Original Article

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The Effects of Intraoperative Oxygen used at Different Concentrations on Oxidative Stress Markers: A Randomized Prospective Study

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Abstract

Aim: In the case of hypoxia, despite the definite benefit of oxygen (O_2) administration, there is controversial evidence regarding the risk/benefit balance of high concentration O_2 inhalation during surgery as a precaution in those not previously hypoxic. The purpose of this study was to determine the effect of inspiratory O_2 (FiO_2) administered at different concentrations on oxidative stress during general anesthesia.

Methods: This randomized prospective study was conducted from February to May 2021. According to intraoperative FiO_2, the patients were divided into two groups: 50% FiO_2 (group 1) and 30% FiO_2 (group 2). Blood samples taken before preoxygenation and at the end of surgery were used to assess arterial partial O_2 pressure (PaO_2), total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI).

Results: The study was completed with 40 patients. Intragroup plasma TOS, OSI, and PaO_2 levels increased significantly at the end of surgery (group 1 p=0.003, 0.003, <0.001, and group 2 p=0.002, 0.044, 0.002) and TAS levels decreased (p<0.001 in both groups) were found. Because of intergroup surgery, TAS, TOS, and PaO_2 levels were higher in group 1 than in group 2 (respectively p=0.002, 0.002, <0.001).

Conclusion: Since the use of high concentrations of O_2 (50%) causes a significant increase in oxidative stress, we think that it is important to use lower concentrations of O_2 in the intraoperative period in suitable patients. More research is urgently needed on perioperative O_2 therapy.

Keywords: Inspiratory oxygen concentrations, oxidative stress index, total antioxidant status, total oxidant status

Introduction

Oxygen (O_2) is the most common drug that's used during general and regional anesthesia. High concentrations of O_2 are applied to prevent tissue hypoxia, especially during the induction and extubation phases of general anesthesia (1,2). It is known that the application of high concentrations of O_2 in the perioperative period can cause various complications (3-7). In the case of hypoxia, despite the definite benefit of O_2 administration, there is controversial evidence regarding the benefit/risk balance of high concentration O_2 inhalation during surgery as a precaution in those not previously hypoxic (3-9). Morkane et al. (10) reported that the amount of O_2 administered intraoperatively to adult patients undergoing major surgery varies greatly [inspiratory O_2 (FiO_2): 25-100%]. The intraoperative administration of O_2 differs widely in clinical practice.

In the plasma, reactive O_2 species (ROS) formed by the partial reduction of O_2 molecules, antioxidant components that inhibit the harmful effects of ROS also exist. The ratio of total oxidant status (TOS) to total antioxidant status (TAS) is the oxidative stress index

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(OSI), which is an indicator of oxidative stress (11-14). ROS are produced because of normal metabolism in cell organelles, particularly mitochondria, or for reasons such as ischemia-reperfusion, aging, radiation, high O_2 pressure, inflammation, and exposure to chemical agents (14-16). In a meta-analysis involving more than 16,000 patients, it was reported that liberal O_2 therapy in adults increases mortality and that supplemental O_2 administration with peripheral O_2 saturation (SpO_2) above 94-98% may also have adverse consequences (17). It has been reported (in laparoscopic surgery) that screening for TAS, TOS, and OSI in procedures with ischemia-reperfusion injury can be used as biochemical parameters in routine, in order to not only prevent oxidative injury but also provide a better treatment option (14). It is known that hyperoxia is a risk factor that increases patients' morbidity and mortality in intensive care units (18). Additionally, it has been reported that excessive ROS production can cause considerable organ damage in both *in vivo* and *in vitro* experiments via oxidative stress (19). The mechanism of action of oxidative stress related to high FiO_2 in inducing the formation of ROS in patients undergoing surgery hasn't been understood yet (20). Additionally, the methods to predict the benefit-risk balance of hyperoxia in such patients are not well identified yet. Currently, there is limited data describing intraoperative O_2 administration by anesthetists. The purpose of this study was to determine the effect of FiO_2 administered at different concentrations on oxidative stress during general anesthesia.

