# Oxidant and antioxidant activities of different anesthetic techniques

## *Propofol versus desflurane*

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## ABSTRACT

**الأهداف:** فحص العلاقة بين عقار بروبوفول وعقار ديسفلوران على ضوء الحالة خلال التأكسد للدهون ونشاط مضادات الأكسدة، والبحث عن تقنية ممكنة لتخدير مضادات للأكسدة.

**الطريقة:** أجريت هذه الدراسة بقسم التخدير والإنعاش – كلية الطب بجامعة سليمان ديميرال – اسبارتا – تركيا، خلال الفترة ما بين يناير 2006م وحتى يوليو 2006م. تم تقسيم عدد 30 مريضاً ASA I–II، تراوحت أعمارهم ما بين 19–55 عاماً على مجموعتين، والذين يخضعون لعملية جراحية اختيارية تحت التخدير العام، المجموعة–P بتلقي عقار بروبوفول، والمجموعة–D باستنشاق ديسفلوران، عقب التحريض القياسي. تم قياس نسبة مالوندیالدیهید (MDA)، جلوثاتيون أثناء التأكسد (GSH)، ديسموتاس فوق التأكسد (SOD)، وتوكوفيرول (فيتامين–E) على التوالي، عند الساعة الأولى قبل العملية الجراحية وفي الساعة الثانية عشرة بعد العملية الجراحية.

**النتائج:** تبين أن (MDA) كان أقل في الساعة الأولى قبل العملية الجراحية في المجموعة–P مقارنة مع المجموعة–D $p<0.05$. في المجموعة–D كان مستوى فيتامين–E منخفض بشكل ملحوظ قبل العملية الجراحية مقارنة مع الفترة بعد العملية الجراحية $p=0.001$.

**خاتمة:** لقد لاحظنا أن جهد التأكسد المنتظم مع عقار ديسفلوران يزداد على ضوء مستويات (MDA)، خمود مشتقات الدهون أثناء التأكسد ونشاط التأكسد الذاتي بواسطة فيتامين–E عند فترة قبل العملية الجراحية فقط. قد يتم تحديد هذه الدراسة فقط من أجل دعم حقيقة أن جذور الأكسجين الحرة تم تخليصها بواسطة عقار ديسفلوران أكثر من عقار بروبوفول.

**Objectives:** To investigate the correlation between propofol and desflurane in terms of lipid peroxidation and antioxidant activity and to search the possible antioxidant anesthesia technique.

**Methods:** The study was performed in the Department of Anesthesia and Reanimation, Medical Faculty, Suleyman Demirel University, Isparta, Turkey, between January 2006 and July 2006. Thirty, ASA I–II patients, with an age range of 19-55 years, undergoing elective surgery under general anesthesia were randomized to receive either propofol infusion (Group P) or desflurane inhalation (Group D) following standard induction. Malondialdehyde (MDA), glutathione peroxidase (GSH), super oxide dismutase (SOD) and alpha-tocopherol (Vitamin E) were measured preoperatively, at peroperatively first hour and postoperatively 12-hour.

**Results:** Malondialdehyde was found lower peroperatively in Group P compared to Group D ($p<0.05$). In Group D, Vitamin E levels were decreased significantly peroperatively compared to preoperative period ($p=0.001$).

**Conclusion:** We observed a systemic oxidative stress increment with desflurane by terms of MDA; a lipid peroxidation product and endogenous antioxidant activity suppression by terms of Vitamin E at only peroperative period. This study may be defined to support the fact that free oxygen radicals were released more by desflurane than propofol.

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Trauma, surgical intervention and anesthesia modify immune functions and contribute to posttraumatic and postoperative disorders.[1] Surgical stress usually induces the pathologic effects of oxidative stress, predominantly caused by an imbalance between the generation of reactive oxygen species and the antioxidant defense system. Oxygen free radicals, which include malondialdehyde (MDA), hydrogen peroxide, and hydroxyl radicals, cause "oxidative stress." Diminished antioxidative defenses, and super oxide dismutase, catalase, and glutathione (GSH), also contribute to oxidative stress.[2] Antioxidant activities of anesthetic agents may be of clinical importance. Propofol is increasingly used as an anesthetic and sedative agent in the operating room and in the intensive care unit.[3] Recently, antioxidant functions of propofol have been demonstrated in vitro and in vivo.[4,5] Though, at the organ and cellular levels, propofol has been shown to attenuate oxidant injury in myocardial tissue,[6] mitochondria, brain synaptosomes,[7] erythrocyte membranes[8,9] and hepatocyte suspensions;[10] and clinical trials on desflurane are still limited. Animal study assessing oxidative stress produced by desflurane was published recently.[11] The aim of this study is to evaluate the correlation between propofol and desflurane in terms of lipid peroxidation (as measured by MDA) and antioxidative response (as measured by GSH, SOD and Vitamin E) in a randomized double-blinded manner.

