Impact of Volatile Anesthetics on Oxidative Stress in Patients Undergoing Laparoscopic Cholecystectomy for Gallstones

Safra Taşları İçin Laparoskopik Kolesistektomi Yapılan Hastalarda Volatil Anesteziklerin Oksidatif Stres Üzerine Etkileri

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ABSTRACT Objective: This study aimed to investigate the total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI) and the paraoxonase and arylesterase activities of patients with gallstones and compare them with healthy individuals as well as to assess the impact of sevoflurane and desflurane on oxidative stress markers in laparoscopic surgery. **Material and Methods:** Forty patients scheduled for laparoscopic surgery (Patient Group) and 30 healthy volunteers as control subjects (Control Group) were enrolled in the study. The patient group was randomized to desflurane group (n= 0) and sevoflurane group (n= 20). Blood samples were collected preoperatively and at postoperative 6 hours in order to measure the levels of TAS, TOS, OSI, and paraoxonase and arylesterase activities. Preoperative and postoperative laboratory findings of sevoflurane and desflurane group were compared with the Mann Whitney U test between groups and the Wilcoxon test within a group. **Results:** Preoperative TOS, OSI levels in the patient group were significantly increased and arylesterase activities were significantly decreased compared to the control group ($p<0.05$) [(TOS (μmol H2O2 equiv/L), 19.64 ± 2.16 vs. 14.25 ± 1.83), (OSI 1.85 ± 0.53 vs. 0.98 ± 0.24), (Arylesterase (U/L), 45.19 ± 6.82 vs. 49.66 ± 4.78)]. There was no statistically significant difference between sevoflurane and desflurane group in laboratory findings of the preoperative and the postoperative period ($p> 0.05$). Preoperative and postoperative TAS, TOS, OSI results and activities of paraoxonase and arylesterase were not significantly different in the sevoflurane group ($p> 0.05$). Although the preoperative and postoperative levels of TAS and TOS and paraoxonase and arylesterase activities in the desflurane group was not significantly different, postoperative OSI was significantly increased ($p< 0.05$) (OSI 1.80 ± 0.57 vs 2.20 ± 0.67). **Conclusion:** Patients with gallstone are exposed to a potent oxidative stress influencing TOS, OSI levels and arylesterase activities. Sevoflurane and desflurane had similar effects on oxidative stress during laporoscopic surgery in this patient group; however, OSI was increased in the desflurane group in the postoperative period compared to preoperative levels ($p< 0.05$).

Key Words: Gallstones; laparoscopy; sevoflurane; desflurane; oxidative stress

ÖZET Amaç: Bu çalışmada, safra taşı olan hastalarda total oksidan seviye (TOS), total antioksidan seviye (TAS), oksidatif stres indeksi (OSİ) seviyelerinin ve paraoksonaz, arilesteraz aktivitelerinin, sağlıklı bireylerdeki parametrelerle karşılaştırılması ve laparoskopik cerrahide oluşan oksidatif stres üzerinde sevofluran ve desfluranın etkilerinin araştırılması amaçlandı. **Gereç ve Yöntemler:** Laparoskopik cerrahi planlanan 40 hasta (hasta grubu) ve 30 sağlıklı gönüllü (kontrol grubu) çalışmaya dâhil edildi. Hasta grubu desfluran (n= 20) ve sevofluran (n= 20) uygulanmak üzere randomize edildi. TAS, TOS, OSİ seviyelerini ve paraoksonaz, arilesteraz aktivitelerini ölçmek üzere kan örnekleri, operasyondan önce ve operasyondan sonraki 6. saatte alındı. Sevofluran ve desfluran gruplarında, operasyondan önce ve sonra elde edilen bulgular, grup içi karşılaştırmalarda Mann Whitney U testi, gruplar arası karşılaştırmalarda ise Wilcoxon testi kullanılarak karşılaştırılmıştır. **Bulgular:** Hasta grubunda TOS, OSİ seviyelerinin operasyon öncesi kontrol grubuna göre anlamlı derecede arttığı ve arilesteraz aktivitesinin kontrol grubuna göre önemli derecede azaldığı tespit edildi ($p< 0,05$) [(TOS (μmol H2O2 equiv/L), 19,64 ± 2,16 ve 14,25 ± 1,83), (OSI 1,85 ± 0,53 ve 0,98 ± 0,24), (Arylesterase (U/L), 45,19 ± 6,82 ve 49,66 ± 4,78)]. Gruplar arası karşılaştırmalarda laboratuar bulguları açısından sevofluran ve desfluran grupları arasında, hem operasyon öncesi hem de operasyon sonrası değerlerde istatistiksel açıdan anlamlı fark yoktu ($p> 0,05$). Grup içi karşılaştırmalarda ise sevofluran grubunda operasyon öncesi ve sonrası TAS, TOS, OSİ seviyeleri ve paraoksonaz, arilesteraz aktiviteleri arasında fark saptanmadı ($p> 0,05$). Desfluran grubunda ise TAS, TOS, ve paraoksonaz arilesteraz aktiviteleri arasında fark bulunmazken, operasyon sonrası OSİ düzeyinde anlamlı bir artış olduğu tespit edildi ($p< 0,05$) (OSİ 1,80 ± 0,57 ve 2,20 ± 0,67). **Sonuç:** Safra taşı olan hastalar, TOS, OSİ seviyelerini ve arilesteraz aktivitelerini etkileyecek şekilde oksidatif stress altındadırlar. Sevofluran ve desfluranın bu hasta grubunda, laparoskopik cerrahideki oksidatif stres üzerinde benzer etkileri bulunmakla birlikte, desfluran grubunda, operasyondan önceki değerler ile karşılaştırıldığında, operasyondan sonraki dönemde OSİ düzeyleri artmaktadır ($p< 0,05$).

