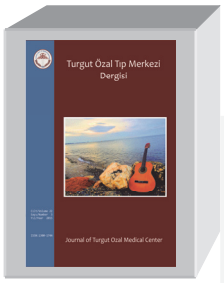

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Comparison of the Effects of Propofol Anaesthesia and Desflurane Anaesthesia on Neutrophil/Lymphocyte Ratios After Coronary Artery Bypass Surgery

Mustafa Aldemir[1], Elif Doğan Bakı[2], Fahri Adalı[1], Evren Tecer[1], Nilgün Kavrut Öztürk[3], Ali Sait Kavaklı[3], Mustafa Emmiler[4], Osman Tansel Darçın[1]

[1]Afyon Kocatepe University, Faculty of Medicine, Department of Cardiovascular Surgery, Afyonkarahisar, Turkey
[2]Afyon Kocatepe University, Faculty of Medicine, Department of Anaesthesiology and Reanimation, Afyonkarahisar, Turkey
[3]Antalya Training and Research Hospital, Anaesthesiology Clinic, Antalya, Turkey
[4]Antalya Training and Research Hospital, Cardiovascular Surgery Clinic, Antalya, Turkey

Abstract

Objective: Coronary artery bypass surgery with cardiopulmonary bypass can induce postoperative systemic leukocytic alterations including leukocytosis, neutrophilia, or lymphopenia. The present study aims to compare the effects of propofol and desflurane anaesthesia on the leukocytic alterations including neutrophil-to-lymphocyte ratios after coronary artery bypass surgery.

Materials and Methods: Sixty patients scheduled for coronary artery bypass surgery were randomly assigned into two groups: group P (n=30), which were anaesthesised with propofol (intravenous anaesthesia) and group D, which were anaesthesised with desflurane (inhalational anesthesia). Differential counts of leukocytes with neutrophil/lymphocyte ratios of peripheral blood were obtained just before anaesthesia induction (for basal values), at the postoperative 12th, 24th, and 48th hours.

Results: At the postoperative 12th decrease in lymphocyte counts in group P was significantly lower than in group D (1.23 ± 0.81, 0.92 ± 1.01, respectively, with a p value of <0.001). Depending on this difference, neutrophil/lymphocyte ratios in group P were lower than in group D, which was statistically significant (11.21 ± 5.01, 22.81 ± 15.24, respectively, with a p value of <0.001). At postoperative 48th hour, it was seen that the statistically significant difference between groups on the basis of lymphocyte counts and neutrophil/lymphocyte ratios dissapeared. But a statistically significant difference appeared between the two groups on the basis of neutrophil counts (in group P 6.57 ± 2.05, in group D 10.20 ± 5.26; p<0.001)

Conclusion: Comparing with desflurane anaesthesia, propofol anaesthesia favorably but transiently modifies leukocytic alterations, including neutrophil-to-lymphocyte ratios in peripheral blood during postoperative period of coronary artery bypass surgery.

Key Words: Coronary Artery Surgery; Propofol And Desflurane Anesthesia; Neutrophil/Lymphocyte Ratio.

Propofol ve Desfluran Anestezisinin Koroner Arter By-pass Cerrahisi Sonrası Nötrofil/Lenfosit Oranı Üzerine Etkilerinin Karşılaştırılması

Özet

Amaç: Kardiyopulmoner by-pass ile yapılan koroner arter by-pass cerrahisi lökositoz, nötrofili ve lenfopeniyi de içeren postoperatif lökosit dağılımı değişikliklerini başlatabilir. Bu çalışma ile kardiyopulmoner bypass kullanılarak koroner by-pass cerrahisine giden hastalarda propofol (intravenöz) ve desfluran (inhalasyon) anestezisinin postoperatif lökositik değişiklikler ve nötrofil/ lenfosit oranı üzerine etkileri incelenmiştir.