**Methods.** The study was performed in the Department of Anesthesia and Reanimation, Medical Faculty, Suleyman Demirel University, Isparta, Turkey between January 2006 and July 2006. After obtaining approval of the Süleyman Demirel University Ethical Committee and written informed consent, 30 ASA (American Society of Anesthesiologists) physical status I–II patients aged 19-55 that was scheduled to undergo elective surgery under general anesthesia was enrolled in this study. Exclusion criteria were malignant or chronic inflammatory diseases, diabetes mellitus, renal dysfunction, auto-immune disease, concurrent medication with anti-inflammatory, immuno-suppressant agents and antioxidant agents or a history of allergy to propofol or desflurane. All patients were assessed preoperatively; on the operation morning premedication was performed by oral diazepam 0.1 mg $kg^{-1}$ for each patient. All patients were attached to standard monitoring device; including heart rate (HR), blood pressure, peripheral oxygen saturation ($SpO_2$), electrocardiogram and end-tidal partial pressure of carbon dioxide ($EtCO_2$). Patients were prospectively randomized by the hospital pharmacy using a computer-generated randomization to receive either desflurane inhalation (n=15, Group D) or propofol (n=15, Group P) infusion regimen for anesthesia maintenance. A standard anesthesia induction was performed for each patient. After an initial dose of 0.5-1 μg $kg^{-1}$ remifentanyl administered over 30-60 seconds; anesthesia was induced with 2-3 mg $kg^{-1}$ propofol, and endotracheal intubation was performed with 0.2 mg $kg^{-1}$ cisatracurium besylate in all cases. Maintenance of anesthesia was performed with 6% desfluran with a 50% mixture of nitrous oxide and oxygen in Group D and in Group P, propofol infusion was started with 8 mg $kg^{-1}h^{-1}$ dosage and reduced to 6 and 4 mg $kg^{-1}h^{-1}$, at 10 min intervals. Remifentanil infusion (0.25 μg $kg^{-1}min^{-1}$) was initiated in all groups in terms of peroperative analgesia management, and the dosage was rearranged according to patient's hemodynamic response. Vecuronium 0.025 mg $kg^{-1}$ was given every 30 minutes until the last 30 minutes of the operation. The radial artery was cannulated to collect blood samples for serum biochemical analysis before and after anesthesia. Blood samples were obtained preoperatively, first hour peroperatively and 12 hours postoperatively in order to measure the levels of MDA, GSH, SOD and Vitamin E. Samples were separated by centrifugation at 1200 rpm within 45 minutes of venesection and stored at -20 °C until they were assayed.

For analyzing lipid peroxidation (MDA) the serum was treated with 8.1% sodium lauryl sulfate, 20% acetic acid, and 0.8% thiobarbituric acid (TBA) and heated in a boiling water for one hour. After cooling, n-Butanol: pyridine (15:1, v:v) was added. After vigorously shaking the mixtures for one minute, samples were centrifuged for 10 minutes at 2600 rpm. The absorbance of the butanol phase was measured spectrophotometrically at 532 nm and the results were expressed as μmol L-1. All biochemical parameters in homogenates were studied on the same day. Measurement of gluthation peroxidase (GSH-Px) activity was performed by using the Ransel Kit (Randox Company) and the RA-XT autoanalyser (Technicon, Tarrytown, NY, USA). The results are presented in U $L^{-1}$. Measurement of superoxide dismutase (SOD) activity was performed by the Cobas Mira autoanalyser (Roche, Lucerne, Switzerland). The results are presented in $Ug^{-1}$ $Hb^{-1}$. For measurement of alpha-tocopherol (Vitamin E) following adding 250 μL serum, 50 μL internal standard and 500 μL precipitation solution in a 1.5 ml reaction tube homogen mixture was performed at 2-8$^0$C and incubated 30 minutes. After incubation, mixture was centrifuged for 10 min and then was injected to high performance liquid chromatography (HPLC) system.