Anahtar Kelimeler: Safra taşları; laparoskopi; sevofluran; dezfloran; oksidatif stres

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Gallstone disease is among the most common gastrointestinal disorders.[1] It is well-known that inflammatory response is induced in chronic diseases such as cholelithiasis. Reactive oxygen species (ROS) produced by neutrophils, macrophages and/or monocytes, provoke oxidative stress that plays an important role in the pathogenesis of many diseases.[2-4] There are few studies reporting increased levels of ROS and toxic degradative products of lipid peroxidation in the plasma of individuals with gallstones.[5]

Laparoscopic cholecystectomy (LC) has gained worldwide acceptance as the gold standard surgical method to treat gallstone disease.[6,7] Although laparoscopic surgery is generally considered safe, there have been several reports on mesenteric ischemia and on bowel infarction after routine laparoscopic procedures.[8,9] These findings have led to the hypothesis that abdominal insufflation and consequently raised intra-abdominal pressure may produce significant organ ischemia, followed by reperfusion injury upon deflation of the abdomen.[10] One of the main consequences of ischemia-reperfusion injury is an imbalance between oxidants and antioxidants causing oxidative stress.[10] Volatile anesthetics used in laparoscopic surgery can also augment the release of inflammatory mediators and free radicals. Thus, general anesthesia (i.e., volatile anesthetics) may impair immunologic defense mechanisms inducing an inflammatory reaction in the macrophages.[11-13] The clinical consequences of oxidative stress of ischemia and reperfusion during laparoscopic procedures have not yet been clearly elucidated.[14,15] Thus, patients with gallstones might be exposed to oxidative stress due to the chronic pattern of the disease, pneumoperitonium during laparoscopic surgery and general anesthesia with volatile anesthetics, which might have significant clinical effects especially in patients with co-morbidities. This study aimed to investigate the impact of sevoflurane and desflurane anesthesia on total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI) and the paraoxonase and arylesterase activity of patients with gallstones after LC.

MATERIAL AND METHODS

1. SUBJECTS

Patients and healthy volunteers were included in the study after giving written informed consent, and the study was approved by the institutional Ethics Committee. The study was run in accordance with the ethical principles for human investigations, as outlined by the Second Declaration of Helsinki. Forty patients with American Society of Anesthesiology (ASA) I–III physical status, who were scheduled for laparoscopic surgery (Patient Group) and 30 healthy volunteers as control subjects (Control Group) were enrolled in the study. Thirty volunteers including non-medical staff of the Harran University Medical Faculty and their relatives composed the control group. All volunteers were healthy individuals without any known medical problems.

