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Comparison of the Effects of Anesthesia Methods on Dynamic Thiol/Disulfide Homeostasis in Patients with Chronic Obstructive Pulmonary Disease Under Surgical Stress

Cerrahi Stres Altındaki Kronik Obstruktif Akciğer Hastalığı Olan Hastalarda Anestezi Yöntemlerinin Dinamik Tiyol/disülfid Dengesine Etkilerinin Karşılaştırılması

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ÖZ

Amaç: Kronik Obstrüktif Akciğer Hastalığı (KOAH), artan oksidatif stres ile bağlantılıdır. Anestezi uygulamalarına bağlı olarak değişen oksidatif stres durumu, cerrahi stresi ve postoperatif komplikasyon insidansını etkileyebilir.
Bu çalışma, inguinal herni operasyonu geçiren KOAH'lı hastalarda genel anestezi (GA) ve spinal anestezinin (SA) dinamik tiyol-disülfid dengesi üzerindeki etkilerini karşılaştırmayı amaçlamaktadır.
Araçlar ve Yöntem: KOAH'ın Teşhisi, Yönetimi ve Önlenmesi için 2017 Küresel Strateji Raporuna göre, hava akımı obstrüksiyonu (%50≤FEV 1<%79) ve FEV1/FVC<0.7 olan hastalar değerlendirildi. Bu gözlemsel çalışmaya inguinal herni cerrahisi planlanan, grup GA (n=26) ve grup SA (n=26) olmak üzere toplam 52 KOAH hastası dahil edildi. Preoperatif dönemde ve postoperatif 24. saatte kan örnekleri alındı. Tiyol/disülfid dengesinin parametreleri analiz edildi.
Bulgular: Hem grup GA hem de grup SA'da anestezi öncesine göre anestezi sonrasında total tiyol, native tiyol ve disülfid değerlerinde bir azalma gözlendi. Ancak sadece Grup SA'da anestezi sonrası total tiyol ($p<0.01$) ve nativ tiyol ($p=0.012$) değerlerinin anestezi öncesi değerlerine göre azalması istatistiksel olarak anlamlıydı. Diğer değişkenlerdeki değişim istatiksel olarak anlamlı değildi. Grup GA ve grup SA arasındaki karşılaştırmalarda anestezi öncesi ve sonrası tiyol/disülfit değişkenlerinde kayda değer bir fark gözlenmedi.
Sonuç: Cerrahi stres altındaki KOAH hastalarında genel ve spinal anestezi yöntemleri dinamik tiyol/disülfid dengesi üzerine benzer bir yanıt göstermiştir.

Anahtar Kelimeler: disülfid; KOAH; oksidatif stres; spinal anestezi; tiyol

ABSTRACT

Purpose: Chronic Obstructive Pulmonary Disease (COPD) is linked to increased oxidative stress. Changing oxidative stress status due to anesthesia applications may affect surgical stress and the incidence of postoperative complications.
This study aims to contrast the impacts of general anesthesia (GA) and spinal anesthesia (SA) on the dynamic thiol-disulfide homeostasis among patients with COPD who are undergoing inguinal hernia surgery.
Materials and Methods: According to the 2017 Global Strategy Report for the Diagnosis, Management and Prevention of COPD, patients with airflow obstruction (50%≤FEV1<79%) and FEV1/FVC<0.7% were evaluated. A total of 52 COPD patients, group GA (n=26) and group SA (n=26), scheduled for inguinal hernia surgery were included in this observational study. Blood samples were collected preoperatively and at 24 hours postoperatively. Parameters of thiol/disulfide balance were analyzed.
Results: In both group GA and group SA, a decrease in total thiol, native thiol and disulfide values was observed after anesthesia compared to pre-anesthesia. However, only in group SA, the decrease in total thiol ($p<0.01$) and native thiol ($p=0.012$) values after anesthesia was statistically significant. The change in other variables was not statistically significant. There was no significant difference between group GA and group SA in the thiol/disulfite variables before and after anesthesia.
Conclusion: General and spinal anesthesia methods demonstrated a similar response on dynamic thiol/disulfide homeostasis in COPD patients under surgical stress.

