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ORIGINAL ARTICLE

The Use of Propofol to Induce Anesthesia can Mitigate the Oxidative Stress Created by Laparoscopic Cholecystectomy, but not Thiopental

Anestezi Indüksiyonu için Propofol Kullanımı Laparoskopik Kolesistektominin Yarattığı Oksidatif Stresi Hafifletebilir Ancak Tiyopental Bunu Azaltamaz

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ABSTRACT

Aim: Laparoscopic cholecystectomy is one of the treatment methods employed in symptomatic cholelithiasis cases, and pneumoperitoneum has been shown to increase oxidative stress. Our aim is to compare propofol and thiopental in terms of their effects on oxidative stress parameters in laparoscopic cholecystectomy cases.
Materials and Methods: After obtaining Ethics Committee permission, patients who underwent laparoscopic cholecystectomy were divided into thiopental and propofol groups according to the agent used for anesthesia induction in the randomized and prospective study. Serum oxidative stress parameters levels were measured in all patients twice before induction of general anesthesia and at the 30th minute postoperatively.
Results: When comparing the preoperative period with the postoperative period, total antioxidant status (TAS) levels increased statistically significantly in the propofol group (preoperatively 1.21±0.21 mmolH2O2/L, postoperatively 1.31±0.18 mmolH2O2/L, p<0.001) compared to the thiopental group (preoperatively 1.23±0.14 mmolH2O2/L, postoperatively 1.27±0.14 mmolH2O2/L, p=0.055). arylesterase (ARES), serum native thiol, total thiol, and disulfide levels decreased statistically significantly in both groups. While Paraoxonase-1 (PON1) level did not change in the propofol group, it decreased in the thiopental group.
Conclusion: We concluded that propofol had a significantly greater oxidative stress reduction effect than thiopental. By increasing the TAS levels, propofol may have a more positive effect on oxidative stress than thiopental. However, neither propofol nor thiopental have oxidative stress-reducing effects on other oxidative stress parameters.

Keywords: Antioxidants, Disulfides, Laparoscopic cholecystectomy, Oxidative stress, Propofol, Thiol, Thiopental

ÖZ

Amaç: Semptomatik kolelitiazis vakalarında laparoskopik kolesistektomi tedavi metodlarından biridir ve pnömoperitoniumun oksidatif stresi arttırdığı gösterilmiştir. Bizim amacımız laparoskopik kolesistektomi olgularında oksidatif stres parametreleri üzerine etkileri açısından propofol ve tiyopentali karşılaştırmaktır.
Gereç ve Yöntem: Etik Kurul izni alındıktan sonra, randomize ve prospektif olarak planlanan çalışmada laparoskopik kolesistektomi geçiren hastalar anestezi indüksiyonu için kullanılan ajana göre tiyopental ve propofol gruplarına ayrıldı. Tüm hastalardan serum oksidatif stres parametreleri düzeylerinin ölçümü için genel anestezi indüksiyonu öncesi ve postoperatif 30. dakikada olmak üzere iki kez kan örnekleri elde edildi.
Bulgular: Total antioxidant statü (TAS) düzeyleri, preoperatif dönem ile postoperatif dönem karşılaştırıldığında propofol grubunda (preoperatif olarak 1.21±0.21 mmolH2O2/L, postoperatif olarak 1.31±0.18 mmolH2O2/L, p<0.001) tiopental grubuna (preoperatif olarak 1.23±0.14 mmolH2O2/L, postoperatif olarak 1.27±0.14 mmolH2O2/L, p=0.055) göre istatistiksel olarak önemli oranda arttı. Arilesteraz (ARES), serum native tiyol, toplam tiyol, disülfid düzeyi her iki grupta istatistiksel olarak önemli oranda azaldı. Paraoxonaz-1 (PON1) düzeyi ise propofol grubunda değişmemiş saptanırken, tiyopental grubunda azalmış olarak tespit edilmiştir.
Sonuç: Propofolün tiyopentalden anlamlı derecede daha fazla oksidatif stres azaltma etkisine sahip olduğu sonucuna vardık. TAS düzeylerinde artış sağlayarak, propofol tiyopentale göre oksidatif stres üzerine daha olumlu etkiye sahip olabilir. Ancak diğer oksidatif stres parametreleri üzerine ne propofolün ne de thiopentalin oksidatif stresi azaltıcı etkileri yoktur.