Gereç ve Yöntemler: Bu prospektif randomize çalışmada elektif koroner arter by-pass cerrahisi planlanan 60 hasta iki eşit gruba randomize edildi. olgulardan 30'unda (grup P, n=30) propofol (intravenöz) anestezi ve diğer 30'unda ise (grup D, n=30) desfluran (inhalasyon anestezisi kullanıldı. Hastalardan lökosit alt tipleri ve nötrofil/lenfosit oranı tayini için anestezi indüksiyonundan hemen önce (bazal değer), postoperatif 12. saat, 24. saat ve 48. saatlerde olmak üzere periferik venden kan örneği alındı.

Bulgular: Postoperatif 12.saat kan sayımlarında lenfosit sayısındaki düşüş grup P'de grup D'ye göre daha az belirgin (sırasıyla 1.23 ± 0.81, 0.92 ± 1.01 ve p değeri <0.001) ve buna bağlı olarak nötrofil/lenfosit oranı grup P'de grup D'ye göre istatistiksel olarak anlamlı şekilde daha düşüktü (sırasıyla 11.21 ± 5.01, 22.81 ± 15.24 ve p değeri <0.001). Postoperatif 48.saatte ise lenfosit ve nötrofil/lenfosit oranları ile ilgili daha önce tespit edilmiş istatistiksel anlamlı farkın ortadan kalktığı ancak nötrofil sayıları arasında istatistiksel anlamlı farkın oluştuğu (grup P'de 6.57 ± 2.05, grup D'de 10.20 ± 5.26, p<0.001) tespit edildi.

Sonuç: Bu çalışmanın sonuçları, propofol anestezisinin desfluran anestezisine göre lökositik değişiklikler ve nötrofil/lenfosit oranı üzerinde olumlu etkileri olduğunu ancak bunun geçici olduğunu göstermektedir.

Anahtar Kelimeler: Koroner By-Pass Cerrahisi; Propofol Ve Desfluran Anestezisi; Nötrofil/Lenfosit Oranı.

INTRODUCTION

In response to surgical stress, systemic leukocytic changes such as neutrophilia, lymphopenia, and leukocytosis may occur by way of various hormones, cytokines, and acute phase reactants. Lymphocyte apoptosis or inhibition of neutrophil apoptosis are two of the surgical stress response mechanisms (1, 2). Cardiopulmonary bypass (CPB) cycle is the main predictor determining surgical stress in cardiac surgery (3). Surface contact with other materials in the CPB blood cycle along with hypoperfusion may increase stress response and secretion of immune system mediators eventually ending up with negative results in perioperative period (4, 5).

It is known that immune response is also influenced by anaesthetic techniques conducted during and after surgery (6). In the literature, there are studies that indicate that total intravenous (TIVA) propofol-remifentanil anaesthesia brings about lower immune mediator levels like stress hormone and cytokine release compared with sevoflurane total inhalation anaesthesia (7). It has also been shown that cellular immunity receives less suppression with TIVA (8). Although there are studies on the relationship between open heart surgery and Neutrophil/Lymphocyte ratios (N/L) (9), there are not any studies on the effects of propofol and desflurane on systemic leukocytic changes especially the N/L ratios. The identification of leukocytic changes including N/L ratios is an extremely useful method in evaluating postoperative inflammatory response. Compared to clinical tests such as the interleukin test, one of the tests used in determining immune mediators, N/L ratio determination is a simpler and more inexpensive test (10). In this study, we aim to emphasise the importance of choosing the right anaesthesia method by analysing the effects of propofol and desflurane anaesthesia on the leukocytic changes after coronary artery bypass surgery and N/L ratios.

