets, and it is used as a predictive marker of cardiovascular diseases. Enlarged and reactive platelets have been shown to be associated with cardiovascular diseases^(5,6). MPV, like RDW, is a prognostic hematological parameter that increases with inflammation⁽¹⁾.

The aim of this study was to evaluate the effect of total intravenous anesthesia (TIVA) and inhalational anesthesia techniques on RDW and MPV in coronary surgery. The effects of midazolam-based TIVA or sevoflurane (SEVO)-based inhalation anesthesia maintenance on postoperative hematological parameters were compared in patients undergoing coronary artery bypass surgery.

MATERIAL and METHODS

The study protocol was approved by the institutional Ethics Committee and written informed consent was obtained from the patients (E-17-1692, 2018). The study was conducted in accordance with the Declaration of Helsinki. Randomization was performed by two independent anesthesiologists using a computer-based system. Emergency surgeries, redo surgeries, combined coronary surgeries, patients with ejection fraction below 40%, patients with cerebrovascular, neurological, or hematological disorders, patients with chronic alcohol usage, or patients under 18 years of age were excluded. The 100 patients included in the prospective study were divided into two groups according to the anesthesia management: The TIVA group included patients with midazolam based total intravenous anesthesia main-

tenance (n=50); the SEVO group included patients with inhalation anesthesia with sevoflurane maintenance (n=50). Demographic, clinical, intraoperative, and postoperative data were recorded. RDW and MPV values were measured and recorded on the day before and after the surgery.

All patients were premedicated with oral diazepam the night before surgery. After routine cardiac anesthesia monitoring, anesthesia induction with 10 µg kg⁻¹ fentanyl, 0.15 mg kg⁻¹ midazolam was performed. Once the bispectral index (BIS™, Covidien, MN, ABD) was stable between 40-50, 0.8 mg kg⁻¹ of rocuronium was used to facilitate tracheal intubation. The respiratory rate was adjusted to keep an end-tidal CO₂ value between 35-45 mmHg, tidal volume was adjusted 7 mL kg⁻¹ of ideal body weight and 5 cmH₂O PEEP was administered. During BIS guided anesthesia maintenance of the TIVA group, 3 µg kg⁻¹ fentanyl, 0.01-0.05 mg kg⁻¹ midazolam, and 0.2 mg kg⁻¹ rocuronium were applied throughout the operation, approximately once every 45 minutes. During BIS guided anesthesia maintenance of the SEVO group, 2-3% sevoflurane (1-2 Minimum alveolar concentration; MAC), 3 µg kg⁻¹ fentanyl and 0.2 mg kg⁻¹ rocuronium were applied throughout the operation. During cardiopulmonary bypass (CPB), sevoflurane vaporizer designed for the pump was used. Hemoglobin concentrations were kept above 7.5 g dL⁻¹ during, and above 8.5 g dL⁻¹ after the operation. CPB was performed using a roller-pump, open reservoir, and Nipro® oxygenator with a target flow of 2.2-2.4 L min⁻¹ per m² at 36°C (Medtronic, Minneapolis, MN). CPB was performed in moderate hypothermia (30-32°C). Crystalloid cardioplegia (Plegisol®) was used and maintained using 1:4 ratio mixed blood cardioplegia at 20 min intervals. After decannulation, the heparin effect was reversed by protamine, the cardiopulmonary bypass was terminated, and the sternum was closed after bleeding control.

Statistical Analysis

All statistical analyses were performed using IBM SPSS 22.0 for Windows. Mean with standard deviation, minimum and maximum values for normally distributed data, median and range values for non-normally distributed data and the number and proportions of patients for categorical variables were calculated as descriptive statistics to define the basic

features of patients. Chi-square analysis was used for comparing TIVA and SEVO groups according to categorical variables. Fisher's exact test was used in the presence of the number of patients equal to or less than 5 and Pearson's chi-square test was used for the number of patients greater than 5. Assumption of normality was tested by the Kolmogorov-Smirnov test. Paired sample t-test or the Wilcoxon signed rank test was used to assess whether the differences between preoperative and postoperative measurements of MPV and RDW are statistically significant or not in both groups. The difference between TIVA and SEVO groups according to continuous variables was investigated using either independent samples t-test or Mann Whitney U test. Since Generalized Linear Model (GLM) can be used to analyze the effects of categorical and continuous independent variables

on normally or non-normally distributed continuous dependent variables, we used GLM to investigate the effects of groups (TIVA or SEVO), gender (female/male), goiter, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), CPB, body mass index (BMI), and age on preoperative and postoperative measurements of MPV and RDW. A p-value<0.05 from two-sided tests was considered statistically significant.