Materials and Methods

Compliance with Ethical Standards

Our study was conducted in the Zonguldak Bulent Ecevit University operating room from February to May 2021, after the approval of the Zonguldak Bulent Ecevit University Non-Invasive Clinical Research Ethics Committee (protocol number: 2021/01, ClinicalTrials.gov Identifier: NCT05099523) and the obtaining of written consent from the patients. The consolidated standards of reporting trials flow diagram was used for patient enrollment (Figure 1) (21).

Patient Population

A total of 40 patients over 18 years old who had American Society of Anesthesiologists (ASA) status I-II, under elective conditions, and under general anesthesia that lasted over 1.5 hours (h) were included in the study. The exclusion criteria were the existence of any cardiovascular, metabolic, severe hepatic, or renal diseases; malignancies; pregnancy; and the usage of drugs with antioxidant properties such as vitamin E-C, acetylcysteine in the last 48 hours, and patients requiring intraoperative 100% O_2 inhalation.

Application of General Anesthesia and Monitoring

The heart rate (HR), non-invasive mean arterial pressure (MAP), and SpO_2 of the patients taken onto the operating table were monitored. In all non-premedicated patients, vascular access was established with a 20-gauge (6) granule and saline infusion was initiated. Allen's test was performed for arterial blood gas analysis of the patients breathing room air, and if possible, a 20 G granule was placed in the radial artery, and the patency of the granule was maintained by intraoperative intermittent heparinization.

In the preoxygenation phase, 100% O_2 was applied to all patients for a duration of 3 minutes, and anesthesia induction was performed with propofol, fentanyl, and rocuronium. In our study, randomization was achieved by the sealed envelope method. According to their intraoperative FiO_2 ratio, the patients were divided into two groups: group 1 was for those with 50% FiO_2, and group 2 with 30% FiO_2. During the maintenance of anesthesia, remifentanil infusion was applied to all patients, and by selecting the automatic gas control mode of the same anesthesia device, ventilation was achieved in accordance with 2% sevoflurane, tidal volume of 8 mL kg^{-1}, and end-tidal carbon dioxide of 35-45 mmHg. During tampon insertion into the nose, the study was terminated by the halt of anesthetic gases. Then, manual ventilation was performed at a flow rate of 8 lt min 1 with 100% O_2, and the patients who started spontaneous respiration were extubated after reversal with neostigmine and atropine (0.05 and 0.01 mg kg 1, respectively).

In our study, it was planned that iv 5-10 mg ephedrine would be administered when MAP decreased more than 20% compared to control, iv 0.5 mg atropine when HR decreased below 50 beats per min, and in the case of SpO_2 below 93%, FiO_2 was planned to be increased to 100% O_2.

Data Management

Hemodynamic measurements in our study were recorded at 5-minute intervals before preoxygenation and after anesthesia induction until the end of surgery. Two different types of blood samples taken from all patients via radial artery cannula before preoxygenation (T0) and at the end of surgery (O_2 just before the concentrations were changed, T1) were transferred to the biochemistry laboratory of our hospital for a short time in a cold environment with the aim of studying their arterial partial O_2 pressure (PaO_2) with TAS, TOS, and OSI values. Samples on which oxidative parameters would be studied were separated by centrifugation at 4000 rpm, 45 minutes after the vessel puncture, and then stored at -20 °C until testing.

Measurement of Oxidant and Antioxidant Stress Markers

TAS and TOS were measured using commercially test kits (Rel Assay Diagnostics kit; Mega Tip, Gaziantep, Turkey) according to the manufacturer's instructions and using their reagents and equipment. The results of the TAS were expressed as mmol of Trolox Eq L^{-1}, whereas the results of the TOS were expressed as μmol H_2O_2 Eq L^{-1}. OSI was calculated using the formula OSI= [(TOS, μmol H_2O_2 Eq L-1)/(TAS, μmol Trolox Eq L-1) × 100] (22,23).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 23.0 (IBM SPSS Inc. Chicago, IL, USA) program. Compliance with the normal distribution was evaluated using the Shapiro-Wilk test. The chi-square test was used to compare categorical variables according to the groups. To evaluate the effects of the group and time main effectors and of their interactions on HR, MAP, and SpO_2 values, the generalized linear model method was used, and Bonferroni correction was used for multiple comparisons. In the comparison of normally distributed data based on the groups, the Independent two-sample t-test was used, and the Mann-Whitney U test was used to compare the non-normally distributed data. The paired two-sample t-test was used to compare the normally distributed data according to time within the group, and the Wilcoxon signed-rank test was used to compare the non-normally distributed data. Analysis results were presented as mean quantitative data ± standard deviation.

