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ORIGINAL

Comparison of The Effects of Low Flow Desfluran and High Flow Desfluran on Oxidative Stress and DNA Damage in Anesthesia Applications

Comparación de los efectos del desflurano de bajo flujo y del desflurano de alto flujo sobre el estrés oxidativo y el daño del ADN en aplicaciones anestésicas

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Abstract

Background: Studies have reported that volatile anesthetics may affect genotoxic and oxidative stress in the present study, we aimed to compare low and high flow anesthesia techniques in terms of DNA damage and oxidative stress.
Methods: We included 60 patients who underwent high and low flow desflurane anesthesia, and those who underwent low and high flow anesthesia were categorized in Groups I (n=31) and II (n=29), respectively. The hemodynamic and respiratory parameters of the patients were recorded and 8-OhdG (8-hydroxy deoxyguanosine) values for DNA (deoxyribonucleic acid) damage, MDA(Malondialdehyde), cystatin C, TAS (total antioxidant status), TOS (total oxidative status), and LPO (lıpıd peroxıd) values for oxidative stress were measured from the blood samples collected from the patients preoperatively, intraoperatively at the third hour and at the postoperative twenty-fourth hour.
Results: Postoperative MDA value was significantly higher in the high flow group than in the low flow group ($p<0.05$). There was no significant intergroup difference in terms of TAS, TOS, cystatin C, LPO and 8 OhdG values ($p>0.05$).
Conclusion: In conclusion, MDA values, an indicator for oxidative stress, increased significantly in high flow desflurane application. There was no intergroup difference in terms of DNA damage.

Key words: Low flow anesthesia, oxidative stress, DNA damage.

Resumen

Antecedentes: Estudios han reportado que los anestésicos volátiles pueden afectar el estrés genotóxico y oxidativo en el presente estudio, nos propusimos comparar técnicas de anestesia de bajo y alto flujo en términos de daño al ADN y estrés oxidativo.
Métodos: Se incluyeron 60 pacientes sometidos a anestesia con desflurano de alto y bajo flujo, y los sometidos a anestesia de bajo y alto flujo se clasificaron en los grupos I (n=31) y II (n=29), respectivamente. Se registraron los parámetros hemodinámicos y respiratorios de los pacientes y los valores de 8-OhdG (8-hidroxi desoxiguanosina) para el daño del ADN (ácido desoxirribonucleico), MDA (Malondialdehído), cistatina C, TAS (estado antioxidante total), TOS (estado oxidativo total), y LPO (lıpıd peroxıd) valores de estrés oxidativo se midieron a partir de las muestras de sangre recogidas de los pacientes preoperatoriamente, intraoperatoriamente a la tercera hora y en el postoperatorio de veinticuatro horas.
Resultados: El valor postoperatorio de MDA fue significativamente mayor en el grupo de alto flujo que en el de bajo flujo ($p<0,05$). No hubo diferencias significativas entre los grupos en cuanto a los valores de TAS, TOS, cistatina C, LPO y 8 OhdG ($p>0,05$).
Conclusiones: En conclusión, los valores de MDA, un indicador de estrés oxidativo, aumentaron significativamente en la aplicación de desflurano a alto flujo. No hubo diferencias intergrupales en cuanto al daño del ADN.

Palabras clave: Anestesia de bajo flujo, estrés oxidativo, daño en el ADN.

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Introduction

low-flow anesthetic techniques are becoming more popular both here and abroad. The main drivers of this growth include benefits like increased economic output, a decrease in the ecosystem-damaging effects of greenhouse gases, and increased physiological heat and humidity loss[1]. Low-flow anesthesia applications have been made possible by high-standard anesthetic equipment and monitors.