Anahtar kelimeler: Antioksidanlar, Disülfitler, Laparoskopik kolesistektomi, Oksidatif stres, Propofol, Tiyol, Tiyopental

Introduction

Laparoscopic cholecystectomy is the excision of the gallbladder using a laparoscope. Pneumoperitoneum is provided by insufflating carbon dioxide to obtain vision inside the abdomen (1). It may increase intra-abdominal pressure. Excessive increase in intra-abdominal pressure may lead to deterioration in splanchnic perfusion. This may increase reactive oxygen species through ischemia reperfusion injury (2). Free radicals, which are reactive oxygen species play a beneficial role in the immune system, intracellular signaling cascades and induction of mitogenic response at low or moderate concentrations. Oxidative stress occurs when the balance between production and detoxification of free radicals is disrupted. Lipids, proteins and DNA are negatively affected by oxidative stress (3). PON1 enzyme is largely produced in liver cells

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and high-density lipoprotein stimulates its release. PON1 protects against lipid peroxidation by binding to cell membranes in tissues and it is effective as an antioxidant (4). Thiols are organic compounds containing sulfhydryl groups and act as antioxidants in oxidative stress. TAS and TOS provide information about oxidant-antioxidant capacity status (5). The effects of intravenous anesthetic agents on oxidative stress are wondered. An animal study comparing the effects of propofol and thiopental on oxidative stress on dogs found an increase in TAS and a decrease in TOS levels with both agents (6). In a study comparing propofol and thiopental in an ischemia reperfusion model caused by testicular torsion in rats, it was found that propofol attenuated tissue malondialdehyde and nitric oxide levels (7). In another study, researchers determined oxidative stress based on glutathione levels in platelet cytoplasm. Citrated blood obtained from surgical patients was centrifuged and it was shown that propofol reduced oxidative stress in platelets more than thiopental (8). Propofol and sevoflurane were compared in terms of serum native thiol and nitric oxide levels in patients undergoing transsphenoidal pituitary surgery. It was suggested both agents had similar antioxidant effects (9). Since there is little information on comparing thiopental and propofol used in anesthesia induction, more clinical research on oxidative stress is needed. Our goal is to compare the effects of thiopental and propofol on oxidative stress in patients undergoing laparoscopic cholecystectomy.

Material and Methods

The randomized and prospectively planned study was carried out after obtaining Ethics Committee permission. Sixty adult patients with American Society of Anesthesiologists Physical Status classification I and II, Mallampati score I and II, and scheduled for laparoscopic cholecystectomy were included in the study. All patients signed informed consent. Patients with severe heart disease, obstructive and restrictive lung disease, kidney and liver failure, patients with a history of alcohol, sedatives, those using sedatives and long-term analgesics were excluded from the study.

Patients were fasted for at least 8 hours and no premedication was administered for preoperative sedation before entering the operating room. Randomization was performed to pick from an envelope labeled 30 propofol and 30 thiopental. Age, gender, smoking, past surgical history, American Society of Anesthesiologists (ASA) Physical Status classification, Mallampati score, duration of anesthesia and duration of operation of the patients were recorded. All patient monitored with the electrocardiography, noninvasive blood pressure device, pulse oximeter, and capnometer. Before induction, 100% oxygen was breathed for 3 minutes. In the propofol group, anesthesia was induced with IV lidocaine 1-1.5 mg/kg (Aritmal 2%, Osel) and IV propofol 2-3 mg/kg, IV remifentanil 1 mcg/kg (Ultiva 2mg GlaxoSmithKline) and IV rocuronium 0.6-1.2 mg/kg (Esmeron 50mg, 5ml vial, Organon). Anesthesia was applied to the Thiopental group with IV lidocaine 1-1.5 mg/kg, IV thiopental 4-7 mg/kg (Pental sodium 0.5 g, I.E. Ulugay) IV remifentanil 1 mcg/kg and IV rocuronium 0.6-1.2 mg /kg. Anesthesia maintenance was continued with remifentanil (0.05 – 0.25 mcg/kg/min) and 40% O2-Air mixture with 2-3% sevoflurane (Sevorane, Abbott Lab.).

It was planned to stop the study if the patient had uncontrolled bleeding and the surgery could not be completed with laparoscopic surgery.

