The Effects of Sevoflurane, Desflurane and Propofol on the Percentages and Activation Molecules of the Lymphocytes: A Flow Cytometry Analysis of Bronchoalveolar Lavage Fluid

Lenfositlerin Aktivasyon Molekülleri ve Oranları Üzerine Propofol, Desfluran ve Sevofluranın Etkileri: Bronkoalveolar Lavaj Sıvısının Akım Sitometrik İncelemesi

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Geliş Tarihi/*Received:* 16.10.2008
Kabul Tarihi/*Accepted:* 12.03.2009

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ABSTRACT Objective: We aimed to investigate the effects of anesthesia with desflurane, sevoflurane or propofol on the cell surface markers and the activation molecules of the lymphocytes in bronchoalveolar lavage (BAL) fluid via flow cytometry. **Material and Methods:** Sixty patients were scheduled for elective surgery. The patients were divided into three groups (Group D=desflurane, Group S= sevoflurane, Group P= propofol). The same induction agents were used for all groups. The anesthesia was maintained with an inhalation agent (1-1,5 MAC) or propofol (the starting dose 12 $mg.kg^{-1}$ of propofol infusion was reduced to 9, 6 and then 3-6 $mg.kg^{-1}$). BAL was performed immediately after induction of anesthesia and surgical procedure with a fiberoptic bronchoscop. Blood pressures, oxygen saturation, end-tidal CO_2 values and minimum alveolar concentration of agents were recorded. The percentages of the lymphocytes and their activation molecules were determined by flow cytometry in BAL samples. **Results:** The percentages of active cytotoxic T-cells ($CD8^+CD25^+$) and active B cells ($CD19^+$ $HLA\text{-}DR^+$) decreased after desflurane anesthesia. The percentage of cytotoxic T-cells decreased after propofol anesthesia. The anesthesia with sevoflurane had no effect on the percentages and the activation molecules of the lymphocytes in the BAL fluid. **Conclusion:** This study showed that desflurane and propofol decreased either the percentages of the cell surface markers or the activation molecules of the lymphocytes during perioperative period in a tissue sample whereas the sevoflurane had no effect on these parameters. We conclude that sevoflurane has no effect on the lymphocytes in the BAL sample.

Key Words: Bronchoalveolar lavage fluid; desflurane; sevoflurane; propofol; flow cytometry

ÖZET Amaç: Bronkoalveolar lavaj (BAL) sıvısındaki lenfositlerin aktivasyon molekülleri ve hücre yüzey işaretleyicileri üzerine desfluran, sevofluran veya propofol anestezisinin etkilerini akım sitometrik olarak incelemeyi amaçladık. **Gereç ve Yöntemler:** Elektif cerrahi için 60 hasta planlandı. Hastalar üç gruba ayrıldı (Grup D= desfluran, Grup S= sevofluran, Grup P= propofol). Tüm gruplarda aynı indüksiyon ajanları kullanıldı. Anestezi idamesinde inhalasyon ajanı (1-1.5 MAK) ya da propofol (infüzyona 12 $mg.kg^{-1}$ dozunda başlanıp, 9, 6 ve daha sonra 3-6 $mg.kg^{-1}$'a azaltıldı) kullanıldı. Anestezi indüksiyonu ve cerrahi girişimden hemen sonra fiberoptik bronkoskop ile BAL yapıldı. Kan basınçları, oksijen saturasyonu, end-tidal karbondioksit değerleri ve ajanların minimum alveolar konsantrasyonları kaydedildi. BAL örneğindeki lenfosit oranları ve aktivasyon molekülleri akım sitometri ile değerlendirildi. **Bulgular:** Desfluran anestezisinden sonra aktif sitotoksik T hücreleri ($CD8^+CD25^+$) ve aktif B hücrelerinin ($CD19^+$ $HLA\text{-}DR^+$) oranları düştü. Propofol anestezisinden sonra sitotoksik T hücrelerinin oranları düştü. Sevofluran anestezisinin BAL sıvısındaki lenfositlerin aktivasyon molekülleri ve oranları üzerine etkisi görülmedi. **Sonuç:** Bu çalışma perioperatif dönem esnasında bir doku örneğinde desfluran ve propofolün lenfositlerin aktivasyon molekülleri ya da hücre yüzey işaretleyicilerinin oranlarını değiştirdiğini, sevofluranın ise bu parametreler üzerine etkisinin olmadığını göstermiştir. BAL örneğindeki lenfositler üzerine sevofluranın en az etkili ajan olduğu sonucuna vardık.