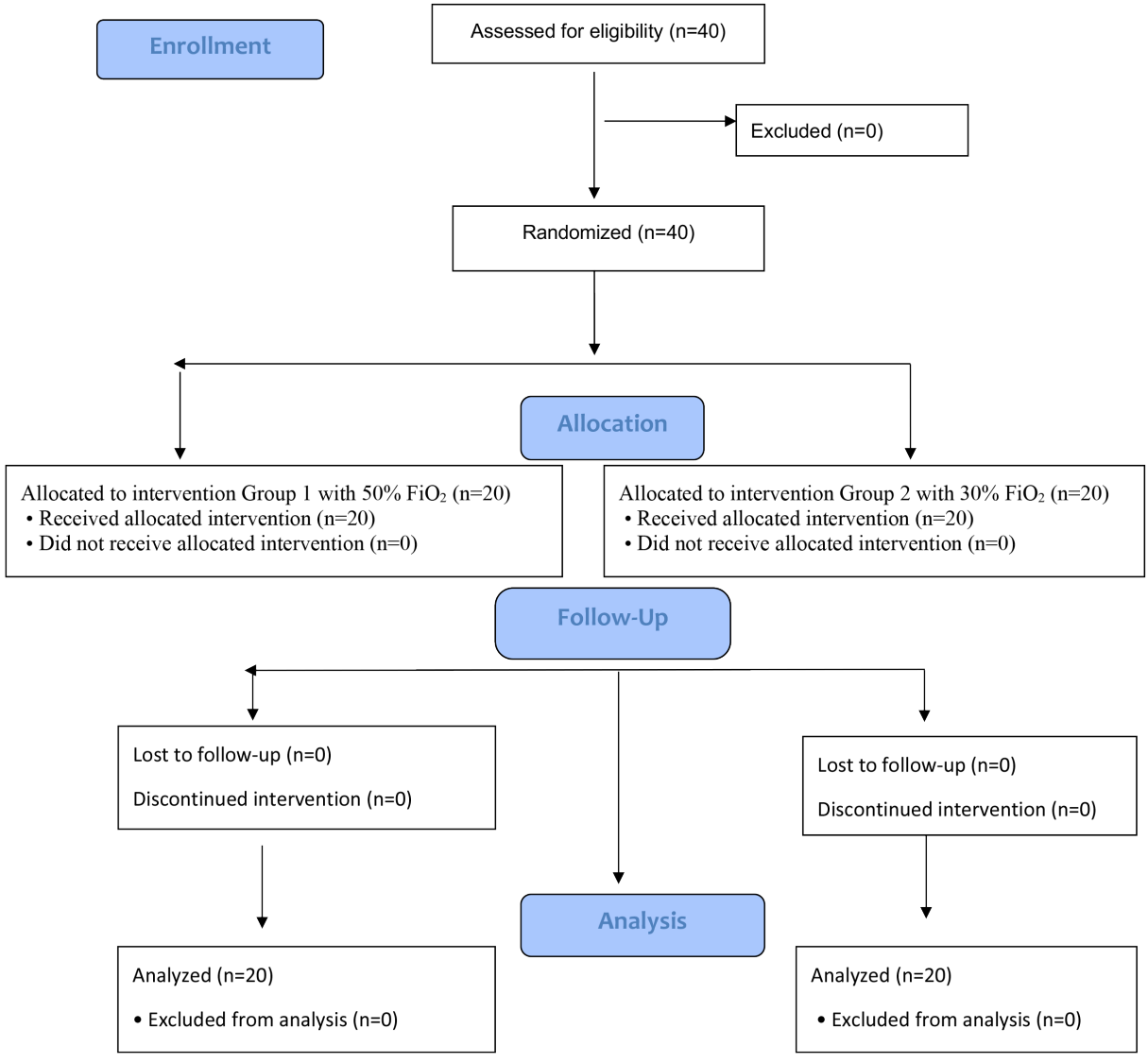

Figure 1. CONSORT flow diagram of the study

The planned sample size required to detect 95.9% test power (1-β), 95% confidence (1-α) and effect size d=1.16 was 9 people per group. We included 20 patients in each group to compensate for patient dropouts (18). A p-value of <0.05 was considered statistically significant.