Venous blood samples were taken from all patients twice before anesthesia induction and at the end of the surgery to measure serum TAS, TOS, PON1, ARES, native thiol, total thiol, and disulfide levels. Blood samples were centrifuged at 3600 rpm for 10 minutes in the biochemistry laboratory and then stored at -80 degrees. They analyzed on the Roche 501/701 modular system automatic analyzer.

Statistical analysis

Data were analyzed using IBM SPSS for Windows V22.0 program. Descriptive statistics were showed as mean±standard deviation, frequency distribution and percentage. To evaluate categorical variables, Pearson Chi-Square Test was used. The suitability of the variables to normal distribution was analyzed with visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk Test). For variables conforming to normal distribution, statistical significance was determined between two independent groups using the Student T Test. Paired Sample T Test was applied between two dependent groups. If there was no normal distribution, Whitney U Test was used between two independent groups and Wilcoxon Signed Rank Test was employed between two dependent groups. Spearman Test was used to find the relationship between variables. $P<0.05$ was accepted as statistically significant.

Results

There was no significant difference between the two groups in terms of clinical characteristics of the patients ($p>0.05$; Table 1).

When comparing the preoperative period with the postoperative period, TAS levels increased statistically significantly in the propofol group (preoperatively 1.21±0.21 mmolH2O2/L, postoperatively 1.31±0.18 mmolH2O2/L, $p<0.001$; Table 2) compared to the thiopental group (preoperatively 1.23±0.14 mmolH2O2/L, postoperatively 1.27±0.14 mmolH2O2/L, $p=0.055$; Table 2). Postoperative PON1 values in the thiopental group decreased significantly. In the propofol group, PON1 levels did not change significantly ($p>0.05$; Table 2).

Postoperatively, ARES, native thiol, total thiol and disulfide levels decreased significantly in both the thiopental and propofol groups.

Table 1. Clinical characteristics of patients

	Thiopental group (n=30)	Propofol group (n=30)	p
Age, yr	47.67±13.05	42.83±13.91	0.170
Gender			
Male	7 (23.3)	6 (20.0)	0.754
Female	23 (76.7)	24 (80.0)	
Smoking	8 (26.7)	11 (36.7)	0.405
Past surgical history	19 (63.3)	14 (46.7)	0.194
ASA			
I	13 (43.3)	14 (46.7)	0.795
II	17 (56.7)	16 (53.3)	
Mallampati score			
I	9 (30.0)	11 (36.7)	0.584
II	21 (70.0)	19 (63.3)	
Duration of Anesthesia (min)	73.17±18.50	74.57±25.71	0.810
Duration of Operation (min)	55.53±20.39	57.33±25.55	0.764
Continuous variables were presented as "mean±standard deviation" and categorical variables were presented as "number (percentage)".			

Table 2. Oxidative stress parameters detected in patients anesthesia induced with thiopental or propofol

	Preoperative	Postoperative	p
Total antioxidant status (mmolH_2O_2/L)			
Thiopental group	1.23±0.14	1.27±0.14	0.055
Propofol group	1.21±0.21	1.31±0.18	<0.001
Total oxidant status (µmolH_2O_2/L)			
Thiopental group	5.26±2.28	5.47±2.35	0.742
Propofol group	4.75±1.47	4.94±1.47	0.943
Paraoxonase (U/L)			
Thiopental group	171.68±95.29	159.83±94.95	0.007
Propofol group	135.55±81.63	131.35±82.78	0.131
Arylesterase (U/L)			
Thiopental group	213.61±51.53	200.78±47.89	0.012
Propofol group	205.53±40.01	194.63±46.13	0.041
Native thiol (µmol/L)			
Thiopental group	359.16±57.07	323.42±51.18	<0.001
Propofol group	375.68±52.04	340.65±54.26	0.002
Total Thiol (µmol/L)			
Thiopental group	384.13±60.69	343.61±53.61	<0.001
Propofol group	402.27±53.71	363.06±58.93	0.001
Disulphide (µmol/L)			
Thiopental group	12.49±3.09	10.10±3.79	0.014
Propofol group	13.30±3.53	11.20±5.11	0.027
Disulphide/Native thiol%			
Thiopental group	3.49±0.74	3.15±1.18	0.216
Propofol group	3.58±0.99	3.30±1.41	0.325
Disulphide / Total Thiol%			
Thiopental group	3.25±0.65	2.94±1.04	0.196
Propofol group	3.33±0.85	3.06±1.24	0.297
Native thiol/ Total Thiol%			
Thiopental group	93.50±1.30	94.12±2.08	0.196
Propofol group	93.34±1.71	93.87±2.49	0.297