Anahtar Kelimeler: Bronkoalveolar lavaj sıvısı; desfluran; sevofluran; propofol; akım sitometri

doi:10.5336/medsci.2008-9364

Turkiye Klinikleri J Med Sci 2011;31(2):443-9

Anesthesia and surgery acutely alter the function of the immune system through a multifactor process, including fear, tissue injury, hypothermia, drugs and blood transfusions, pain, infection, hyperglisemia and increased stress. Each of these factors effects the immune system, either by enhancing the inflammatory response or by suppressing adaptive immunity after surgery.[1-5] Decreased function of the adaptive immunity in the early days following surgery is often due to a decrease in total lymphocyte counts, altered T-cell subsets, diminished lymphocyte proliferation, and a shift to the T-helper type 2 (Th2) cytokine profile.[6,7]

Immune dysfunction due to anesthesia and surgery cannot be evaluated properly because of insufficient number of human studies. Most of the studies about anesthetic-related immune response were either in vitro or in peripheral blood cells. These studies differ in design, in the subpopulations of leukocytes and in the terms of various pathophysiological constellations investigated, and thus offer conflicting results.[1,8-12] Peripheral blood samples could not reflect immunological activity precisely as the response in the tissue.

The expression of CD25 on lymphocytes, the α chain of the IL-2 receptor, is accepted as an activation marker on the activated T cells. The expression of HLA-DR on lymphocytes may also be used as another activation marker for T and B lymphocytes. The changes of these activation molecules within time might demostrate the functional capacity of the lymphocytes under different conditions such as drugs and infections, as reflecting the immune response.[6,13]

We could not find any studies about the effects of propofol, sevoflurane and desflurane on the blood cells in bronchoalveolar lavage (BAL), a tissue-derived sample, in the literature. We have studied the in vivo effects of various anesthetic agents on the cell surface markers and the activation molecules of the lymphocytes in BAL via four color flow cytometry.

MATERIAL AND METHODS

This study was approved by the local ethics committee of the Selcuk University, Meram Medical Faculty. All study patients gave their written informed consents. Between September 2006 and February 2007, 60 ASA physical status I patients, between 18 and 40 years of age scheduled for elective plastic and reconstructive surgery were studied. Exclusion criteria were malignant or chronic inflammatory disease, anaemia (hemoglobin < 10 g dl^{-1}), cardiovascular or respiratory disease, smoking, endocrine and immune system disease, hepatic or renal disease, and chronic therapy with, or abuse of, benzodiazepines or opioids. The patients were randomly assigned to one of three groups (Group D= Desflurane, Group S= Sevoflurane, Group P= Propofol, n= 20 each). Patients were premedicated with intramuscular (im) diazepam (10 mg) and atropine (0.5 mg) one hour before surgery. The heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP), oxygen saturation (SpO_2), end-tidal CO_2 ($ETCO_2$) values and minimum alveolar concentration (MAC) of desflurane and sevoflurane were continuously monitorized. Anesthesia was induced with 2-3 mg. kg^{-1} propofol (Propofol 1% Fresenius Kabi ®) and 1 mcg.kg^{-1} fentanyl (Fentanyl citrat USP Abbott®) administered intravenously (IV), and muscle relaxation was achieved with rocuronium bromide (0.6 mg.kg^{-1}, Esmeron Organon®). Then the trachea was intubated. The patients were ventilated with a lung protective ventilation strategy [V_T= 8-10 ml.kg^{-1}, 10-12 /min, PEEP= 4 cm H_2O, peak airway pressure=15-20 cm H_2O (Drager Primus)]. Anesthesia was maintained with either volatile anesthetics (1-1.5 MAC desflurane or sevoflurane in 50% O_2-air, total flow 4 L.min^{-1}) or propofol. For the propofol group, anesthesia was maintained with 12 mg kg^{-1} h^{-1} propofol for the first 20 min, 9 mg kg^{-1} h^{-1} for the second 20 min, 6 mg kg^{-1} h^{-1} for the third 20 min and titrated doses of 3-6 mg kg^{-1} h^{-1} thereafter. In all groups, neuromuscular block was maintained with intermittant doses of rocuronium (0.2 mg.kg^{-1}). Nitrous oxide was not used in either group. SBP, DBP, SpO_2, $ETCO_2$, MAC of the desflurane and sevoflurane were recorded at 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120th minutes.