Keywords: COPD; disulfide; oxidative stress; spinal anesthesia; thiol

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INTRODUCTION

The World Health Organization reports that the prevalence of chronic obstructive pulmonary disease (COPD) is increasing day by day worldwide and it ranks as the third leading cause of death.[1] COPD is a heterogeneous disease characterized by permanent abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema). Inflammation in the respiratory tract is accompanied by increased airflow resistance. Airflow obstruction, hyperinflation, ventilation/perfusion mismatch, weakening hypoxic pulmonary vasoconstriction, hypoxemia, and hypercapnia lead to respiratory failure.[2] Therefore, the perioperative anesthesia management of patients with COPD involves numerous challenges.

Oxidative stress (OS) stands as a paramount factor in the pathophysiology of COPD. Oxidative stress arises due to an excess production of reactive oxygen species (ROS) surpassing the inherent antioxidant defense mechanisms.[3-5] Oxidative stress plays a key role in proteolytic activity, gene expression of proinflammatory mediators, protein modification, signal transduction, and apoptosis mechanisms.[6,7] Existing COPD may be exacerbated by increased OS and other comorbidities may increase through systemic OS.[2,8] However, in the perioperative period, OS is associated with a complex acute phase response that includes many factors such as the severity of tissue damage caused by surgical intervention, anesthesia duration and technique, and underlying comorbidities.[4,9] It is reported that patients with COPD undergoing surgical procedures are at high risk of morbidity and mortality.[10,11] Additionally, increased OS is associated with postoperative complications.[12] Better clinical results and less postoperative complications can be seen with the application of anesthesia, which reduces exposure to OS.[4,8,13-16] The mechanism underlying this pathological link between often overlooked OS and postoperative complications remains uncertain. The main reason for this uncertainty could be the complexity of measuring ROS and oxidative stress-mediated damage.[4] Until today, OS levels have been studied using numerous complex methods. The search for more practical approaches in this regard continues. Studies on OS, particularly through the thiol/disulfide balance, are frequently addressed in the current literature.[14,17-20]

Dynamic thiol-disulfide homeostasis indicates the status of thiols and disulfides in metabolism. Thiol compounds are organic compounds that contain the sulfhydryl (-SH) group, and this group helps prevent the formation of oxidative stress. When oxidative stress is present, two thiol groups undergo oxidation, leading to the formation of reversible disulfide (-SS-) bonds. Converting disulfide bonds into thiol structures ensures the continuous equilibrium of dynamic thiol-disulfide homeostasis.[21] In the past, the bidirectional dynamic nature of thiol-disulfide homeostasis was analyzed in a unidirectional manner. Today, with the method developed by Erel and Neşelioğlu, the parameters in both directions of equilibrium can be measured separately and collectively.[18] When we reviewed the current literature, we found that there is not enough research on the effects of anesthesia applications on dynamic thiol/disulfide homeostatic status in COPD patients.

In this study, dynamic thiol/disulfide homeostatic responses of general and spinal anesthesia methods in COPD patients under surgical stress were evaluated.

MATERIALS and METHODS

Study Design and Ethical Considerations

This prospective observational study was approved by Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee (date 10.10.2017 and number 2017-15/174). The study was organized in accordance with the principles set out in the Declaration of Helsinki.

Patients, Inclusion and Exclusion Criteria

The study was conducted at Kırşehir Ahi Evran University Training and Research Hospital between January 2018 and December 2018.

Patients scheduled for elective unilateral inguinal hernia surgery were evaluated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program's Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2017 Report. Patients defined as GOLD 2, with airflow obstruction ($50\% \leq FEV1 < 79\%$) and a forced expiratory volume

in 1. second to forced vital capacity ratio (FEV1/FVC) < 0.7, were accepted for the study.[5]

The research involved individuals aged 18 or above, diagnosed with COPD, and possessing an ASA (American Society of Anesthesiologists) physical status classification of II. Patients who stopped smoking and alcohol at least 2 years before participating in the study were accepted.