Discussion

In this study, we showed that TAS levels increased statistically significantly in the propofol group, but not in the thiopental group, when we compared the pre- and postoperative periods. While there was no change in PON1 level in the propofol group, a decrease was observed in the thiopental group. De La Cruz et al. administered IV 4 mg/kg thiopental or IV 2 mg/kg propofol for patients undergoing curettage, ligation fallopian tubes, inguinal hernia or cholecystectomy. They found that propofol decreased thiobarbituric acid reactive substances production by 25.7% and increased total glutathione content by 24.6%. On the other hand, thiopental did not change any of the variables of platelet oxidative stress (8). Zhang et al. showed protective effects of propofol on H2O2-induced cardiomyocyte injury and myocardial ischemic/reperfusion injury in rats (10).

The effects of antioxidants and anesthetic agents on oxidative stress due to ischemia-reperfusion injury have been investigated in some previous studies (11). Lee J Y et al. showed that oxidative stress in the propofol group was significantly lower than in the thiopental group in dogs underwent surgery (6). Kanbak et al. found that propofol attenuated the effects of ischemia-reperfusion injury on tissues (12). Tsuchiya et al. showed that propofol had a safe keeping effect against oxidative damage in red blood cell (13).

Thiopental may increase oxidative stress in the heart, bronchial tissues and brain of rats (14). In another study, Nishina et al. reported that thiopental significantly may decrease reactive oxygen products released from lymphocytes (15). Yağmurdur et al. stated in a study on testicular ischemia-reperfusion injury in rats that propofol reduced germ cell apoptosis more than thiopental did (7).

PON1 has an antioxidant effect against lipid peroxidation (16). Turkoglu et al. has reported that PON1 levels in patients with metabolic syndrome are lower than in healthy individuals without metabolic syndrome (17). In Parkinson's patients compared to healthy individuals, PON1, arylesterase and TAS levels were lower and TOS levels were higher (18). There are few studies investigating the effects of propofol and thiopental on oxidative stress in humans. Yagmurdur et al. compared the effects of etomidate, thiopental and propofol on malondialdehyde levels during laparoscopic cholecystectomy. They showed that malondialdehyde levels were lower both before and after desufflation in the propofol group. On the contrary, malondialdehyde levels were higher in the etomidate and thiopental groups than in the propofol group at both times (19). Propofol and sevoflurane were compared in patients underwent transsphenoidal pituitary surgery and it was suggested that both agents had similar antioxidant effects (20). Kutluhan et al. compared the effects of propofol and desflurane on surgical stress response in vertebra surgery. They found that post-operative thiol values were higher in the propofol group ($p<0.05$). However, the disulfide level was lower (21).

Simsek et al. compared the thiol-disulfide balance in general and spinal anesthesia in total knee replacement surgery. They used propofol for induction of general anesthesia. They found an increase in natural thiol and total thiol levels in the propofol group compared to the spinal anesthesia group and a decrease in disulfide (22).

Limitations

Limitations of this study include the possibility that multiple factors may influence the outcome. It was not possible to measure an agent given only for anesthesia induction without the effect of other applications during anesthesia maintenance.

Conclusion

In conclusion, TAS level increased statistically significantly in the propofol group than the thiopental group. ARES, native thiol, total thiol and disulphide levels decreased in both groups. PON1 level did not change in the propofol group, however it decreased in the thiopental group. Compared with thiopental, propofol can significantly increase TAS levels, therefore, it may preferable anesthetic agent for patients undergoing laparoscopic cholecystectomy.

Ethical Approval

Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee approved the study with decision number 235 on 17 December 2014.

Author Contributions: AGÇ generated the study conception. AGÇ and ŞMA designed the study. AGÇ acquired the data. AGÇ and ŞMA analyzed and interpreted the data. AGÇ, ATDÖ, DG and ŞMA were involved in writing of the manuscript. ŞMA and DG critically reviewed the manuscript. The manuscript has been approved by all authors for publication.

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