Bronchoalveolar lavage was performed from right middle lobe in all patients immediately after induction of anesthesia (t0) and after surgical procedure (t1) by a fiberoptic bronchoscop (Karl Storz

11302 BD1). The anesthetist who performed BAL procedure was blinded to the anesthetics used in this study.

In order to evaluate the cell surface markers and the activation molecules of the lymphocytes, bronchoalveolar lavage samples were obtained in Falcon tubes. After the centrifugation of the BAL fluid (approximately 20-30 ml), 100 μL of the sediment sample aliquots were mixed with subpopulation-specific or activation marker-specific monoclonal antibodies. Immunophenotyping of the BAL cells was performed by using the panel of monoclonal antibodies (Moab) directed against human antigens. The following combination of mouse antihuman Moabs (listed in Table 1) were used: $CD4^+$-FITC/$CD8^+$-PE/$CD3^+$-PERCP/$CD25^+$-APC and $CD3^+$-FITC/$CD19^+$-PE/$CD45^+$-PERCP/HLA-DR^+-APC (Becton Dickenson, California, USA). Four color staining of cells was performed to determine the expression of activation markers such as CD25, HLA-DR by CD4+, CD8+ and HLA-DR by CD19+ cells, and to assess the percentage of CD3+ cells that expressed CD4 and CD8. After 20 minutes of incubation at room temperature, erythrocytes were lysed by adding 2 mL hypotonic lysing solution. The suspension was washed twice in phosphate buffered saline (PBS) plus 1% bovine albumin, suspended in 400 μL fixation solution and analyzed at flow cytometry (Becton Dickenson, FACS Calibur II, California, USA). Data were analyzed using CellQuest software for the BD FACS Calibur II.

Lymphocytes were identified and gated by forward (FSC) and side (SSC) light scattering properties. An analytical gate were used for precise discrimination of the desired lymphocytes (Figure 1). The percentages of the lymphocytes and activation marker expressions were assessed as follows: Total T-cell population ($CD3^+$), helper T-cell population ($CD3^+$ $CD4^+$), cytotoxic T-cell population ($CD3^+$ $CD8^+$), B cell population ($CD19^+$), the expressions of activation markers on total T cells ($CD3^+$ $CD25^+$ and $CD3^+$ HLA-DR^+), helper T cells ($CD4^+$ $CD25^+$), cytotoxic T cells ($CD8^+$ $CD25^+$) and B cells ($CD19^+$ HLA-DR^+). The flowcytometer operator was blinded to the anesthetics being used in the samples.

TABLE 1: Description of monoclonal antibodies used for immunophenotyping of lymphocytes and their activation molecules.

Monoclonal antibody specificity	Major function/marker of	Clone
CD45	Common leukocyte antigen	2D1
CD3	T cells	SK7
CD4	T cell subset	SK3
CD8	T cell subset	SK1
CD19	B cells	SJ25C1
CD25	Activation marker for T cells	2A3
HLA-DR	Activation marker for T and B cells	L243

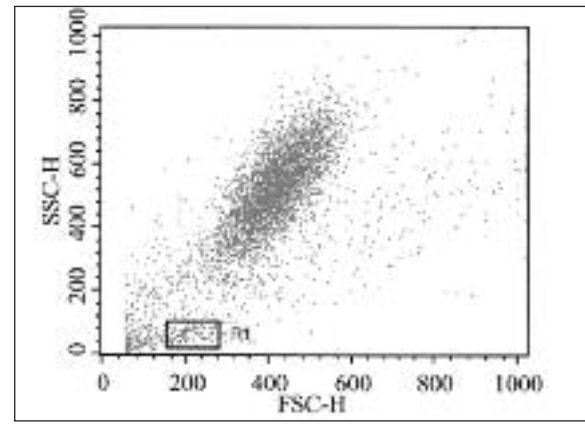

FIGURE 1: The identification of the lymphocytes and gating by forward (FSC) and side (SSC) light scattering properties. R1: The analytical gate used for the lymphocytes.