MATERIALS and METHODS

After obtaining the approval from the Ethics Committees of Afyon Kocatepe University, Faculty of Medicine, and Antalya Training and Research Hospital, this clinical randomised study was conducted at Afyon Kocatepe University, Faculty of Medicine Hospital, Department of Cardiovascular Surgery and Antalya Training and Research Hospital, Cardiovascular Surgery Clinic between February 2014 and May 2014 on 68 patients who underwent coronary artery bypass surgery after receiving their full consent with informed consent forms. In the postoperative period, 3 of the patients suffered from pulmonary failure while one of the patients had neurological complications, 2 patients had wound infections, and another 2 had tamponade-related re-exploration. Thinking that these complications may affect blood cell counts, we excluded all these (8 cases) patients from the study. We randomly divided the patients into two groups: 30 patients for intravenous propofol anaesthesia (Group P, n=30) and 30 patients for desflurane inhalation anaesthesia (Group D, n=30). Besides, we also excluded the following patients from the scope of our study: those who underwent coronary artery bypass surgery along with heart valve replacement or similar other surgical procedures; those with an ejection fraction of 30% and below; those who underwent emergency surgery, those who required preoperative intra-aortic balloon pump or inotropic medication support; those who had liver disfunction, autoimmune diseases, collagen vascular diseases, or systemic inflammatory diseases; those who were re-operated; those who were diagnosed with tumours, or with acute or chronic renal failure (preoperative serum creatinine ≥ 1.5 mg/dL); morbidly obese patients (body mass index > 35 kg/m2); those who were chronically on immunosuppressants; and those who had undergone chemotherapy within the past year. During the preoperative period, the patients were allowed to use their standard cardiac medications. Before they were taken to the operating room, all patients were administered with oral midazolam premedication. All patients were continuously monitored in the operation room through electrocardiography (Datex-Ohmeda Avance, GE Healthcare, Helsinki, Finland), capnography, pulse oximetry, entropy (state and response), central venous pressure (CVP), and invasive blood pressure monitoring. Prior to tracheal intubation, we used 0.9 mg/kg of rocuronium, 0.2-0.5 mg/kg of etomidate, and 3 mcg/kg of fentanyl for the induction. For the maintenance of both patient groups, we continued the infusion of 0.1 mg/kg/hour of rocuronium and 0.25 mcg/kg of remifentanil throughout the operation.

We maintained the anaesthesia with 5 mg/kg of propofol infusion in the propofol group and with a MAC desflurane entropy state of 40-60 in the desflurane group. We increased the end-tidal concentration of desflurane when the entropy values exceeded 60 and we continued to do this until the entropy values fell below 60. In cases when the entropy value fell below 40, we decreased the concentration of end-tidal desflurane and maintained this state until the values reached over 40. The total amount of the consumed desflurane was recorded on the anaesthesia apparatus and the amount of propofol used was recorded on the infusion pump in millilitres. Patients in both groups were ventilated with a tidal volume of 6-8 ml/kg while the inhaled airborne oxygen fraction (FiO2) was 50%. The respiratory rate was set so as to keep arterial pCO2 value at 35-45 mmHg as we set the end-tidal volume according to CO2. We also administered 5cmH2O PEEP. To determine the total leukocytes, neutrophils, lymphocytes, and N/L ratios, we collected blood samples from a peripheral vein immediately before the induction and within 12, 24, and 48 hours. Using the percentages calculated by the automated cell counter (Beckman Coulter LH780 Analyzer, Beckman Coulter Inc. Diagnostic Division Headquarters, CA, USA) we determined the differentiated neutrophil and lymphocyte counts (11).

To reach the N/L ratio, we used the absolute neutrophils and lymphocyte numbers. All patients underwent surgery with median sternotomy. Maintaining an

activated clotting time (ACT) of 400 and over during the cardiopulmonary bypass, we applied 300 units/kg of heparin to all patients. Cardiopulmonary bypass was achieved with aortic and right atrial cannulation. The membrane oxygenator (Hilite 7000, Medos, Stolberg, Germany) was primed with 1000-500cc Ringer's lactate solution to keep haematocrit level at 26%±2 during cardiopulmonary bypass. To keep arterial pressure at 50-70 mmHg, the non-pulsatile flow was set to 2.2-2.4 L/min/m2 throughout cardiopulmonary bypass. The myocardial protection achieved with intermittent antegrade cardioplegia and 33 degrees C moderate hypothermia. We also applied heparin neutralisation with protamine sulphate after cardiopulmonary bypass. Cardiopulmonary bypass was terminated when body temperature reached 37 degrees C and heart rhythm was stable at 90/min in atrioventricular mode.