The imbalance between insufficient antioxidant cell defense and the generation of reactive oxygen species (ROS), which results in molecule damage, is known as oxidative stress[2]. Oxidative stress is exacerbated by aging, inflammatory conditions, cancer, degenerative disorders, and drug exposure (including xenobiotics and anesthetics)[3]. Anesthesia-induced oxidative stress can have an impact on DNA, proteins, and lipids. Lipids are the ones that are most vulnerable to oxidation[4]. Plasma MDA levels are the most popular method used in investigations to assess the oxidative stress brought on by anesthetics[5]. TAS and TOS are additional oxidative stress indicators.

The majority and most mutagenic of the >20 oxidative base damage products produced by ROS in DNA is 8-OhdG (8-hydroxydeoxyguanosine)[6]. Most research[7] have relied solely on 8-OHdG as a measure of oxidative DNA damage.

There aren't many research on humans comparing the effects of low and high flow desflurane anesthesia on oxidative stress and DNA damage. In this study, desflurane was used as an inhaler agent to examine the effects of low flow and high flow anesthetic procedures on DNA damage and oxidative stress.

Materials and methods

Study Design, Population, and Data

This study was planned as a prospective randomized controlled trial. An informed consent form was signed by all patients included in the study. Approval was obtained from the Dicle University Ethics Committee dated 25.03.2021 and numbered 187. An informed consent form was signed by all patients included in the study Patients who did not want to participate in the study and who wanted to leave while the study was ongoing were excluded. The study was planned in accordance with the 2008 Declaration of Helsinki. All patients included in the study were provided detailed information related to the study, and their written informed consent was obtained. The randomization sequence was generated by a computerized random number generator and sealed in numbered envelopes.

Sixty patients with an ASA score of I–II and between the ages of 17-70 years, who were to undergo general anesthesia with desflurane, were included in the study. Patients aged <17 and >70 years, patients with liver and/or kidney failure, obese patients (BMI >30), trauma patients, ASA III-IV patients, patients with bleeding disorders, those using drugs that may affect the coagulation system, patients with cardiomyopathy, cerebrovascular disease, immobility, and malnutrition were excluded from the study.

Preoperative and intraoperative routine

Blood samples were collected from the patients 30 minutes before the operation. After intravenous (i.v.) premedication with 1.5 mg midazolam, standard anesthesia monitoring (ECG, noninvasive blood pressure, peripheral O_2 saturation, temperature) was performed on the operating table. Before the induction of anesthesia, preoxygenation was applied at a rate of 4 L/min for 3 minutes to all patients. Furthermore, 1 mcg/kg fentanyl for anesthesia induction, 2 mg/kg propofol IV, and 0.6 mg/kg rocuronium bromide (Esmeron Organon, The Netherlands) i.v. as a neuromuscular blocker were administered within 20-30 seconds. All patients were manually ventilated with 100% O_2 until endotracheal intubation was performed after the drugs administered. Intubation was performed with a cuffed endotracheal tube of the appropriate diameter for the patient's age and body structure. After intubation, ventilation was performed in volume control mode with a Dräger Primus (Dräger, Medizintechnik, Germany) anesthesia device adjusted to tidal volume 6-8 ml/kg, respiratory frequency 12-16/min, PEEP 5-8 cm H_2O. Soda-lime (Sorbolime, Berkim, Turkey) was used as CO_2 absorbent in the anesthesia machine.

The patients were randomly divided into two groups. In both groups, the total gas flow (TGF) was set to 4L/min (FiO_2: 50%, air: 50%) and the desflurane volume was 7% until MAC (minimum alveolar concentration) was 1 in the maintenance of anesthesia.

In the low flow anesthesia group (Group I), TGF: 0.5 L/min (FiO_2: 70%, Air: 30%) was continued and the desflurane percent volume was set to MAC: 1.

In the high flow anesthesia group (Group II), TGF was continued at 4 L/min (FiO_2: 50, Air: 50%) and the desflurane volume was adjusted to to MAC: 1.