RESULTS

Demographic data including age, gender, body mass index (BMI), Euroscore II values, and preoperative comorbidities were similar in both groups (Table I). Table I provides intraoperative clinical data such as

Table I. Demographic, hematological and operative data in groups

Variables	Group TIVA (n=50)	Group SEVO (n=50)	p-value
Age (years)	57.14±8.88 (39-73)	59.56±8.14 (32-75)	0.159 ^Y
Gender (female/male)	9 (18.0): 41(82.0)	10 (20.0): 40 (80.0)	0.799 ^Y
BMI (kg m ⁻²)	28.92±3.39 (23.43-39.10)	29.00±3.60 (22.13-40.00)	0.903 ^Y
Euroscore II (%)	0.91 (1.69)	0.78 (4.37)	0.275 ^W
Preoperative glucose (mg dL ⁻¹)	117.50 (123)	102 (125)	0.122 ^W
Goiter, n (%)	6 (12.0)	3 (6.0)	0.487 ^t
COPD, n (%)	4 (8.0)	5 (10.0)	1.000 ^t
Diabetes mellitus, n (%)	19 (38.0)	14 (28.0)	0.288 ^Y
Hypertension, n (%)	35 (70.0)	39 (78.0)	0.362 ^Y
Hyperlipidemia, n (%)	31 (62.0)	32 (64.0)	0.836 ^Y
Hematological parameters			
Preoperative hemoglobin (g dL ⁻¹)	13.70 (134.7)	14.65 (7.1)	0.123 ^W
Preoperative platelet count (x10 ³ μL ⁻¹)	239.0 (435)	239.50 (241)	0.942 ^W
Preoperative RDW (%)	13.10 (4.4)	12.90 (6.4)	0.175 ^W
Preoperative MPV (fL)	10.45±1.05 (8.5-13.3)	10.15±0.85 (9.0-12.1)	0.118 ^X
Postoperative hemoglobin (g dL ⁻¹)	8.80 (4.1)	9.35 (9.3)	0.154 ^W
Postoperative platelet count (x10 ³ μL ⁻¹)	160.0 (320)	169 (194)	0.393 ^W
Postoperative RDW (%)	13.70 (10.2)	13.25 (3.7)	0.093 ^W
Postoperative MPV (fL)	10.94±1.04 (9.2-14.3)	10.62±0.78 (8.6-12.2)	0.083 ^X
Intraoperative parameters			
Cross clamp duration (min)	56 (90)	59.50 (129)	0.461 ^W
CPB duration (min)	93.40±28.43 (32-194)	106.40±37.83 (33-207)	0.063 ^X
Duration of surgery (min)	282.50 (225)	300 (556)	0.164 ^W
Urine output (mL)	1200 (1850)	1000 (1800)	0.151 ^W
Blood products transfusions (U) n (%)	13 (26.0)	18 (36.0)	0.280 ^Y
Postoperative parameters			
Extubation time (h)	9.06±3.66 (4-22)	6.89±1.74 (4-13)	0.001 ^{X*}
Length of ICU stay (days)	1 (5)	1 (4)	0.996 ^W
Length of hospital stay (days)	5 (13)	5 (8)	0.493 ^W
Postoperative AF, n (%)	3 (6.0)	2 (4.0)	1.000 ^t
Postoperative pneumonia, n (%)	1 (2.0)	1 (2.0)	1.000 ^t
Postoperative CVA, n (%)	2 (4.0)	1 (2.0)	1.000 ^t
Drainage (24h, mL)	600 (1950)	600 (1850)	0.790 ^W
Postoperative blood products transfusions (U), n (%)	20 (40.0)	15 (30.0)	0.295 ^Y
Mortality within 30 days, n (%)	0 (0.0)	1 (2.0)	1.000 ^t

BMI Body mass index, COPD chronic obstructive pulmonary disease, RDW red cell distribution width, MPV mean platelet volume, CPB cardio-pulmonary bypass, AF Atrial fibrillation, CVA Cerebrovascular accident

Variables are presented as mean±SD or number (%) with (min-max).