In both groups, we started and continued remifentanil infusion during their transfers from the operating room to intensive care unit. We terminated sedation when the patients were hemodynamically stable in intensive care, had normothermia (temperature: 36.5°C), or had required ventilatory parameters (FIO2<50%; PaO 2>60 mmHg). Patients who were hemodynamically stable without significant arrhythmia issues, those who had a chest tube drainage of less than 100 cc/hr, patients who were alert and could respond to verbal instructions, and those who had suitable respiratory parameters (FIO2<45%; peak end-expiratory pressure: <7.5 cm H2O; respiratory rate> 10/min; and ventilation-per-minute> 100 mL/kg) were all extubated.

Statistical analyses were performed with SPSS version 15.0 (SPSS, Inc., Chicago, IL). The compliance of variables with normal distribution were evaluated visually (histograms and probability plots) and analytically (Kolmogorov-Smirnov test). Descriptive analyses for normally distributed variables were given in mean and standard deviation. The comparisons in both groups were carried out using the Student t-test, Mann-Whitney U test, and Pearson Chi-Square test.p<0.05 value was considered statistically significant.

RESULTS

The total patient population consisted of 60 patients. We used intravenous propofol in 30 of these patients (group P, n=30); the other 30 patents were given desflurane inhalation anesthesia (group D, n=30). In terms of the preoperative and demographic characteristics of these patients, 4 of the group P patients (13%) and 2 of the group D (7%) patients had chronic obstructive pulmonary disease (COPD) and this difference was statistically significant (p<0.001). Apart from the presence of COPD, patient characteristics were similar in the two groups (Table I).

Table I. Demographic and preoperative characteristics of the patients.

	Group P (n=30)	Group D (n=30)	p value
Age (Years)	58.17±10.01	60.31±8.49	0.378
Height (Meters)	161.5±10.49	164.53±8.87	0.343
Weight (Kilograms)	70.18±11.43	76.86±15.65	0.371
Sex (Males)	18(%60)	16(%53)	0.870
DM	12(%40)	8(%27)	0.173
COPD	4 (%13)	2 (%7)	*0.001*
CVD	3 (%10.0)	5 (%16.7)	0.448
Smoking	18(%60)	17(%57)	0.479
Hypertension	14(%46.7)	9(%30)	0.073
USAP	2(%6.7)	4(%13.3)	0.671

DM:Diabetes Mellitus; COPD:Chronic Obstructive Pulmonary Disease; CVD: Cerebrovascular Disease; USAP: Unstable Angina Pectoris.

There was no statistically significant difference between the groups in terms of cardiopulmonary bypass time, cross-clamping time, and the number of distal anastomosis (p-values are shown in Table II). The number of red blood cell suspension transfusions for group P was 2.99±0.98; this value was 2.74±0.69 for group D, which shows no statistically significant difference (p=0.21). The postoperative MI, inotropic support, and intra-aortic balloon support requirements, all of which could be regarded as signs of postoperative myocardial dysfunction, were similar in both groups. Again, there was no statistically significant difference between the two groups in terms of time duration of mechanical ventilation and intensive care stay. The length of hospital stays were 6.49±2.28 and 9.87± 2.63 for group P and group D, respectively, and this difference was statistically significant (p<0.001).

Blood samples taken immediately before the induction in both groups showed no statistically significant difference in terms of total leukocytes, neutrophils, lymphocytes, or NL (which is calculated from the absolute values, i.e. baselines values, of leukocytes, neutrophils, and lymphocytes) values (Table III). Although there was no statistically significantly difference between the two groups in terms of leukocyte and neutrophil counts as seen in the total blood count at the postoperative 12th hour, there was a less significant decrease in the number of lymphocytes in group P than in group D (1.23±0.81 and 0.92±1.01, respectively, with a p value of <0.001); accordingly, the N/L ratio was remarkably lower in group P compared to group D (11.21±5.01 and 22.81±15:24, respectively, with a p value of <0.001). The same statistical picture continued at the postoperative 24th hour (Table III).