The study excluded participants who were set to undergo bilateral inguinal hernia surgery, individuals taking multivitamins, those with inflammatory conditions, cancer diagnoses, established cardiovascular issues, cerebrovascular disorders, kidney or liver ailments, metabolic or endocrine disorders, current smokers and alcohol users, patients with a body mass index (BMI) exceeding 35. Additionally, patients with other lung diseases apart from COPD (e.g., tuberculosis, bronchiectasis) were also excluded from the study.

Determining Sample Size

After the preliminary study, Priori power analysis was used to determine the sample size. In the power analysis, with α=0.05 and Power (1-β)=0.80, the total sample size was calculated as 52 for the independent t-test and 34 for the paired t-test. Following the conclusion of the research, a post hoc power analysis was performed to assess the statistical power of the study findings. According to the results of the power analysis, 52 subjects were used in the study.

Procedure

Prior to the surgery, all patients underwent monitoring using non-invasive blood pressure (NIBP), electrocardiography (EKG) and peripheral oxygen saturation (SpO2). Patients were subjected to intravenous catheterization using an 18-G catheter, and intravenous infusion of 10 ml/kg 0.9% NaCl was initiated. The type of anesthesia was determined by the anesthetists who were not included in the study, depending on whether the patients accepted spinal anesthesia or not.

The study population consisted of 52 patients who were categorized into two groups based on the administered anesthesia technique: Group GA (General anesthesia, n=26) and Group SA (Spinal anesthesia, n=26).

General Anesthesia Application

After monitoring the patients in the general anesthesia group, venous blood samples were taken 5 minutes before preoxygenation and at the postoperative 24th hour. Following preoxygenation at a rate of 4 L/min for 2 minutes, the anesthesia induction was carried out using propofol (2 mg/kg), fentanyl citrate (2 μg/kg), and rocuronium bromide (0.6 mg/kg). The patients were intubated after 2 minutes of ventilation with 100% O_2. Anesthesia was maintained with 4L/min flow (50% O_2 + 50% dry air) and 2% sevoflurane. For postoperative analgesia, a combination of tramadol hydrochloride (1 mg/kg) and paracetamol (1 g vial) infusion solution was administered. For decurarization, neostigmine methylsulfate (0.04 mg/kg) + atropine sulfate (0.5 mg) were given.

Spinal Anesthesia Application

After monitoring, venous blood samples were collected from patients in the spinal anesthesia group both before the spinal procedure and at the 24-hour mark postoperatively. With the patient in a seated position, the intrathecal space between the L4-L5 vertebrae was accessed using a 26-gauge atraumatic spinal needle (Atraucan; Braun, Germany). A single dose of 0.5% hyperbaric bupivacaine hydrochloride (10 mg) was injected. The patient was positioned lying on their back, and the extent of sensory block was assessed through the Pinprick test. The surgical procedure was initiated upon achieving the T10 dermatome level with the spinal block.

Thiol/Disulfide Laboratory Examination

Two venous blood samples taken preoperatively and postoperatively were collected in gel serum tubes. The tubes were placed in a centrifuge and spun at 1500xg for 10 minutes. The resulting supernatant serum was then preserved at -80°C until the point of analysis for thiol-disulfide parameters. Using the technique outlined by Erel and Neselioğlu, the status of thiol-disulfide homeostasis was examined via a commercial kit (Rel Assay Diagnostics,

Gaziantep, Türkiye) on the Cobas 501 autoanalyzer (Roche Diagnostics, Germany).[22] Calculations were performed to determine dynamic parameters related to thiol/disulfide homeostasis, including ratios of disulfide/native thiol (%), native thiol/total thiol (%) and disulfide/total thiol (%). The recorded data encompassed the age, body mass index (BMI), anesthesia method, and dynamic thiol/disulfide homeostasis parameters of patients diagnosed with COPD who had undergone inguinal hernia surgery.

Statistical Analysis

In this study, primarily, the dynamic thiol/disulfide homeostasis parameters of both the GA and SA groups were evaluated before and after surgical stress. Secondarily, the thiol/disulfide homeostasis statuses between the GA and SA groups were compared.