Data are expressed as the mean ± standard deviation (SD) or median (25-75% percentile). A P-value less than 0.05 was considered as statistically significant. Normality analysis was assessed with the Shapiro-Wilk Test. Age and weight showed a normal distribution after Shapiro-Wilk Test. Age and weight were analyzed by one way ANOVA. A Shapiro-Wilk test indicated a non-normal distribution of height, duration of anesthesia and differences of the percentage of the cell surface markers and the activation molecules of the lymphocytes. Kruskal-Wallis analysis was used for the analysis of height and duration of anesthesia. The Wilcoxon Signed Ranks Test was used for the analysis the percentage of the cells surface markers and the activation molecules of the lymphocytes within the groups before and after anesthetic exposure. Sex was analyzed by Chi-Square test. SPSS for Windows statistical package was used.

RESULTS

The demographic data are summarized in Table 2. Sex, age, weight, height and duration of anesthesia were similar in all groups (P> 0.05).

There were no significant differences among the groups for HR, SBP, DBP, SpO_2 or $ETCO_2$ values.

The effects of anesthesia on the surface markers of the lymphocytes in BAL fluid within the groups:

The anesthesia with desflurane had no effect on the percentages of total T cells, helper T-cells, cytotoxic T cells and B cells (Table 3).

The percentage of cytotoxic T-cells decreased after propofol anesthesia (P= 0.019) (Figure 2) whereas anesthesia had no effect on the percentages of total T cells, helper T-cells and B cells (Table 4).

The anesthesia with sevoflurane had no effect on the percentages of the lymphocytes (Table 5).

The effects of anesthesia on the activation molecules of the lymphocytes in BAL fluid within the groups:

The anesthesia with desflurane had no effect on the activation molecules on total T-cells and helper T-cells. The active cytotoxic T-cells ($CD8^+$ $CD25^+$) and active B cells ($CD19^+$ $HLA\text{-}DR^+$) decreased after desflurane anesthesia (P= 0.049 and P= 0.028, respectively) (Figures 3 and 4).

The percentage of active cytotoxic T lymphocytes ($CD8^+$ $CD25^+$) decreased after propofol anesthesia but the differences were not found to be statistically significant (P= 0.07). The anesthesia with propofol had no effect on activation molecules on the total T-cells, helper T-cells or B cells (Table 4).

The anesthesia with sevoflurane had no effect on the activation molecules on the lymphocytes (Table 5).

DISCUSSION

In the present study, we have studied the in vivo effects of desflurane, propofol and sevoflurane on the percentages of the surface markers and the activation molecules of the lymphoctes in BAL fluid. A homogenous population of healthy patients (ASA I) were selected undergoing equal type of minimal invasive surgery, and a standard lung protective mechanical ventilation procedure was used. The main results of our study are: (*i*) the percentages of active cytotoxic T-cells ($CD8^+$ $CD25^+$) and active B cells ($CD19^+$ $HLA\text{-}DR^+$) decreased after desflurane anesthesia, (*ii*) the percentage of cyto-

TABLE 2: The characteristics of the patients.

	Group D	Group S	Group P	P
Sex (Male/Female)	12/8	16/4	11/9	> 0.05
Age (year)	32.9 ± 8.1	31.4 ± 8.5	32.6 ± 8.6	> 0.05
Weight (kg)	71.2 ± 12.2	71.8 ± 11.5	69.5 ± 13.8	> 0.05
Height (m)	1.72 (1.62-1.76)	1.72 (1.65-1.75)	1.65 (1.58-1.72)	> 0.05
Duration of anesthesia (min)	130 (120-140)	130 (122-138)	132 (120-140)	> 0.05

Data are median (25 %-75 % percentile) for height and duration of anesthesia, mean ± SD for age and weight or number of patients for sex.