*: p<0.05, X: Two-sample t-test, W: Mann-Whitney U test, Y: Pearson chi-square test, t: Fisher exact test

CPB duration, operation duration, and blood product transfusions. The same table also depicts postoperative characteristics like extubation duration, ICU-hospital stay, complications, and mortality. Except that the extubation time was shorter in the SEVO group ($p<0.001$), no difference was observed between the groups in terms of all these variables (Table I).

In Table I, preoperative and postoperative measurements of RDW and MPV for both TIVA and SEVO groups are also given. There was a statistically significant increase in postoperative RDW and MPV

measurements in the TIVA group ($p<0.001$, $p<0.001$ respectively). There was a statistically significant increase in postoperative RDW and MPV measurements in the SEVO group ($p<0.001$, $p=0.001$ respectively). There was no statistically significant difference between the groups in terms of preoperative RDW and preoperative MPV measurements ($p=0.175$, $p=0.118$ respectively). Additionally, based on classical statistical methods, there was no statistically significant difference between the groups in terms of postoperative RDW and MPV measurements ($p=0.093$, $p=0.083$ respectively). However, according to the results of GLM analysis in Table II, postopera-

Table II. Results of GLM analysis for preoperative RDW and postoperative RDW measurements

Parameter	Preoperative RDW				Postoperative RDW			
	β	SE	Wald χ^2	p-value	β	SE	Wald χ^2	p-value
Intercept	2.592	0.106	599.7	<0.001	2.507	0.119	443.5	<.001
Group (TIVA)	0.020	0.015	1.879	0.170	0.041	0.017	6.115	0.013*
Gender (Female)	-0.032	0.021	2.383	0.123	-0.003	0.023	0.014	0.905
Goitre	-0.021	0.027	0.610	0.435	-0.031	0.031	1.044	0.307
COPD	-0.026	0.028	0.865	0.352	-0.025	0.031	0.669	0.413
DM	0.012	0.017	0.509	0.476	0.032	0.019	2.968	0.085
HT	-0.012	0.018	0.487	0.485	-0.031	0.020	2.378	0.123
HL	-0.023	0.016	2.088	0.148	-0.008	0.018	0.199	0.656
CPB<120 min	-0.011	0.017	0.413	0.520	0.003	0.019	0.023	0.879
BMI (18.5-24.9)	0.039	0.079	0.245	0.621	0.096	0.088	1.191	0.275
BMI (25-29.9)	0.016	0.075	0.046	0.829	0.027	0.084	0.101	0.750
BMI (30-34.9)	0.022	0.074	0.083	0.773	0.015	0.084	0.031	0.860
BMI (35-39.9)	0.022	0.078	0.078	0.781	-0.032	0.088	0.133	0.716
Age	0.005	0.001	0.027	0.869	0.002	0.001	3.107	0.078

GLM: Generalized Linear Models, RDW: Red Cell Distribution Width, TIVA: Total intravenous anesthesia, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CPB: Cardiopulmonary bypass, BMI: Body mass index
*: $p<0.05$, SE: Standard error

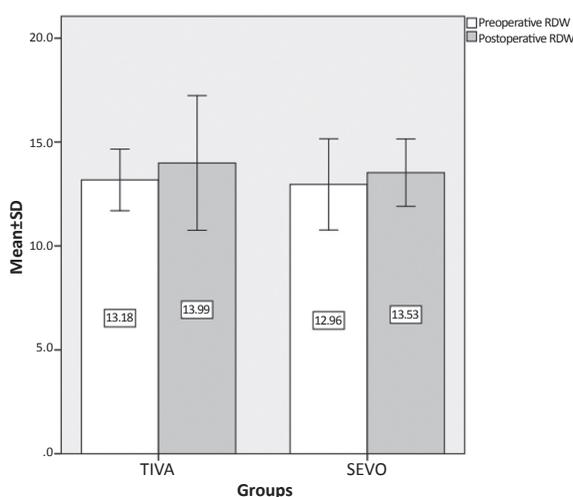


Figure 1. Comparison of preoperative and postoperative measurements for RDW in TIVA and SEVO groups.