For this purpose, the data for native thiol (μmol/L), total thiol (μmol/L), disulfide (μmol/L), disulfide/native thiol (%), native thiol/total thiol (%) and disulfide/total thiol (%) were determined. The statistical analysis of the study was conducted using the Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA) and power analyses were performed using G-Power 3.1.9.4. The normal distribution assumption for quantitative variables was assessed via the Shapiro-Wilk test. It was determined that the data was normally distributed. The descriptive statistics of the variables were presented as Mean ± Standard deviation. In all statistical assessments, results with a p-value lower than 0.05 were considered to indicate statistical significance.

Dependent variable comparisons were conducted using the paired sample T-test, while intergroup comparisons were executed through the utilization of Student's T-test.

RESULTS

A total of 64 patients who underwent inguinal hernia surgery within the specified date range were examined. Following the pre-test results, the data of a total of 52 male patients (GA (n=26) and SA (n=26)) were evaluated statistically.

The mean age was 63.32∓9.78 in group GA and 60.58∓8.92 in group SA. In group GA, the average BMI was 25.88±2.83, while in group SA, it was 26.25±2.08. Age and BMI exhibited resemblances across the groups. Explanatory statistics and analysis results of the variables that we evaluated the thiol/disulfide balance before and after anesthesia in group GA and group SA are given in Table 1.

Table 1. The effects of general anesthesia (Group GA) and spinal anesthesia (Group SA) applications on dynamic thiol/disulfide balance before and after surgical stress.

Variables	Group	preoperative	postopoperative	pa
Total thiol	GA	340.73∓47.97	324.95∓62.93	0.276
	SA	343.74∓57.29	317.66∓50.44	0.003*
p b		0.840	0.649	
Native thiol	GA	305.47∓43.22	290.98∓57.64	0.268
	SA	307.34∓57.54	286.59∓49.83	0.012*
p b		0.897	0.772	
Disülfid	GA	17.62∓8.13	16.98∓4.61	0.731
	SA	18.20∓6.63	15.53∓4.95	0.066
p b		0.784	0.284	
Disülfid/Total thiol	GA	5.11∓2.14	5.26∓1.15	0.752
	SA	5.46∓2.57	5.01∓1.96	0.318
p b		0.602	0.575	
Disülfid/Native thiol	GA	5.81∓2.76	5.92∓1.49	0.865
	SA	6.34∓3.66	5.66∓2.60	0.273
p b		0.564	0.677	
Native thiol/Total thiol	GA	89.76∓4.28	89.47∓2.32	0.758
	SA	89.046∓5.15	89.99∓3.90	0.296
p b		0.589	0.565	

The data is presented as mean±SD.
[a] Paired Sample T-test was used to compare dependent variables
[b] Student T test was used for comparisons between group

According to Table 1, initially, each group was evaluated both before and after anesthesia. In both the GA group and the SA group, a reduction was observed in the total thiol, native thiol, and disulfide values after anesthesia compared to before anesthesia. However, this decrease was statistically significant only in Group SA, with post-anesthesia total thiol (p=0.003) and native thiol (p=0.012) values being significantly different from their pre-anesthesia values. The changes in other variables were not statistically significant. In comparisons between Group GA and Group SA, there were no significant differences detected in relation to thiol/disulfide variables, both prior to and post anesthesia.

After the completion of the research, power analysis was conducted using Post-Hoc power. The lowest power value for Independent t-test results was 0.79, and the lowest power value for paired t-test results was found to be 0.85. These power values show that the study results are reliable and robust results.

DISCUSSION

This study was conducted with the objective of exploring the connection between the anesthesia approach and the dynamic thiol/disulfide equilibrium among COPD patients undergoing surgical stress. We observed similar levels of OS in patients received general anesthesia and spinal anesthesia. The findings of our study specifically conducted on COPD patients address the existing gap in the literature on this topic.