Subjects with any metabolic, endocrine, hepatic, cardiac or renal diseases, malignancies, recent use (within 48 h) of any drug with anti-oxidant properties, such as nebivolol, carvedilol, vitamins E and C, and acetylcysteine were excluded from the study. Twelve patients were excluded based on exclusion criteria. Demographic and clinical data (age, weight, height) of the patient and the control groups were noted as well as anesthesia and operation time in the patient group.

2. STUDY PROTOCOL

The patient group was randomized to sevoflurane (n= 20) and desflurane (n= 20) groups with sealed envelope technique. The patients were intravenously premedicated 30 min before the induction of anesthesia with midazolam 0.15 mg kg^{-1}. Anesthesia was induced with propofol 2-2.5 mg kg^{-1}, remifentanil 0.15 μg kg^{-1}, and rocuronium bromide 0.5 mg kg^{-1} together with 100% oxygen. After tracheal intubation, the fresh gas-flow rate was set to 4 L min^{-1} and 0.20 μg kg^{-1} remifentanil infusion was started in all groups. Anesthesia was maintained with sevoflurane or desflurane in 50% O_2-50% medical air mixture. Volatile anesthetic concentrations were adjusted to maintain sevoflu-

rane at 1 minimum alveolar concentration (MAC) and desflurane at 1 MAC with systolic blood pressure within ± 20% of the baseline. Remifentanil infusion or sevoflurane or desflurane concentration (25% increase or decrease) were changed with 20% changes in heart rate or systolic blood pressure. Ventilation was controlled with a tidal volume of 10 mL kg–1 and respiratory rate was adjusted to maintain an end-tidal carbon dioxide ($EtCO_2$) value between 35 and 45 mmHg. The anesthetic machine used was Datex-Ohmeda Aspire 7100 anesthesia system (GE health care). All patients were monitored by electrocardiography (ECG), noninvasive blood pressure (BP), peripheral oxygen saturation (SpO_2), and end-tidal carbon dioxide ($EtCO_2$) measurement (Datex Ohmeda, ADU, S/5, Helsinki, Finland). Intraabdominal pressure was held at 10 mmHg during laparoscopy and a constant CO_2 flow of 2 L min^{-1} was administered.

3. BLOOD SAMPLING

Blood samples were collected preoperatively and at postoperative 6 hours in order to measure the levels of TAS, TOS, OSI, paraoxonase and arylesterase. Samples were separated by centrifugation at 1200 rpm within 45 min of venipuncture and were stored at -20°C until testing.

4. DETERMINATION OF THE TOTAL ANTIOXIDANT CAPACITY

Total antioxidant capacity (TAC) of plasma was determined using an automated measurement method.[16] In this method, hydroxyl radical, which is the most potent biological radical, is produced. In the assay, ferrous ion solution, which is present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. The sequentially produced radicals such as brown colored dianisidinyl radical cation, produced by the hydroxyl radical, are also potent radicals. The oxidation reactions progress among dianisidyl radicals and further oxidation reactions develop. The color formation is increased with further oxidation reactions. Antioxidants in the sample suppress the oxidation reactions and color formation. Using this method, the antioxidative effect of the sample against the potent free radical reactions, which is initiated by the produced hydroxyl radical, is measured. The results were expressed as mmol Trolox Equiv./L.

5. MEASUREMENT OF TOTAL OXIDANT STATUS

Total oxidant status of plasma was determined using an automated measurement method, developed by Erel.[17] Oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Equiv./L).

6. OXIDATIVE STRESS INDEX

Percent ratio of TOS level to TAC level was considered the oxidative stress index (OSI). For calculation, the resulting unit of TAC was changed to mmol/l, and the OSI value was calculated according to the following formula. OSI (Arbitrary Unit)= TOS (μmol H_2O_2 Equiv. /L) / TAC (mmol Trolox Equiv. /L).

7. MEASUREMENT OF PARAOXONASE AND ARYLESTERASE ACTIVITIES

Serum PON activity was measured in the absence of basal activity. The rate of paraoxon hydrolysis (diethyl-p-nitrophenylphosphate) was measured by monitoring the increase in absorbency at 412 nm at 37°C. The amount of generated p-nitrophenol was calculated from the molar absorptivity coefficient at pH 8, which was 17 000 $M^{-1}cm^{-1}$.[18] Paraoxonase activity was expressed as U/L serum. Phenylacetate was used as a substrate to measure the arylesterase activity. Enzymatic activity was calculated from the molar absorptivity coefficient of the produced phenol, 1310 $M^{-1}cm^{-1}$. One unit of arylesterase activity was defined as phenol generated (μmol/min) under the above conditions and was expressed as U/L serum.[19] Coefficients of variation (CV) for measurement of serum PON and arylesterase activities were 2% and 3% respectively.