Abbreviations: RDW: Red cell Distribution Width, TIVA: Total Intravenous Anesthesia, SEVO: Sevoflurane based anesthesia

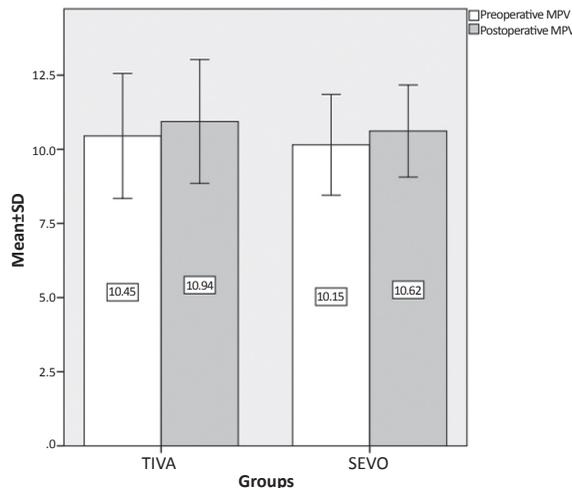


Figure 2. Comparison of preoperative and postoperative measurements for MPV in TIVA and SEVO groups.

Abbreviations: MPV: Mean Platelet Volume, TIVA: Total Intravenous Anesthesia, SEVO: Sevoflurane based anesthesia

Table III. Results of GLM analysis for preoperative MPV and postoperative MPV measurements

Parameter	Preoperative MPV				Postoperative MPV			
	β	SE	t	p-value	β	SE	t	p-value
Intercept	10.383	1.507	6.888	<.001	11.301	1.415	7.988	<.001
Group (TIVA)	0.344	0.209	1.644	0.104	0.359	0.196	1.830	0.071
Gender (F)	-0.099	0.298	-0.331	0.741	-0.502	0.279	-1.799	0.075
Guatre=0	0.578	0.386	1.496	0.138	0.041	0.362	0.114	0.909
COPD=0	0.025	0.393	0.064	0.949	-0.087	0.369	-0.235	0.815
DM=0	-0.095	0.239	-0.398	0.691	-0.025	0.225	-0.112	0.911
HT=0	0.014	0.253	0.055	0.956	0.085	0.237	0.358	0.721
HL=0	0.035	0.230	0.151	0.880	-0.009	0.216	-0.044	0.965
CPB<120	-0.083	0.245	-0.341	0.734	-0.250	0.229	-1.089	0.279
BMI (18.5-24.9)	-1.097	1.119	-0.980	0.330	-0.874	1.050	-0.833	0.407
BMI (25-29.9)	-0.945	1.071	-0.883	0.380	-1.062	1.005	-1.056	0.294
BMI (30-34.9)	-0.676	1.068	-0.633	0.528	-0.735	1.002	-0.733	0.465
BMI (35-39.9)	-1.074	1.115	-0.963	0.338	-1.565	1.047	-1.495	0.139
Age	0.004	0.013	0.288	0.774	0.010	0.012	0.842	0.402

GLM: Generalized Linear Models, MPV: Mean Platelet Volume, TIVA: Total intravenous anesthesia, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CPB: Cardiopulmonary bypass, BMI: Body mass index, SE: Standard error

tive RDW measurements were found to be statistically significantly lower in the SEVO group compared to the TIVA group ($\beta=0.041$, $p=0.013$). Figure 1 shows the course of the preoperative and postoperative changes of RDW between groups and Figure 2 shows the mean values of preoperative and postoperative MPV for both groups.

As seen in Table II, age ($p=0.869$, $p=0.078$ respectively), gender ($p=0.123$, $p=0.905$ respectively), comorbidities (Goiter $p=0.435$, $p=0.307$; COPD $p=0.352$, $p=0.413$; DM $p=0.476$, $p=0.085$; HT $p=0.485$, $p=0.123$; HL $p=0.148$, $p=0.656$ respectively), and CPB ($p=0.520$, $p=0.879$ respectively) variables have no statistically significant effects on preoperative RDW and postoperative RDW values. In Table III, age ($p=0.774$, $p=0.402$ respectively), gender (0.741 , $p=0.075$ respectively), comorbidities (Goiter $p=0.138$, $p=0.909$; COPD 0.949 , $p=0.815$; DM $p=0.691$, $p=0.911$; HT $p=0.956$, $p=0.721$; HL $p=0.880$, $p=0.965$ respectively), and CPB ($p=0.734$, $p=0.279$ respectively) variables also have no statistically significant effects on preoperative MPV and postoperative MPV values. Based on the results of GLM analysis in Table III, there was no statistically significant difference between the groups in terms of preoperative and postoperative MPV measurements ($p=0.104$, $p=0.071$ respectively).

DISCUSSION

In this study, in which the inhalation and total intra-

venous anesthesia methods were compared in the maintenance of anesthesia, RDW, an inflammatory marker, was found to be significantly lower in the inhalation group than in the TIVA group. However, there was no significant change in MPV value.