In both groups, blood was collected from the patients in the same way at the 3rd hour of the operation. In the last 30 minutes of the operation, Tramadol Hydrochloride 100 mg i.v, paracetamol 1 gr i.v and dexketoprofen 50 mg i.v were administered for postoperative analgesia. In the high flow anesthesia group, after the last skin suture was placed, the inhalation agent was turned off and 100% O_2 was started. The fresh gas flow was opened at 8 L/min. In the low flow anesthesia group, the inhalation agent was turned off 20 minutes before the end of the surgical period. The flow was continued at 0.5 L/

min until the last skin suture was placed, and then the fresh gas flow was turned on at 4 L/min. After starting spontaneous respiration, the patients in both groups were administered 0.03 mg/kg neostigmine and 0.01 mg/kg atropine intravenously and they were extubated. After the operation, the patients were collected to the postoperative care unit.

Blood was taken from the patients in both groups at the postoperative 24th hour with the same method. Respiratory parameters, hemodynamic data, and anesthesia durations of the patients included in the study were recorded. The blood taken from the patients in the perioperative period was centrifuged and was stored at -80°C.

In our study, lipid hydroperoxide (Catalogue No: 201-12-0727), cystatin C (Catalog No: 201-12-1105), 8-OHdG (Catalogue No: 201-12-1437) and MDA (Catalogue No: 201-12- 1372) levels were evaluated by ELISA method.

TAS levels were measured by automatic measurement method using 2,2'-Azinobis (3-ethylbenzothiazoline 6-sulfonic acid) in accordance with the method of Erel et al. The results were expressed as micromole Trolox® equiv./L[8].

TOS levels were measured using Erel's TOS method, which is based on the measurement of color change that occurs after the oxidants in the samples oxidize Fe+2 to Fe+3, and the amount of oxidant substances with the kits used by spectrophotometric methods. The results were expressed as micromoles of H_2O_2 equiv./L[9].

Statistical Analysis

The necessary sample size was evaluated utilizing G-Power software. Assuming a one-tailed alpha error of 0.05, power of 0.80, an allocation ratio of N2/N1=1, and an effect size of 0.8, the minimum number of patients needed was 42 (21 in the Low Flow group and 21 in the High Flow group).

The statistical analysis was conducted using Windows-compatible SPSS 16.0 software. Categorical data are expressed as frequency and percentage, whereas continuous data are expressed as mean and standard deviation. The Fisher's exact test and the chi-square test were used to compare the category data. The distribution of the numerical data was examined using the Kolmogorov-Smirnov test. Data with a normal distribution were examined using the Student's t-test, while data with an abnormal distribution were examined using the Mann-Whitney U test. All comparisons were deemed significant if $P<0.05$.

Results

A total of 62 patients were included in the study. Since 2 patients in group 2 were discharged early, their postoperative blood samples could not be taken. Therefore, these two patients were excluded from the study and the study was completed with 60 patients. The mean age of the patients enrolled in the study was 36.35±15.5 years. The demographic data of the patients are shown in **table I**. There was no significant intergroup difference in terms of age, BMI, sex, ASA score, preoperative and intraoperative hemodynamics and respiratory parameters ($p>0.05$).

Table I: Demographic data of patients.

Characteristic	Group 1 (n = 31)		Group 2 (n = 29)		p value
	Frequency	Percent	Frequency	Percent	
Sex					**0.46**
Female	11	35.5	13	44.8	
Male	20	65.5	16	55.2	
ASA*					0.62
I	13	41.9	14	48.3	
II	18	58.1	15	51.7	
Total	31	51.7	29	48.3	
	Mean±Std		Mean±Std		
Age	36.45	16.37	36.24	14.99	0.95
BMI**	23.31	2.82	25.03	3.82	0.052
AI0***	82.8	10.92	79.79	12.6	0.32
AI30	72.12	10.99	72.58	12.28	0.88
AI90	68.25	10.75	66.68	10.61	0.57
MAP0****	99.51	12.27	96.31	14.03	0.13
MAP30	74.86	15.84	77.1	15.26	0.5
MAP90	72	9.28	76.41	13.27	0.13
$SPO_2$0*****	98.19	1.72	98.44	1.5	0.63
$SPO_2$30	98.54	1.12	98.37	2.07	0.49
$SPO_2$90	98.32	1.24	98.41	1.47	0.58
$ETCO_2$0******	32.93	3.8	33.14	4.84	0.54
$ETCO_2$30	31.74	2.7	30.85	2.46	0.19
$ETCO_2$90	32.38	2.87	30.51	3.57	0.032