At the postoperative 48th hour, we found out that the previously detected differences between lymphocyte and N/L had disappeared giving way for a statistically significant difference in terms of neutrophil counts (group P: 6.57±2:05; group D: 10.20±5.26; p<0.001).

Table II. The intraoperative and postoperative analyses of the patients.

	Group P (n=30)	Group D (n=30)	p value
Number of Distal Anastomosis	3.15±1.04	2.88± 0.72	0.23
Operation duration (Minutes)	162.45±39.6	151.5±34.5	0.35
Duration under anaesthesia (Minutes)	202.15±37.7	180.7±38.4	0.07
Number of transfusions	2.99 ± 0.98	2.74 ± 0.69	0.21
Number of CPB (Minutes)	102.87±40.39	98.88±28.26	0.91
CC time (Minutes)	56.96±26.93	56.93±19.34	0.62
Inotropic support	14(%47)	16(%52)	0.73
IABP support	2(%6.7)	4(%13.3)	0.66
Postoperative MI	0 (%0.0)	2(%6)	0.489
MV duration (Hours)	6.31±2.97	5.83±1.68	0.879
ICU stay (Days)	2.06±0.75	2.02±1.32	0.247
Hospital stay (Days)	6.49±2.28	9.87±2.63	***<0.001***

CPB: Cardiopulmonary Bypass; CC:Cross clamp; IABP: Intra-aortik balloon pump; MI: Myocardial infarctio; MV: Mechanical ventilation; ICU: Intensive care unit.

Table III. Comparion of the two groups in terms of leukocytic changes.

	GROUP P (n=30)	GROUP D (n=30)	p value
Pre-operative			
Total leukocytes (103/mL)	8.35 ± 1.96	7.78 ± 1.71	0.453
Neutrophils (103/mL)	4.61± 1.18	4.60 ± 1.07	0.597
Lymphocytes (103/mL)	2.40 ± 0.79	2.48 ± 1.05	0.612
N/L ratio	2.31 ± 0.78	2.28 ± 0.84	0.712
Postoperative 12th hour			
Total leukocytes (103/mL)	13.94±5.06	14.42 ± 4.33	0.453
Neutrophils (103/mL)	10.92 ±4.55	12.60 ± 3.89	0.081
Lymphocytes (103/mL)	1.23 ± 0.81	0.92 ± 1.01	<0.001
N/L ratio	11.21 ± 5.01	22.81 ± 15.24	<0.001
Postoperative 24th hour			
Total leukocytes (103/mL)	11.85±4.30	12.26 ± 3.68	0.417
Neutrophils (103/mL)	9.30 ±3.87	10.71 ± 3.31	0.079
Lymphocytes (103/mL)	1.05 ± 0.69	0.78 ± 0.86	<0.001
N/L ratio	9.53 ± 4.26	19.39 ± 12.95	<0.001
Postoperative 48th hour			
Total leukocytes (103/mL)	10.32±2.45	13.45 ± 5.23	0.003
Neutrophils (103/mL)	6.57 ± 2.05	10.20 ± 5.26	<0.001
Lymphocytes (103/mL)	1.94 ± 0.78	1.90 ± 0.71	0.873
N/L ratio	4.08 ± 1.44	6.77 ± 4.23	0.007

N/L: Neutrophils/Lymphocytes

DISCUSSION

Suppression of cellular immunity in response to surgical stress may cause several negative results due to overproduction of inflammatory mediators. For example, decline in the number of lymphocytes and increase in the number neutrophils are some of the indicators of the development of postoperative infection (12). Changes in lymphocytes that emerge in response to surgical stress have been proved to accompany the release of inflammatory mediators such as interleukin-6 (13). It has often been pointed out that practitioners should consider neutrophil, lymphopenia, and increased neutrophil/lymphocyte ratios in addition to total leukocyte count as a risk factor in the mortality and morbidity of cardiovascular diseases (14, 15). N/L ratio check in the cardiovascular postoperative period does not only provide information about the immunological state but also helps is predicting postoperative morbidity and mortality. In addition to all these advantages, it should also be kept in mind that determining N/L ratio through blood sample taken from peripheral vein is a cheap and practical test.