For statistical analysis, data were given as mean values ± standard deviation. An inter-group comparison of patient characteristics was performed using Chi-square test. One-way analysis of variance was

performed for analyzing the biochemical values derived in 3 time periods. Least significant differences (Tukey HSD, Bonferroni) and Dunnett T3 test were used for intergroup comparison of these biochemical values. The significance level was set at $p<0.05$ for all statistical tests.

**Results.** All patients were hemodynamically stable throughout the procedure and all patients completed the study. There were no significant differences among groups overtime in HR, arterial mean pressure, End-tidal carbon dioxide concentration in the expired air ($ETCO_2$), saturation of peripheral oxygen ($SpO_2$), and respiratory rates. The demographic data, which were matched for gender, age, weight, height and operation time are shown in **Table 1**. There were no statistically significant differences in all groups ($p>0.05$). The mean levels of MDA, SOD, GSH and Vitamin E and statistical comparisons between preoperative-intraoperative and preoperative-postoperative periods in both groups were given in **Table 2**. Malondialdehyde levels did not change statistically significantly in Group D and Group P in the peroperative and postoperative periods comparing to preoperative period. When 2 groups were compared; MDA found lower in the peroperative period in Group P compared to Group D ($p<0.05$). Malondialdehyde alteration between groups is shown in **Figure 1**. Superoxide dismutase and GSH levels did not exhibit statistically significant alterations both throughout the study periods within each group and between the groups. Superoxide dismutase and GSH alterations between groups are shown in **Figures 2 and 3**. Vitamin E levels were decreased significantly in Group D in peroperative period compared to preoperative period ($p=0.001$) (**Figure 4**). In Group P Vitamin E levels did not alter in 3 interval times. When compared with Group P to Group D in terms of Vitamin E, no significant alteration was shown.

**Table 1 -** Demographic characteristics, perioperative, and postoperative data.

| Demographic characteristics | Group D (n=15) | Group P (n=15) | *P* values |
|---|---|---|---|
| Male/Female | 6 / 9 | 7 / 8 | 0.7* |
| Age (years) | 32.4 ± 8.5 | 32.4 ± 12.7 | 0.9† |
| Weight (kg) | 70.2 ± 12.7 | 69.2 ± 7.7 | 0.8† |
| Height (cm) | 168.4 ± 10.3 | 169.5 ± 9.3 | 0.7† |
| Operation time (minutes) | 96 ± 22.2 | 108 ± 30.5 | 0.2† |

*Mann-Whitney U test, †Independent samples t-test

**Discussion.** The findings of this study suggest that Desflurane may cause higher lipid peroxidation compared to propofol by means of MDA. In the

**Table 2 -** Malondialdehyde (MDA), superoxide dismutase (SOD), gluthatione peroxidase (GSH), Vitamin E (Vit E) mean levels in Group D and Group P, and statistical comparisons between preoperative-intraoperative and preoperative-postoperative periods.

| Parameters of the study | Group D | [a]*P* value | Group P | [b]*P* value |
|---|---|---|---|---|
| Preoperative MDA (nmol/g Hb) | 107.92 ±19.89 | - | 108.89±21.63 | - |
| Intraoperative MDA (nmol/g Hb) | 116.81±21.40 | 0.579 | 102.69±12.81 | 0.630 |
| Postoperative MDA (nmol/g Hb) | 115.01±30.20 | 0.705 | 107.06±19.57 | 0.959 |
| Preoperative SOD (U/g Hb) | 465.39±47.16 | - | 473.40±50.91 | - |
| Intraoperative SOD (U/g Hb) | 477.17±34.60 | 0.731 | 487.99±66.76 | 0.745 |
| Postoperative SOD (U/g Hb) | 493.65±44.78 | 0.176 | 482.32±43.01 | 0.895 |
| Preoperative GSH (mg/g Hb) | 1.68±0.27 | - | 1.50±0.61 | - |
| Intraoperative GSH (mg/g Hb) | 1.62±0.44 | 0.948 | 1.47±0.61 | 0.987 |
| Postoperative GSH (mg/g Hb) | 1.78±0.78 | 0.865 | 1.35±0.38 | 0.726 |
| Preoperative Vit E (mg/L) | 13.20±3.02 | - | 9.69±2.21 | - |
| Intraoperative Vit E (mg/L) | 9.79±1.89 | 0.001 | 9.05±1.93 | 0.687 |
| Postoperative Vit E (mg/L) | 11.11±2.43 | 0.074 | 9.35±2.16 | 0.903 |

[a] significance value of group D between preoperative-intraoperative, and preoperative-postoperative.
[b] significance value of group P between preoperative-intraoperative, and preoperative-postoperative.