*ASA:American Society of Anesthesiologist; **BMI:Body Mass Index; ***AI:Apical Impulse;
****MAP; Mean Arterial Pressure; *****SPO_2:Oxygen Saturation; ******$ETCO_2$:End Tidal Carbon Dioxide

When groups I and II were compared in terms of $ETCO_2$ values, $ETCO_2$ values at the 90th minute were found to be statistically significantly higher in group 1 (**Figure 1**) (p=0.032).

When groups I and II were compared in terms of preoperative, intraoperative, and postoperative TAS and TOS values, there was no statistically significant difference between the groups (p>0.05) (**Table II**). The TOS value measured at the third hour intraoperatively was higher in Group 2, but the difference was not statistically significant (p = 0.05).

When groups were compared on preoperative, intraoperative, and postoperative MDA values, there was no statistically significant difference between the groups on preoperative and intraoperative MDA values (p>0.05), but the MDA values at the postoperative 24th hour were statistically significantly higher in group 2 (p=0.048) (**Table III**).

When groups were compared on preoperative, intraoperative, and postoperative LPO and Cyt C values, there was no statistically significant difference (p>0.05) (**Table III**). In general, LPO and Cyt c values were higher in group 2, but the difference was not statistically significant.

When both groups were compared in terms of preoperative, intraoperative, and postoperative 8-OhdG values, there was no statistically significant difference (p>0.05) (**Table IV**). The 8-OhG values at the intraoperative 3rd hour were higher in group 2 but the difference was not statistically significant. (p=0.052)

Figure 1: Variation of Mean $ETCO_2$ Values Over Time According to the Given Flow.

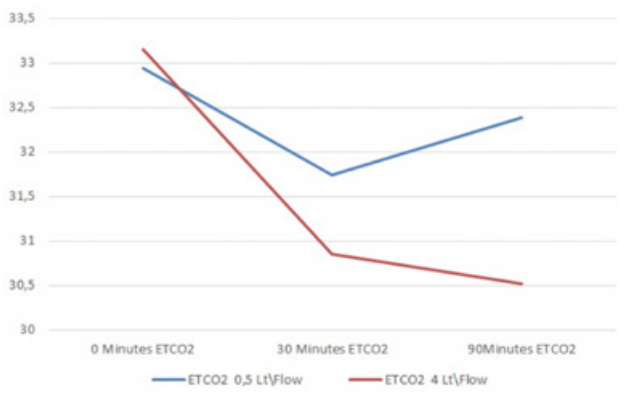

Table II: Comparison of groups in terms of total antioxidant status and total oxidant status values.

Characteristic	Group 1 (n=31) Mean±Std		Group 2 (n=29) Mean±Std		p value
TAS* Preoperative	1.55	0.27	1.52	0.32	0.66
TAS Intraoperative	1.59	0.4	1.60	0.22	0.13
TAS Postoperative	1.55	0.28	1.62	0.36	0.4
TOS** Preoperative	18.09	16.77	24.24	3.11	0.16
TOS Intraoperative	18.96	17.68	36.59	48.62	0.050
TOS Postoperative	20.54	25.59	62.33	119.56	0.14

*TAS:Total Antioxidant Status, **TOS:Total Oxidant Status

Table III: Comparison of groups in terms of lipid peroxide, malondialdehyde, and cystatin C values.