Since volatile agents can cause myocardial depression and arrhythmogenic effect, and defibrillation resistance and coronary stealing often cause serious problems for patients in cardiac surgery, volatile methods are avoided in cardiac anesthesia, and TIVA techniques have been adopted. While TIVA has been widely used since the 1990s, volatile agents were again considered in cardiac surgery when it was determined that inhalation agents were preconditioned against myocardial ischemia and reduced the incidence of infarction^(7,8). Sevoflurane has become the most widely used volatile agent in general anesthesia practice due to the disadvantages of isoflurane such as the stealing phenomenon, more reflex tachycardia, late onset, and late termination of the effect. In cardiac surgery, as compared to the TIVA techniques, the inhalation method is easy to apply, does not require dose adjustment according to body weight, is not affected by hemodilution, is cardioprotective, provides rapid recovery, and its elimination is independent of liver and kidney⁽⁹⁾.

In recent years, rapid recovery (fast-track) and enhanced recovery after surgery (ERAS) protocols in cardiac surgery have been a focus of the literature. With these protocols, surgical trauma, respiratory

and gastrointestinal system depression decreases, metabolic stress decreases, and organ functions return to normal in a short time ⁽¹⁰⁾. The most appropriate anesthesia technique for these protocols is inhalation anesthesia, the effect of which begins and recedes quickly. These positive clinical effects of inhalation methods are observed in cardiac surgery patients. The hypothesis of this study is to investigate the changes in hematological parameters related to inflammation occur.

The literature has discussed in detail sevoflurane's antioxidant and anti-inflammatory effects on various cells ⁽¹¹⁾. In patients using sevoflurane for anesthesia, studies have been conducted on its anti-inflammatory effects, and pulmonary inflammatory cytokines such as TNF- α , IL-1 β , IL-6 and IL-8 have been reported to be inhibited by volatiles ⁽¹²⁾. It was found that sevoflurane attenuated inflammatory response after one-lung ventilation compared to intravenous anesthesia technique ⁽¹³⁾. Another important result is that sevoflurane does not cause DNA damage in operating room staff ⁽¹⁴⁾. Considering that the RDW value, which reflects oxidative stress, increases as the intensity of inflammation increases, it is important that postoperative RDW was found lower in the inhalation anesthesia group in our study. This result indicates lesser inflammation with sevoflurane, in parallel with other studies ^(1,4,11). Although the values determined for RDW in the literature are higher than those found in our study, the increase in RDW values compared to the baseline value of each patient group was evaluated. Furthermore, less increase with inhalation anesthesia in RDW was not shown previously ^(1,4,15).

Mean platelet volume is associated with an indicator of platelet activity and plays an important role in the pathogenesis of atherosclerosis. As RDW values, MPV levels increase with inflammation. Although the number of platelets decrease after CABG, the tendency to thrombosis increases due to large and reactive platelets ^(1,16). In studies, high MPV levels were associated with negative results such as postoperative atrial fibrillation, early vein-graft occlusion, and increased mortality ^(1,17,18). In our study, although we observed a significant increase in the postoperative RDW values in the TIVA group, we did not find any significant increase in MPV. Research

has found that RDW is superior to MPV in predicting postoperative results in cardiac surgery, and even three parameters consisting of NLR-MPV-RDW are higher than the two parameters ⁽¹⁾. Similarly, MPV is a prognostic factor in another study, and studies have demonstrated that the MPV/platelet count ratio is effective in determining poor postoperative outcomes ⁽¹⁶⁾. Considering that higher RDW is the leading poor outcome predictor, MPV can be said to be a less valuable marker. Although postoperative MPV levels were lower in the SEVO group, no statistically significant difference was found according to our results. Our study is not a predictive study, but similarly, we might have not detected a significant change in MPV value, perhaps because the MPV change was less pronounced. Given as much, we hope that future large-scale studies may be decisive. In our study, there was no difference in terms of postoperative complications and mortality. Relatively low complication rates and a small number of patients may be the factor for this, studies involving more patients will be beneficial.

The present study found that the postoperative RDW value showing the severity of inflammation was lower in the inhalation anesthesia group compared to the TIVA group. There was no significant difference in MPV value, and no changes were observed between the two groups in terms of postoperative complications and mortality.

Ethics Committee Approval: Ankara Province 1st Region Public Hospitals Union General Secretariat SBU Ankara Numune SUAM Clinical Research Ethics Committee approval was obtained (03.01.2018/E-17-1692)

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