TABLE 3: The comparison of the lymphocyte subsets and the activations markers of the lymphocytes in the BAL fluid after induction of anesthesia (t0) and after surgical procedure (t1) in the desflurane group. Values are presented as median (25-75 % percentile).

	CD3+	CD19+	CD3+ CD4+	CD3+ CD8+	CD 3+ HLA-DR+	CD 3+ CD25+	CD4+ CD25+	CD8+ CD25+	CD19+ HLA-DR+
t0	0.10 (0-0.1)	0.10 (0-0.4)	0.20 (0-0.5)	2.25 (0-5.3)	0.46 (0.1-1.1)	0.14 (0-0.5)	0.16 (0-1.0)	0.95 (0-9.5)	0.55 (0.1-1.4)
t1	0.07 (0-0.4)	0.04 (0-0.2)	0.21 (0-0.5)	1.45 (0-5.3)	0.36 (0-0.9)	0.09 (0-0.4)	0.10 (0-0.7)	1.00 (0-2.7)*	0.31 (0-0.7)*

* p< 0.05 indicates significance compaired with t0 within the group.

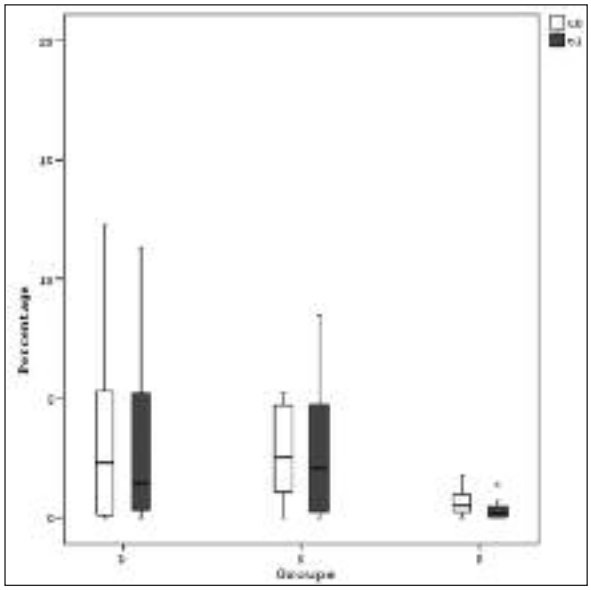

FIGURE 2: The percentage of cytotoxic T lymphocytes after induction of anesthesia (t0) and after the surgery (t1).

* Indicates significance (p= 0.019) compaired with t0 within the group.

toxic T-cells decreased after propofol anesthesia, and (*iii*) the anesthesia with sevofurane had no effect on the percentages and the activation molecules of the lymphocytes in the BAL fluid. This study showed that desflurane and propofol altered either the percentages of the cell surface markers or the activation molecules of the lymphocyte during perioperative period in a tissue sample. Sevoflurane had no effect on these parameters.

The percentage of IL-2Rα (CD25+) on the T cell, which is also expressed on the activated cytotoxic T cells, was tound reduced after surgery in group D (P< 0.05) and P (P= 0.07) but not in group S. These findings may indicate a disturbed activation of lymphocytes after the anesthesia with desflurane and propofol, and suggest that the activation of the cytotoxic T cells was effected by the anesthesia with desflurane and propofol. The percentage of HLA-DR expression on B cells, which may also be used as a marker of activation molecule, reduced after surgery in group D but not in group P and S. This finding may indicate that desflurane has also an effect on another activation molecule (HLA-DR) of the lymphocytes. According to these results we assumed that the effects of desflurane on the activation markers of the lymphocytes in BAL fluid was more pronounced than propofol. The suppressing effects of desflurane on active T and B cells had been observed in BAL. We did not observe the same effects with sevoflurane. This observation may correlate with the fact that sevoflurane should be chosen for inhalation anesthesia in patients with pulmonary infection because this study showed that sevoflurane had no effect on the percentages and the activation markers of lymphocytes.

Schneemilch et al.[13] compared the immune effects of total intravenous anesthesia (propofol, sufentanil) with balanced inhalation anesthesia

TABLE 4: The comparison of the lymphocyte subsets and the activations markers of the lymphocytes in the BAL fluid after induction of anesthesia (t0) and after surgical procedure (t1) in the propofol group. Values are presented as median (25 %-75 % percentile).