Characteristic	Group 1 (n=31) Mean±Std		Group 2 (n=29) Mean±Std		p value
LPO* Preoperative	24,57	23,47	35,34	32,75	0,41
LPO Intraoperative	24,52	24,28	37,52	32,91	0,13
LPO Postoperative	23,11	24,18	38,09	34,33	0,06
MDA** Preoperative	25,19	19,85	34,47	28,96	0,34
MDA Intraoperative	26,36	20,54	37,35	30,43	0,14
MDA Postoperative	23,21	19,95	35,79	28,98	0,048
Cyt c*** Preoperative	28,82	21,45	34,80	25,82	0,53
Cyt c Intraoperative	28,29	21,52	37,87	25,15	0,18
Cyt c Postoperative	25,33	18,76	35,64	26,48	0,33

*LPO: Lipid Peroxide, **MDA:Malondialdehyde and ***Cyt c:Cystatin C

Table IV: Comparison of groups in terms of 8-hydroxydeoxyguanosine values.

Characteristic	Group 1 (n=31) Mean±Std		Group 2 (n=29) Mean±Std		p value
Preoperatif 8-OHdG	23.25	22.13	33.88	30.16	0.12
Intraoperative 8-OHdG	24.27	22.56	36.51	30.55	0.052
Postoperative 8-OHdG	22.25	22.03	35.44	29.84	0.15

*8-OHdG: 8-hydroxydeoxyguanosine

Discussion

In this work, we evaluated the effects of low flow and high flow desflurane anesthesia on oxidative stress and DNA damage. We discovered that the high flow desflurane group had considerably higher postoperative MDA levels than the low flow group. Although the hemodynamic characteristics of our patients were similar, we discovered that the low flow group had a considerably higher 90th minute $ETCO_2$ value. The two groups did not vary when we analyzed DNA damage and other oxidative stress indicators.

As is well known, membrane lipids are the components of cells that suffer the most harm from free oxygen radicals. MDA, a byproduct of lipid peroxidation, is utilized as a sign of damage brought on by oxidative stress[10] Allaouchiche et al. evaluated MDA levels after giving desflurane and propofol to pigs in their study. Animals treated with desflurane had considerably greater MDA concentrations than those treated with propofol, according to the researchers[11]. Desflurane and sevoflurane anesthesia were contrasted in laparoscopic cholecystectomy patients by Köksal et al. They noted that systemic and local lipid peroxidation as well as MDA levels were significantly greater in the desflurane administered group[12] Nevertheless, Kantekin et al. looked into how desflurane at various flow rates affected oxidative stress and free radicals in rats. The researchers separated the rats into three groups and found that the high flow desflurane group had considerably greater serum, brain, and liver MDA and SOD levels than the other groups[13]. We found results in our investigation that were comparable to those of Kantekin et al. Patients who underwent high flow desflurane anesthesia exhibited significantly greater MDA levels than the low flow desflurane group at the 24-hour postoperative mark.

The occurrence of hyperoxia in high flow anesthetic treatments is unavoidable. In cell culture and ischemia reperfusion experiments, hyperoxia results in an increase in ROS[14,15,16]. As a result, we believe that one of the reasons of oxidative stress is the high flow anesthetic approach. Because the increase in oxidative stress measures can be explained by high FiO_2 exposure, given that the desflurane MAC values in our study groups were equal. As the level of breathed oxygen declines as the fresh gas flow is lowered, the patient's risk of hypoxia rises. Obata et al. reported in their investigation that sufficient oxygen levels were given during maintenance with FiO_2 set at 30% to prevent hypoxia[17]. In our study, we determined that the minimum inspired oxygen concentration should be 32%. None of our patients experienced clinical hypoxia.

The study by Yüce et al., in which they analyzed individuals who were to have thyroid and parathyroid surgery, must be emphasized when the studies in the literature on TAS, Cyct-C, LPO, and TOS, which are other markers of oxidative stress, are examined. In this investigation, the patients were split into two groups and given desflurane at rates of 0.5 L/min and 1 L/min, respectively, to examine the preoperative, intraoperative, and postoperative oxidative stress markers. At the first postoperative hour, the TAS and Cyct-C were statistically significantly lower in the 0.5 L/flow group than in the 1 L/flow group. There was no discernible difference between the two groups' TAS and CYct-C levels at the postoperative 24th hour[18] The preoperative, intraoperative, and postoperative TAS, CYct-c, LPO, and TOS values in our investigation, however, did not show a statistically significant difference.