8. STATISTICAL ANALYSIS

Data were given as mean values ± standard deviation. Baseline clinical and laboratory characteristics between the patient and the control groups were compared using independent sample t test. Baseline clinical and laboratory characteristics, operation and anesthesia time between the sevoflurane and the desflurane groups was compared using the Mann Whitney U test. In the sevoflurane and desflurane groups, paired-samples t test in the overall patient population, Wilcoxon test in related data and Mann Whitney U test in independent data were used to compare preoperative and postoperative laboratory findings. Two sided p value< 0.05 was considered statistically significant.

RESULTS

There were no significant differences between the control and the patient groups and between the sevoflurane and the desflurane groups with regard to mean age, weight, and height (Table 1). Operation and anesthesia time also did not show significant difference between the sevoflurane and the desflurane groups (Table 1). While TOS and OSI levels in the patient group were significantly increased, arylesterase activities were significantly decreased compared to the control group (p< 0.05) (Table 2). All patients were hemodynamically stable throughout the procedure and all patients completed the study. Heart rate and mean blood pressure values in at baseline, 1, 5, 15, 30, 45, 60, and 90 minutes were shown in Figure 1 and 2. Hemodynamic parameters did not differ significantly between the sevoflurane and the desflurane groups during the operation (p> 0.05). Total remifentanil

TABLE 1: Demographic data and operation/anesthesia durations in the study population.

	Patient Group (n=40)		Control Group (n=30)
	Desflurane Group (n=20)	Sevoflurane Group (n=20)	
Age (year)	42 ± 7.25	41 ± 10.48	40 ± 11.18
Height (cm)	164 ± 6.47	160 ± 11.26	162 ± 9.72
Weight (kg)	71 ± 12.45	73 ± 09.52	70 ± 15.42
Operation time (min)	74 ± 12.52	81 ± 06.52	
Anesthesia time (min)	82 ± 3.49	91 ± 4.72	

Data are expressed as mean ± standard deviation.

TABLE 2: Preoperative TAS, TOS, OSI levels and paraoxonase and arylesterase activities of the study population.

	Patient Group (n= 40)	Control Group (n= 30)	p
TAS (mmol Trolox equiv/L)	1.11 ± 0.25	1.04 ± 0.19	0.206
TOS (μmol H_2O_2 equiv/L)	19.64 ± 2.16	14.25 ± 1.83	0.001*
OSI	1.85 ± 0.53	0.98 ± 0.24	0.001*
Paraoxonase (U/L)	89.68 ± 13.56	89.93 ± 17.88	0.945
Arylesterase (U/L)	45.19 ± 6.82	49.66 ± 4.78	0.003*

*: p<0.05

Data are expressed as mean ± standard deviation.

Abbreviations: TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index.

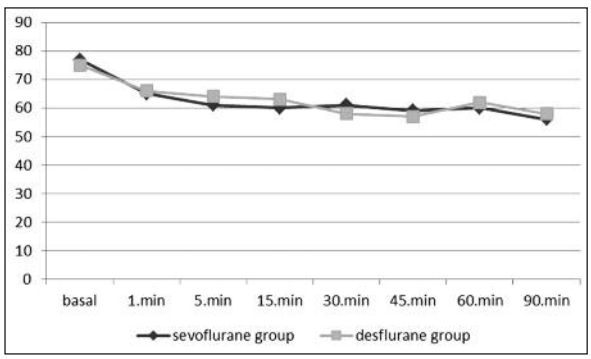

FIGURE 1: Mean blood pressure of sevoflurane and desflurane during operation (Values are mmHg).

Min: minute

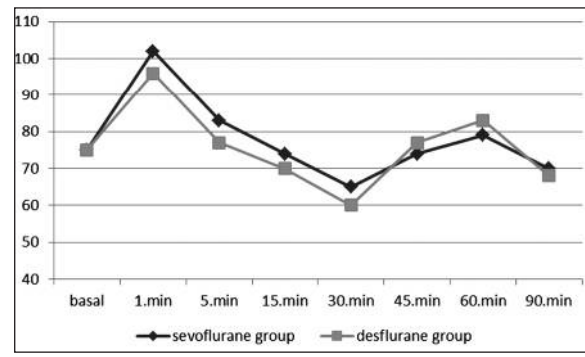

FIGURE 2: Heart rate of sevoflurane and desflurane groups during operation. (Values are beat per minute).