	CD3+	CD19+	CD3+ CD4+	CD3+ CD8+	CD 3+ HLA-DR+	CD 3+ CD25+	CD4+ CD25+	CD8+ CD25+	CD19+ HLA-DR+
t0	0.14 (0-0.6)	0.25 (0-0.3)	0.23 (0-0.5)	0.47 (0-0.9)	0.46 (0.2-1.0)	0.33 (0-0.5)	0.49 (0-0.6)	3.70 (1-6.8)	0.63 (0.2-1.3)
t1	0.08 (0-0.6)	0.16 (0-0.6)	0.03 (0-0.2)	0.15 (0-0.5)*	0.34 (0.1-1.1)	0.09 (0-0.3)	0.16 (0-0.5)	0.85 (0-3.3)	0.51 (0-1.06)

* p< 0.05 indicates significance compaired with t0 within the group.

TABLE 5: The comparison of the lymphocyte subsets and the activations markers of the lymphocytes in the BAL fluid after induction of anesthesia (t0) and after surgical procedure (t1) in the sevoflurane group. Values are presented as median (25 %-75 % percentile)

	CD3+	CD19+	CD3+ CD4+	CD3+ CD8+	CD 3+ HLA-DR+	CD 3+ CD25+	CD4+ CD25+	CD8+ CD25+	CD19+ HLA-DR+
t0	0.08 (0-0.7)	0.10 (0-0.3)	0.25 (0-0.6)	2.50 (0-4.7)	0.35 (0.1-1.1)	0.15 (0-0.4)	0.19 (0-0.5)	1.85 (0.8-4.8)	0.37 (0.1-0.7)
t1	0.20 (0-0.7)	0.01 (0-0.1)	0.16 (0-0.4)	2.05 (0-5.2)	0.42 (0.1-1.1)	0.12 (0-0.2)	0.18 (0-0.5)	1.35 (0-4.0)	0.24 (0-0.5)

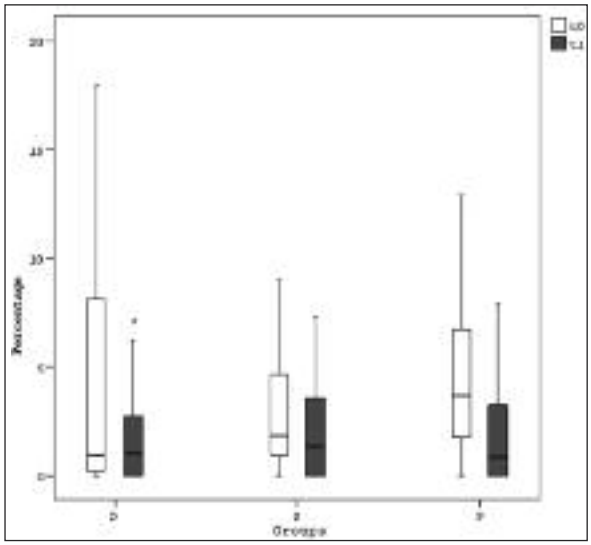

FIGURE 3: The percentage of active cytotoxic T lymphocytes after induction of anesthesia (t0) and after the surgery (t1).
* Indicates significance (p= 0.049) compaired with t0 within the group.

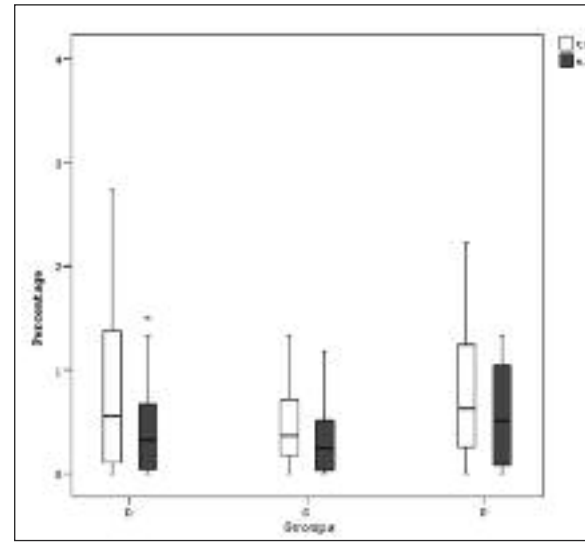

FIGURE 4: The percentage of active B lymphocytes after induction of anesthesia (t0) and after the surgery (t1).
* Indicates significance (p= 0.028) compaired with t0 within the group.