The results of this study have shown that propofol anaesthesia gives lower N/L ratios at the postoperative 12th and 24th hours compared to desflurane anaesthesia. Thorughout our survey of the literature, we were unable to find a study that provides a decisive

explanation of whether it is high neutrophil levels or low lymphocytes levels that is more effective on the N/L ratios. However, our study has demonstrated that, due to the statistically significantly difference between the two groups, low lymphocyte levels are more effective on the N/L rations compared to high neutrophil levels at the postoperative 12th and 24th hours. N/L ratios can be regarded as a sign of cellular immunity due to their relation to lymphocytes while they may also be associated with inflammatory response because of their relations to neutrophils. It is possible to claim that N/L ratio increases due to remarkable neutrophils when cellular immunity is suppressed. Because of these reasons, the positive model of systemic leukocytes changes can be defined by decreased suppression of cellular immunity, which is itself an indicator of the measure for the lymphocyte count, and a less activated inflammatory response, which is the measure for the neutrophil count (10). In other words, low N/L ratios may be referred to as the intended result (16).

Analysing the preoperative characteristics of the groups in this study, the risk of chronic obstructive pulmonary disease (COPD) is observed to be statistically significantly higher in the propofol group. Rather than a clear relationship between COPD and N/L ratios, there are only studies in the literature that claim increased leukocytes to be an indicator of poor prognosis in COPD (16, 17). Though COPD rate was higher in the propofol anaesthesia group in our study, there were no differences between the basal N/L ratios; but, in the blood picture at the postoperative 12th and 24th hours, we have observed that there were fewer changes with regards to leukocytes in the propofol group than the desflurane group. The hospital stay durations were also lower in the propofol group. In this respect, we can say that propofol anaesthesia is more protective in terms of leucocytic changes and associated prognosis in comparison to desflurane anaesthesia. Despite the fact there were no statistically significant differences between the groups in terms of postoperative MI incidence and the need for inotropic support and intra-aortic balloon pump support, each of which can be regarded as one of the postoperative prognosis criteria, these conditions reared less in the propofol group and this can be considered as a factor behind shorter hospital stays of the patients in the propofol group.

Although there is no defined critical value for neutrophil/lymphocyte ratio in terms of prognosis, a study investigating the prognostic value of N/L ratios on patients who would undergo coronary bypass surgery has reported ratios over 3.36 were associated with low survival rates (9). In another study conducted outside coronary surgery, Neal CP et al. (10) have shown that a N/L ratio of over 5 is the critical value for poor prognosis in resectable colorectal liver metastases. Although our analysis in this study does not resemble to those of the above mentioned studies, we have aimed to underline the effect of the method of anaesthesia on N/L ratios. In previous studies, results similar to our findings have been reported showing propofol and sufentanil anaesthesia to be more effective than sevoflurane anaesthesia in reducing lymphocyte apoptosis rate in partial discectomy surgery (18). Analyses on cytokine responses (7) and auxiliary T1 cells/T2 cells (8) ratios (Th1/Th2) following major surgical procedures have shown that intravenous anaesthesia surgery is more effective than inhalation anaesthesia in terms of reducing adverse immune response induced by stress.

The results of this study have shown that, in contrast to desflurane (inhalation) anaesthesia, propofol (intravenous) anaesthesia has positive but temporary effects on leukocytic changes.

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Correspondence/İletişim

Mustafa ALDEMİR
Afyon Kocatepe Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi Anabilim Dalı, AFYONKARAHİSAR, TURKEY
E-mail: draldemir@yahoo.com

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