Min: minute

consumption between the groups was not significant either (for the sevoflurane group 0.92 ± 0.15 mg, for the desflurane group 0.89 ± 0.13 mg; p> 0.05) and there was no case requiring inhalation anesthetics higher than 1 MAC in either group. There was no statistically significant difference between the sevoflurane and the desflurane group in preoperative and postoperative laboratory findings (p> 0.05) (Table 3). Preoperative and postoperative TAS, TOS, and OSI levels and activities of paraoxonase and arylesterase were not significantly different in the sevoflurane group (p> 0.05) (Table 3). While postoperative TAS, TOS levels and paraoxonase, arylesterase activities in the desflurane group was not significantly different than preoperative levels, postoperative OSI was significantly increased compared to preoperative values (p= 0.044) (Table 3). Post hoc power analysis with G Power 2 power analysis program revealed a power of p= 0.99 for the comparison of patient and control group preoperative OSI results (alfa= 0.05, n1= 40, n2= 30). The power for the comparison of preoperative and postoperative OSI results of the desflurane group (alfa= 0.05, n= 20) was p= 0.6572.

DISCUSSION

According to the results of this study, patients with gallstones have increased TOS and OSI levels and lower arylesterase activities compared to healthy volunteers. There are few studies reporting increased levels of oxidative stress markers like TOS and OSI in patients with gallstones.[1,5] In addition to similar findings in our study, serum arylesterase activities were decreased in patients with gallstones. Paraoxonase, a high-density lipoprotein (HDL)- associated enzyme, has many enzymatic activities, including those associated with paraoxonase, arylesterase, diazoxonase and Ca^{2+}-dependent serum esterase.[20] Decreased paraoxonase activity was observed in many diseases such as coronary artery disease, hypercholesterolemia, and type 2 diabetes.[21,22] Gallstones can induce inflammation in the gallbladder wall and the activated phagocytes can produce reactive oxygen metabolites, which result with oxidative stress. Therefore, oxidative stress may contribute to an inflammatory response induced by cholelithiasis.[1] Chronic inflammatory process in cholelithiasis might cause increased levels of TOS and OSI and decreased levels of arylesterase activity.

Although laparoscopic cholecystectomy is among the most common elective surgical procedures, insufflations of the peritoneal cavity with carbon dioxide (CO_2) may be associated with negative consequences.[23,24] Increased intraabdominal pressure decreases perfusion in abdominal organs, decreases blood flow in the inferior vena cava and increases the risk of thrombotic disease.[25] Furthermore, insufflation during surgery and subsequent desufflation at the end of surgery creates an ischemia-reperfusion due to the fluctuations in splanchnic circulation.[26] Various animal[10,27,28] and human[29-31,32] studies have investigated the ischaemia–reperfusion injury that occurs as a result

TABLE 3: Preoperative and Postoperative TAS, TOS, OSI levels and paraoxonase and arylesterase activities of the sevoflurane and the desflurane group.

	Preoperative		Postoperative	
	Sevoflurane	Desflurane	Sevoflurane	Desflurane
TAS (mmol Trolox equiv/L)	1.09 ± 0.21	1.13 ± 0.29	1.02 ± 0.18	1.04 ± 0.19
TOS (μmol H_2O_2 equiv/L)	20.06 ± 1.73	19.21 ± 2.49	19.65 ± 3.04	20.31 ± 2.39
OSI	1.90 ± 0.42	1.80 ± 0.57	1.95 ± 0.58	2.20 ± 0.67*
Paraoxonase (U/L)	89.10 ± 9.09	90.35 ± 17.15	91.30 ± 6.59	95.45 ± 8.31
Arylesterase (U/L)	44.79 ± 8.86	45.59 ± 4.08	46.51 ± 2.93	46.65 ± 3.94

Data are expressed as mean ± SD.

Abbreviations are same as on Table 2.