(sevoflurane, N_2O, fentanyl) in minor surgery. They found that the absolute number of $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes, the expression of HLA-DR and activation markers such as CD25, CD26 and CD69 decreased more in response to balance inhalation anesthesia. The expression of the activation molecules reduced statistically significantly three days after sevoflurane anesthesia, and the expression of HLA-DR on peripheral blood mononuclear cells (PBMC) showed a decrease on the third postoperative day. In contrary, the current study showed that sevoflurane had no effect on BAL fluid cells. This condition can be explained by the fact that the same agent may act differently on BAL cells, which is a tissue derived sample, than peripheral blood cells. Because they show the direct effects of the agents, experiments conducted on tissue fluids may be considered as more valuable. Since the changes in peripheral blood may be affected by multiple factors, the reflection these changes in the peripheral blood in the tissue is unpredictable. In addition, we showed that the expressions of CD25 on the cytotoxic T-cells and the expression of HLA-DR on the B cells decreased after desflurane anesthesia. We could not find any other studies investigating the effects of the desflurane on the immune function in BAL cells.

Inada et al.[14] reported that the number of $CD4^+$ T lymphocytes in peripheral blood did not change significantly after surgery with either propofol or isoflurane. Isoflurane was not used as an anesthetic agent in our study. Our findings in propopol group are similar with the results of Inada et al. In addition, the effects of desflurane and sevoflurane on $CD4^+$ T lymphocytes in BAL have not been reported. In the current study, both sevoflurane and desflurane did not change the number of $CD4^+$ T lymphocytes. According to these results, we assume that the effects of these agents on $CD4^+$ T lymphocytes in peripheral blood and in BAL can be considered as similar. On the other hand, the suppressing effects of desflurane on cytotoxic T lymphocytes and B lymphocytes in BAL may contribute to pulmonary infection. We did not observe these suppressing effects with sevoflurane. Our findings are in accordance with the other studies which indicate that sevoflurane is the inhalation agent that affected the immune system the least.[1,15,16] This observation may correlate with the fact that sevoflurane might also be choosen for inhalation agent in patients with pulmonary infection.

Schneemilch et al.[13] similarly showed that $CD8^+$ T cells were unchanged with propofol whe-

reas the number of $CD3^+$ T cells, $CD4^+$ T cells and $CD19^+$ B cells increased two hours after surgery in the peripheral blood. On the contrary, this study demonstrated that propofol suppressed the $CD8^+$ T cells, and had no effect on the $CD3^+$ and $CD4^+$ T cells and $CD19^+$ B cells. These findings reflect the different effects of the same agent on the different tissue samples such as peripheral blood and BAL fluid. Although propofol which is an intravenous anesthetic agent decreased the percentage of $CD8^+$ T lymphocytes, sevoflurane which is an inhalation agent had no effect on the BAL fluid. We conclude that sevoflurane is an agent that affected tissue immune system the least.

There is no human data suggesting that the immunosupressive effects of volatile anesthetics are harmful to patients, according to Schneemilch et al.'s report.[6] This can be explained by the difficulty of separating the effects of volatile anesthetics from other immune supressive events in the perioperative process, such as surgery itself or the transfusion of blood and also by the design of the studies such as peripheral blood experiments.[6] The suppression of immune response may have minor importance in subjects with normal immune system but it may have relevance in patients with a preexisting immune dysfunctions. At the same time, the desflurane-propofol related effects shown in the present study may be transient. The limitation of our study is that we are not able to take BAL in the postoperative period. A better understanding of the immunological properties of commonly used anesthetic drugs in the postoperative period might enhance their use to improve patient safety in the long term. Further studies including the investigations in the postoperative period are needed to explain the time-dependent effects of anesthetic agents on immune system.

Acknowledgements

The author would like to thank Prof. Said Bodur for his excellent help and support in statistics.

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