Results

Our study was completed with 40 patients. Demographic characteristics, ASA risk classes, and the duration of surgery and anesthesia of the patients were similar (Table 1).

In all patients, hemodynamics were stable during the procedure, and the HR, MAP, and SpO_2 levels of the patients did not show significant differences between and within the groups. We did not have any patients who were desaturated and therefore excluded by increasing the O_2 concentration.

Before preoxygenation and at the end of surgery, TAS, TOS, OSI, and PaO_2 levels are summarized in Table 2.

Discussion

It was observed that intraoperative O_2 used at 30% and 50% concentrations caused a significant increase in post-surgical plasma TOS, OSI, and PaO_2 levels, while decreasing TAS levels compared with the levels before preoxygenation in both groups. Changes in postsurgical plasma TAS, TOS, and PaO_2 levels were found to be higher in the FiO_2 50% group.

During the induction and extubation of anesthesia to prolong the desaturation development time when unexpected difficulties arise in airway management, 100% O_2 application is widely used (1,2,6). The World Health Organization recommends the use of intraoperative high FiO_2 to prevent surgical site infections (24). However, while many anesthesiologists use high FiO_2 only during anesthesia induction and extubation, relatively low FiO_2 is used for anesthesia maintenance. The fact that intraoperative high FiO_2 was demonstrated to be associated with postoperative major respiratory complications and 30-day mortality limits intraoperative high O_2 application (7,20). Although there are many studies on the subject, the results regarding the optimal FiO_2 to be administered intraoperatively are still controversial (6,10,24). In daily anesthesia practice, FiO_2 rate appears to be determined according to the preference of patients or routine application regimen rather than evidence-based guidelines (6,25). A recent Cochrane systematic review reports that the evidence to support the routine use of high FiO_2 during anesthesia in humans is insufficient (20). Park et al. (26) investigating the effects of the reduction FiO_2 on postoperative gas exchange during microvascular decompression surgery, demonstrated that the reduction of FiO_2 from 1.0 to 0.3 during anesthesia induction and extubation, and from 0.5 to 0.3 in the intraoperative period, improved postoperative PaO_2/FiO_2 rate.

In the literature, it has been stated that oxidative stress in animals exposed to high concentrations of O_2 is increased (27,28). Chongphaibulpatana et al. (27) in their study conducted in dogs to determine the effects on oxidative stress markers, reported that O_2 application at 3 different concentrations (40%, 60%, and 100%) during general anesthesia with sevoflurane lasting 3 hours caused no significant difference between the 3 groups; actually, 100% O_2 application did not change the level of oxidative stress. However, Kumar et al. (28) speculated that antioxidant enzyme activity may exist differently among species. Although they are the main antioxidant enzymes in humans, the activity of some antioxidant enzymes didn't appear to increase in rabbits exposed to O_2.

Table 1. Demographic data concerning with patients

	Group 1 (n=20)	Group 2 (n=20)	p-value
Female/Male	8/12	10/10	0.525
Age (year)	28.40±8.60	28.80±9.59	0.890
Weight (kg)	70.90±15.34	71.95±15.18	0.829
ASA (I/II)	12/8	11/9	0.749
Operation time (min)	168.75±58.86	175.35±52.62	0.711
Anesthesia time (min)	182.75±60.76	188.65±53.21	0.746

Data are presented as mean ± standard deviation or number (n)
Group 1: FiO_2 50%, Group 2: FiO_2 30%
min: Minute, ASA: American Society of Anesthesiologists