Desflurane-related genotoxicity has been noted in investigations on the production of DNA damage by anesthetics when cells are exposed to desflurane in vitro. Halothane, isoflurane, sevoflurane, and desflurane are volatile anesthetics that Kaymak et al. reported to cause DNA damage in cells in their in vitro tests. However, no genotoxic effect was found at any desflurane exposure dose when sperm cells were evaluated[19]. Desflurane can increase genotoxicity in a dose-dependent manner, as Karpinski et al. demonstrated in their experimental investigation[20] Akin et al. demonstrated in a related investigation that desflurane exposure increases sister chromatid exchange in human cells. As a result, they stated that exposure to large doses of desflurane may result in genetic harm[21]. However, Branz et al investigations. 's examining the genotoxic effects of inhaler (isoflurane and sevoflurane) and intravenous (i.v.) anesthetic drugs (propofol) found no indication of DNA damage[22]. In order to assess the local genotoxicity of sevoflurane and desflurane in bronchoalveolar cells and to identify systemic DNA damage, Zafer et al. measured 8-OHdG levels in preoperative and postoperative bronchoalveolar lavage and serum samples from patients who were scheduled to undergo lumbar discectomy. They discovered no discernible change in 8-OHdG levels or comet properties between the two groups. But compared to the baseline levels, they discovered a significant rise in both the sevoflurane and desflurane groups[23]. Nogueira et al. examined desflurane-air and desflurane-60% N_2O anesthesia maintenance techniques in their prospective randomized clinical investigations and discovered no significant differences in the biomarkers assessed for DNA damage[25]. There was no discernible change in the blood levels of 8-OHdG across the groups in Kantekin et al study's on rats (Group 1: control group; Group 2: patients treated desflurane at an 8 L/min flow rate; Group 3: patients administered desflurane at a 2 L/min flow rate). Both groups' levels of 8-OHDG in brain and liver tissue were greater than those in the control group[14]. Our study's findings are consistent with those of Kantekin et al. In our investigation, we were unable to find a significant difference between the two groups' serum 8-OHdG levels. Elmacolu et al. divided patients into three groups according to fresh gas flow rate as medium flow (2 L/min), low flow (1 L/flow), and minimum flow (0.5 L/flow) after taking into account studies in

the literature examining the effects of low and high flow inhaled agents on hemodynamic and respiratory parameters. In terms of hemodynamics, there was no statistically significant difference between the groups[25] In patients receiving one-lung ventilation, Geyik et al. compared the effects of 1L/min and 2L/min desflurane anesthesia on hemodynamic parameters, arterial blood gas values, and gas consumption. They discovered that $EtCO_2$ was statistically significantly lower in the 2L/flow group, particularly between 30 and 75 minutes of one-lung ventilation[26] This outcome is comparable to what we found in our investigation. In our investigation, there was no hemodynamic distinction between the two groups. Only at 90 minutes did the $ETCO_2$ levels between the two groups differ significantly. The low flow group was found to have considerably greater $ETCO_2$. Rebreathing during the use of low flow anesthetic was assumed to be the cause. In conclusion, in our study, there was no difference in terms of DNA damage in patients who were administered low flow desflurane anesthesia compared to the patients who were administered high flow desflurane, but the oxidative stress in the group administered high flow desflurane increased at the postoperative 3rd hour.

This study has some limitations. First, it was a single-center study. Secondly, the number of our patients was not high enough. This issue warrants multicenter and multidisciplinary studies with more patients.

Considering the use of safe anesthesia devices, its positive effects on the ecological system, the decrease in the amount of economically used volatile agent, the formation of a more suitable mucociliary clearance, and the reduction of heat-moisture loss, we recommend the use of low flow anesthesia with close monitoring of the patient.

Conflicts of interest

The authors declare no conflicts of interest.

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