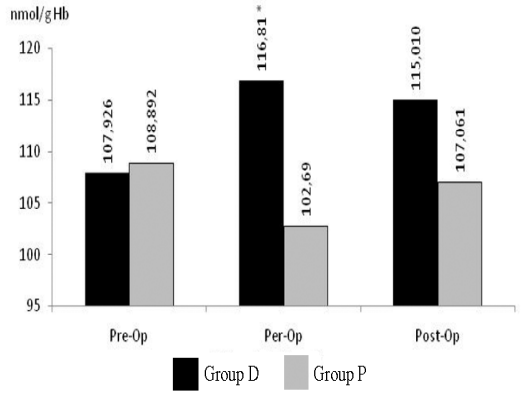


**Figure 1 -** Changes of malondialdehyde (MDA), values in the pre-per and postoperative periods. *$p$<0.05 desflurane group (group D, n=15) and compared with propofol group (group P, n=15). Pre-op - preoperative, per-op - perioperative, post-op - postoperative

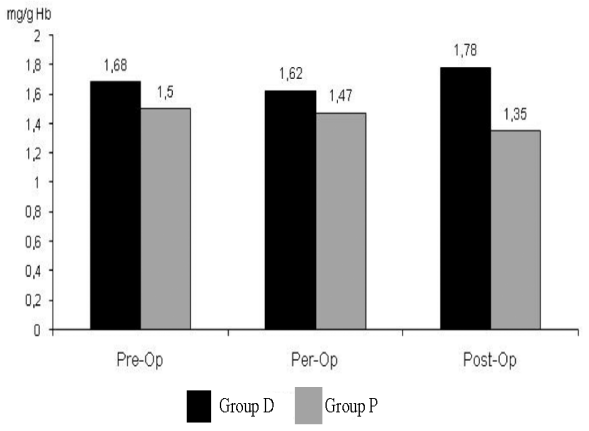


**Figure 3 -** Changes of glutathione peroxidase (GSH), values in the pre-, per- and post- operative periods. *$p$<0.05 desflurane group (group D, n=15) and compared with propofol group (group P, n=15). Pre-op - preoperative, per-op - perioperative, post-op - postoperative

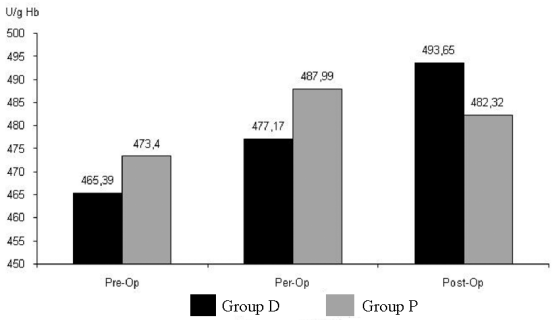


**Figure 2 -** Changes of superoxide dismutase (SOD), values in the pre-, per-, and post- operative periods. *$p$<0.05 desflurane group (group D, n=15) and compared with propofol group (group P, n=15). Pre-op - preoperative, per-op - perioperative, post-op - postoperative

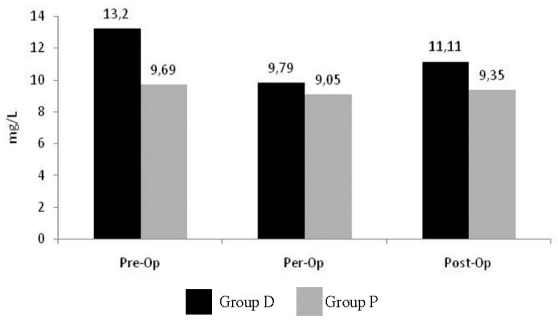


**Figure 4 -** Changes of alpha-tocopherol (Vitamin E), values in the pre-, per- and post- operative periods. *$p$<0.05 desflurane group (group D, n=15) and compared with propofol group (group P, n=15). Pre-op - preoperative, per-op - perioperative, post-op - postoperative