*: statistically significant (p= 0.044) increase in the postoperative period compared to the desflurane group.

of pneumoperitoneum. Although those studies used a wide range of outcome measures of oxidative stress including endogenous antioxidant levels, peroxidation markers, paraoxonase and arylesterase activities, derived gastric intramucosal pH, cytokine levels and histological findings, there is no consensus on which peroxidation markers or detection methods are most valid.[7,32] There is clear evidence from animal studies that pneumoperitoneum results directly in end-organ ischaemia and injury. A study by Nickkholgh et al. demonstrated that pneumoperitoneum at 12 mmHg for 90 minutes induced histological (in vivo light microscopy) and biochemical (plasma liver enzyme levels) evidence of liver reperfusion injury in rats.[10] A significant increase in oxidative stress (MDA, protein carbonyls) was also observed in a rat model of laparoscopic donor nephrectomy.[33] Extra-abdominal organs also demonstrate oxidative stress with pneumoperitoneum, such as significantly increased MDA levels in rat lungs 2 and 6 h after deflation.[34]

In humans, studies comparing plasma markers of lipid peroxidation between laparoscopic and open cholecystectomy reported increased levels of markers in both groups with significantly increased levels in open surgery.[7,30,35]

Pneumoperitoneum performed in rats with a pressure of 5, 10 or 15 mmHg resulted in an incremental increase in the formation of free oxygen radicals in lung and liver tissues.[36] In the study by Nickkholgh and colleagues,[10] histological and biochemical evidence of liver reperfusion injury was demonstrable at 12 mmHg but not at 8 mmHg. Schilling and co-workers demonstrated that reduction in organ perfusion was pressure dependent by studying the effect of different insufflation pressures in laparoscopic cholecystectomy.[37]

The most widely used gas, CO_2 has the advantage of being readily available, quickly absorbed and excreted, inexpensive and noninflammable.[32,38] On the other hand, Yılmaz and colleagues showed a significantly greater increase in oxidative stress markers when carbon dioxide was used compared with helium as a non-reactive alternative gas.[14] In our study, although there was a slight decrease in TAS and increase in TOS and OSI levels, the difference between preoperative and postoperative levels was not significant. This may be attributed to routine usage of low intraabdominal pressure (10 mmHg) during the laparoscopic procedure in our clinic.

Several simple measures such as using the lowest possible inflation pressure, releasing gas intermittently, gasless surgery using various abdominal wall lifting devices, avoiding head-up position, intravascular volume expansion before pneumoperitoneum are recommended to limit pneumoperitoneum-related oxidative stress in patients with significant co-morbidity, especially those with cardiovascular compromise.[32]

Volatile anesthetics have different impact on oxidative stress. In studies comparing inhalation agents in clinical settings regarding oxidative stress, desflurane was found to induce more lipid peroxidation in a swine model than sevofluran.[13] Sıvacı et al.[11] showed that desflurane with N_2O increased MDA levels and protein carbonyl content and decreased protein sulfhydryl consumption more than sevoflurane in laparoscopic surgery. They emphasized that postoperative complication rate might increase due to high ROS and low antioxidant activity; thus, desflurane would not be preferred in laparoscopic surgical procedures with regard to oxidative stress. In our study, there was no significant difference between the desflurane and the sevoflurane groups, although postoperative OSI level was significantly increased in the desflurane group compared to preoperative levels. We could not collect perioperative samples due to economic reasons in our study. We decided to take blood samples at postoperative 6 hours; thus, the authors believed that TAS, TOS, OSI arylesterase and paraoxonase levels would still be decreased or increased at postoperative 6 hours.

There were several limitations in this study including small sample size and the absence of anesthetic depth monitoring with bispectral index in the sevoflurane and the desflurane group as well as limited perioperative and postoperative blood sampling. Further large-scale prospective studies are

required to clarify the clinical effect of different volatile agents on oxidative stress.

In conclusion, patients with gallstone are exposed to a potent oxidative stress influencing TOS, OSI levels and arylesterase activities. Although sevoflurane and desflurane had similar effects on oxidative stress in laporoscopic surgery of this patient group, OSI was postoperatively increased in the desflurane group compared to the preoperative period. Clinical and prognostic significance of controlling chronic oxidative stress and limiting pneumoperitoneum-associated oxidative stress with novel anesthetic approaches in LC remains to be investigated.

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