Table 2. Comparison of oxidative stress parameters and PaO_2 levels

	Group 1 (n=20)	Group 2 (n=20)	p-value
TAS (mmol Trolox equiv/L)			
T0	1.38±0.37	1.07±0.43	**0.019**
T1	1.09±0.39	0.69±0.37	**0.002**
P*	**0.003**	**0.002**	
TOS (μmol H_2O_2/L)			
T0	4.48±1.32	3.81±1.05	0.123
T1	6.08±1.98	4.49±1.14	**0.002**
P*	**0.003**	**0.044**	
OSI (arbitrary unit)			
T0	0.34±0.11	0.41±0.18	0.267
T1	0.66±0.40	0.93±0.66	0.332
P*	**<0.001**	**0.002**	
PaO_2			
T0	98.34±13.48	104.36±26.26	0.561
T1	214.60±35.43	146.90±43.88	**<0.001**
P*	**<0.001**	**<0.001**	

Group 1: FiO_2 50%, group 2: FiO_2 30%
p: comparison between groups
p*: comparison in-group
TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, PaO_2: Arterial partial oxygen pressure, T0: Before preoxygenation; T1: The end of surgery (just before the alteration of O_2 concentrations)

The anesthetic agents used in general anesthesia and the duration of anesthesia, along with the stress of surgical trauma, are important factors that disrupt the immunological and antioxidant barrier systems of the body (5,14,26,28,29). In the inspired O_2 concentration, its effects on ROS and antioxidant capacity have been demonstrated in many studies (3-5,13,14,20,28,29). It has been reported that the antioxidant capacity decreases after exposure to intraoperative 50% O_2 in adult patients undergoing colorectal surgery (30). Baysal et al. (14), in their study investigating the oxidant and antioxidant status in laparoscopic surgeries in pediatric patients, reported that after exposure to intraoperative 50% O_2, post-surgical TAS levels decreased, while TOS and OSI levels increased. They concluded that ROS is produced during the laparoscopic procedure, possibly because of the ischemia-reperfusion phenomenon induced by inflation and deflation of the pneumoperitoneum, thus resulting in the consumption of plasma antioxidants.

During anesthesia induction and extubation in our clinic, 100% O_2 is used, and FiO_2 in 50% concentration is often used in anesthesia maintenance. In our study, the fact that TAS increased statistically and TOS decreased in both groups at the end of surgery suggests that our findings are consistent with the literature. While in our study, the oxidant/antioxidant and PaO_2 levels of the FiO_2 50% group were higher than those of the FiO_2 30% group at the end of surgery, no difference was found with regard to OSI levels. Since the initial TAS level was higher in the FiO_2 50% group, we think that there is no difference in OSI levels between the groups. The fact that the duration of anesthesia was approximately 3 hours, the surgery was minimally invasive, and the hemodynamics were stable, suggests that our results may be responsible for unpredictable findings on oxidative stress markers. Thus, the clinical implications and appropriate pathophysiological mechanisms of the findings of this study require further clarification by larger-scale studies.

Study Limitations

Our study has several limitations. First, patients with serious comorbidities were not included. Therefore, it is difficult to know whether there is a beneficial effect of decreasing intraoperative O_2 concentration in patients at high risk. Additionally, studies investigating longer O_2 exposure durations of oxidative stress markers need to be evaluated. Despite its limitations, our study is a valuable study because it makes us think that we should be more sensitive in the use of intraoperative O_2 and it is one of the few studies that contribute to the literature by showing that O_2 is an effective factor in the increase in oxidative stress markers.

Conclusion

Since the use of high concentrations of O_2 (50%) causes a significant increase in oxidative stress, we consider that it is important to use lower concentrations of O_2 in the intraoperative period in suitable patients. More research is urgently needed on perioperative O_2 therapy.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Zonguldak Bulent Ecevit University Non-Invasive Clinical Research Ethics Committee (protocol number: 2021/01, ClinicalTrials.gov Identifier: NCT05099523)

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.K., B.G.A., H.A., Design: G.K., B.G.A., H.A., M.C., Data Collection and/or Processing: G.K., E.B., M.C., Analysis and/or Interpretation: B.G.A., H.A., Literature Research: G.K., B.G.A., Writing: G.K., B.G.A., H.A., M.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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