The effects of anesthesia methods during the perioperative period have frequently been compared in the literature. Rodgers et al.[23] evaluated 141 prospective randomized studies comparing neuraxial anesthesia with general anesthesia in the general patient population. According to this review, patients receiving neuraxial anesthesia experience reduced mortality, decreased postoperative pulmonary and cardiac complications, lower incidence of renal failure, and decreased occurrence of deep vein thrombosis. Hausman et al.[24] reported that patients with COPD undergoing surgical operations carry an increased risk of postoperative complications. The authors have demonstrated that the choice of regional anesthesia in COPD patients is associated with lower morbidity, postoperative pneumonia, prolonged mechanical ventilator requirement, and unplanned postoperative intubation. Avoiding general anesthesia in patients with COPD is considered to potentially provide benefits. Therefore, traditionally, if the patient accepts regional intervention and there is no contraindication for the procedure, regional anesthesia is preferred. In surgical patients with COPD, it is necessary to elucidate the critical importance of adding OS changes due to anesthesia application onto the existing chronic OS in this preference. In our study, we compared OS levels in COPD patients who underwent surgical procedures according to different anesthesia methods. However, we found that patients who underwent general anesthesia and those who underwent spinal anesthesia had similar OS levels. The findings of our study do not support the advantages of preoperative and postoperative spinal anesthesia in this patient group as observed in other studies.

There are studies comparing OS levels using different methods. For example, Aremu et al.[25] evaluated the OS levels of general and spinal anesthesia in orthopedic surgery patients as biomarkers (malondialdehyde, glutathione, catalase and nitrile). The authors have reported that anesthesia could lead to different effects on OS and inflammatory cytokines in patients undergoing surgery.

Thiol/disulfide hemostasis studies investigating the relationship between anesthesia methods and surgical stress and OS are generally performed on the patient population without COPD. In one of these studies, a comparison was made between spinal anesthesia and general anesthesia in laparoscopic gynecological surgery. Similar to our study, no difference was found in the evaluation of total oxidant, antioxidant levels and OS index.[26]

In another study, the effects of sevoflurane and desflurane anesthesia during laparoscopic cholecystectomy on lipid peroxidation were compared in a non-COPD patient group. It was determined that plasma malondialdehyde and superoxide dismutase concentrations increased more with desflurane administration compared to sevoflurane.[27] We also administered sevoflurane during general anesthesia. There was no statistically notable alteration detected in the thiol/disulfide balance prior to and subsequent to anesthesia within the GA group. In the study by Kulacoğlu et

al.,[28] the effects of local, spinal, and general anesthesia types on inflammatory response and OS in Lichtenstein hernia repair were compared in the general population. The total antioxidant status showed slight changes across the three anesthesia types. According to the findings of this study, local and spinal anesthesia methods are suggested as better alternatives in terms of OS compared to general anesthesia.[28] On the other hand, our study has shown similar results regarding the effects of general and spinal anesthesia on dynamic thiol/disulfide homeostasis in COPD patients under surgical stress.

Limitations

This study has some limitations. The study included COPD patients with moderate airflow obstruction (50% ≤ FEV1 < 79%) and FEV1/FVC < 0.7. It does not reflect patients with more severe COPD clinic. Severe COPD patients often have secondary comorbidities. Regional anesthesia is applied in this patient group to minimize the risk of perioperative complications. In order to reach a general conclusion about patients with COPD, a larger sample size including different surgical procedures is needed. Additionally, our study population included COPD patients who were ex-smokers. Patients who stopped smoking and alcohol at least 2 years before participating in the study were accepted.[29,30] It is a scientific fact that there is a process in which the effects of smoking on oxidative stress will be seen, even if the COPD patient is an ex-smoker. Therefore, it is important to clarify the oxidative stress status in the COPD group that has never actively smoked.

In conclusion, the OS levels of COPD patients who underwent inguinal hernia surgery were similar for both general anesthesia and spinal anesthesia applications. Based on these findings, considering the OS responses, it can be observed that both anesthesia methods can be applied in patients with mild to moderate COPD, provided there are no other contraindications.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

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Ethics Committee Permission

The study was approved by Ahi Evran University Clinical Research Ethics Committee (dated 10.10.2017 and numbered 2017-15/124).

Authors' Contributions

Concept/Design: FÇ. Data Collection and/or Processing: FÇ, RD, Bİ. Data analysis and interpretation: FÇ, RD. Literature Search: FÇ. Drafting manuscript: FÇ, RD. Critical revision of manuscript: FÇ, RD, Bİ. Supervisor: FÇ, RD, Bİ.

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