present study this difference was observed significantly in the peroperative period. The effects of all agents might be higher in the preoperative period and the oxidant effect of Desflurane also might have exhibited highest manner in this period. Vitamin E levels were decreased significantly in desflurane group in peroperative period compared to preoperative period. Propofol and Desflurane did not exhibit antioxidative response difference compared to each other. In this present study, antioxidant consumption was statistically significant in desflurane group in preoperative period but we have not observed difference by this term between 2 groups. Wider series may be required for evaluating Vitamin E consumption difference between different anesthetic agents. The main limitation of our study is performing induction of anesthesia with propofol in both of the groups although maintenance was performed by different anesthetic agents. We have preferred to use propofol for induction in both of the groups since desflurane can cause complications such as coughing, increased secretions, laryngospasm, apnea, and oxyhemoglobin desaturation if it is used for an inhalation induction in adults. Also our sample size was small, the results might be more significant if the size was greater. The antioxidant potential of propofol has been shown in many situations. The agent decreases secretion of proinflammatory cytokines, alters the expression of nitric oxide, impairs monocyte and neutrophil functions, and has potent, dose-dependent radical scavenging activity similar to the endogenous antioxidant vitamin E.[12] In a clinical trial planned to evaluate the effects of propofol, desflurane, and sevoflurane on the systemic redox balance in patients undergoing laparohysterectomy; MDA levels decreased slightly throughout the study periods in propofol group and increased in desflurane group.[13] In our study, MDA exhibited significant decrease between groups in the preoperative period, but no difference was shown within groups throughout study periods. Since propofol has been used widely for anesthesia during

surgical procedures and for sedation of patients;[14] we performed a standard induction with propofol in both groups. Then, maintenance was performed both with inhalation (Desflurane) and total intravenous anesthesia (Propofol) oxidative and antioxidative response between 2 different anesthetic techniques was compared Dikmen's experimental study evaluating the free radical metabolism, hepatocellular enzymes and histopathological changes in desflurane and sevoflurane exposure rats has demonstrated that sevoflurane might cause more cellular damage than desflurane by causing higher activation of free radical metabolizing enzymes.[11] This in vitro study is controversial to the clinical trials indicating the oxidative property of desflurane. Our present study is one of the few clinical trials comparing an intravenous general anesthetic with a volatile one. We did not observe statistically significant differences between groups in the postoperative period. Relying upon the fact that MDA is one of the end products in lipid peroxidation and is both an indicator and effector of oxidative stress,[2] this study may be defined to support the fact that free oxygen radicals were released more by desflurane than propofol. The other free radicals, SOD and GSH, which we have been researched, did not differ significantly both between groups and during the study periods according to basal values. The antioxidant property of anesthetic agents have been measured by terms of SH groups and GSH in a majority of these experimental and clinical trials. The antioxidant vitamin E plays a role in the endogenous defenses against the peroxidation of membrane lipid.[15] Alpha tocopherol is a potent antioxidant that effectively protects biological membranes against oxidative injury through coordination with ascorbic acid. In an animal study planned to examine the effect of propofol on oxidative injury of human erythrocytes; the investigators concluded that propofol interacts with ascorbic acid, thereby exhibiting potent antioxidant activity in and around membranes as does alpha-tocopherol.[9] In an another experimental study, the presence of DNA damage with repeated sevoflurane anesthesia and the genoprotective role of antioxidant supplementation on DNA damage in mononuclear leukocytes of rabbits by highly sensitive comet assay was pointed out.[16] We did not meet clinical studies investigating the effects of general anesthetics on endogenous antioxidant alpha tocopherol consumption. In the present work, vitamin E levels were decreased throughout the study periods in desflurane group but not changed significantly in propofol group. This may be related to the fact that antioxidant effect of propofol was believed to be related to the structural similarity to alpha-tocopherol.[17,18] It is worth paying attention to decrease of an endogenous antioxidant after exposure to an inhalation anesthetic agent in a short time period. In a long time period, Sardas et al[19] carried out a study to estimate the genoprotective role of antioxidant supplementation in technical anesthesiology staff working in operating theatres and Vitamin E (300 mg/day) plus vitamin C (500 mg/day) was supplemented to staff for 12 weeks. The results showed that vitamin E supplementation significantly decreased possible oxidative DNA damage caused by occupational exposure to anesthetic gases.[19]

In conclusion, present findings of our study support the previous studies' data indicating desflurane's oxidative stress inducing capacity. A newer finding of this study is the fact that the Vitamin E consumption enhances in desflurane group throughout the exposure period. But the comparison of desflurane with other inhalation and intravenous agents by this term needs further clinical trials. The role of exposure time may be investigated.

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