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Effects of Open versus Laparoscopic Cholecystectomy on Oxidative Stress in Dogs

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Abstract : In the present study, we investigated and compared the oxidant-antioxidant status of dogs undergoing open and laparoscopic cholecystectomy. Ten male beagle dogs, 4-6 years old, weighing 7-12 kg were used. The animals were randomly assigned to one of two groups according to the type of surgical procedure; open (group 1, n = 5) or laparoscopic cholecystectomy (group 2, n = 5). Heart rate, mean arterial pressure, end-tidal carbon dioxide, peripheral oxygen saturation, and respiratory rates were measured. Plasma total oxidant status (TOS) and total antioxidant status (TAS) levels for the evaluation of oxidative stress were measured. The ratio of the TOS to the TAS gave oxidative stress index (OSI), which is an indicator of the degree of oxidative stress. TOS, OSI and TAS levels were significantly changed after surgery in comparison to levels of before anesthesia. There were no significant different between groups. In the present study, we showed that oxidative stress parameters were found similar in dogs underwent laparoscopic or open cholecystectomy.

Key words **:** cholecystectomy, laparoscopic surgery, oxidative stress, dogs.

Introduction

Laparoscopic surgery is nowadays a common daily-performed procedure worldwide, replacing many types of open surgeries. Many advantages of laparoscopic surgery have clearly been demonstrated including shorter length of stay, decreased postoperative pain and recovery time, and less adhesion formation (9,10). In addition, laparoscopic technique has become standard for cholecystectomy with results comparable to those of open surgery.

Surgery results in a wide spectrum of unfavorable alterations in normal body homeostasis, which are collectively referred to as surgical stress (7). Reactive oxygen species (ROS) function as key metabolites that can impair biological processes, resulting in various pathological conditions. The pathological increase of oxygen free radical generation has already been recognized in many diseases. The increase in the production of ROS due to surgical stress has been reported and it's known that surgical trauma causes an increase in free radical production (5). Moreover, adverse hemodynamic changes and reduction of abdominal visceral perfusion could be an important cause of oxidative stress during laparoscopic surgical procedures (2). However, no controlled studies have been conducted to evaluate oxidant-antioxidant status of laparoscopic surgery in dogs.

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In the present clinical study, we investigated and compared the oxidant-antioxidant status of dogs undergoing open and laparoscopic cholecystectomy.

Materials and Methods

Animals and anesthesia

Ten male beagle dogs, 4-6 years old, weighing 7-12 kg were used. All dogs were healthy based on clinical examinations. The experimental and housing protocols were approved by the Chungnam National University Animal Care and Use Committee (approval no. CNU-0038). This study was conducted 14 days after procuring the dogs. The dogs were kept in a quiet room to avoid any stress-inducing factors during this period. Food was withheld for 8-12 h prior to anesthesia, but access to water was allowed. The animals were randomly assigned to one of two groups according to the type of surgical procedure; open (group 1, n = 5) or laparoscopic cholecystectomy (group 2, n = 5).

The dogs were premedicated with atropine sulfate (Atropine sulfate inj®, Je Il Pharm. Korea; 0.04 mg/kg, SC), cefazoline (Cefazolin inj®, ChongKun Dang Pharm, Korea; 20 mg/kg, IV) and an analgesic agent (butorphanol, Butopan inj®, Myungmoon Pharm; 0.2 mg/kg, IM) before the induction of anesthesia. Anesthesia was induced with propofol (Aanepol inj®, Hana Pharm; 4-6 mg/kg) and 100% oxygen. After endotracheal intubation, anesthesia was maintained with isoflurane, at an end-tidal concentration of 2%, using a

Datex ohmeda ADU anesthesia system (Helsinki, Finland), with an oxygen flow rate of 2 L/min. Heart rate, mean arterial pressure, end-tidal carbon dioxide, peripheral oxygen saturation, and respiratory rates were measured. During the anesthesia, the dogs were given IV fluid (Hartmann's solution, 10 ml/kg/h).

Open surgery

A standard ventral midline incision was made from xiphoid process of the sternum to the umbilicus. The gallbladder was bluntly dissected out of hepatic fossa, then dissection was continued down the cystic duct to its junction with the common bile duct. Double ligation of the cystic duct and artery was applied with 2-0, nonabsorbable suture material. The duct was transected distal to the ligatures, and the gallbladder was removed. The abdominal, subcutaneous, and skin layers were sutured routinely.

Laparoscopic procedure

Laparoscopic cholecystectomy was performed through a three-port technique (a baseball infield), including a subumbilical camera port (5 mm) and two instrument ports (5 mm). One instrument port was placed 5 to 7 cm lateral and 3 to 5 cm cranial to the umbilicus on the right side and other was placed 4 to 6 cm lateral and 2 to 3 cm cranial to the umbilicus on the left side. Insufflations with CO2 were provided via an automatic insufflator with pressure set at 10 to 12 mm Hg. The gallbladder was elevated with grasping forceps and was dissected around the cystic duct and artery with 5 mm right-angle dissecting forceps. Three hemostatic clips were placed around the cystic duct and artery, and transected distal to the second clip with dissecting scissor. The gallbladder was then dissected out of hepatic fossa and removed thorough 1 to 2 cm incision of abdomen at port site.

Monitoring and postoperative care

Baseline values for heart rate, respiratory rate, rectal temperature, blood pressure, and blood samples were obtained for analysis before anesthesia and the end of surgery. After surgery, each animal was monitored until it was ambulatory. Dogs were given butorphanol 0.2 mg/kg intramuscularly at the end of the surgical procedure for postoperative analgesia. A second dose of butorphanol 0.1 mg/kg was given intramuscularly 6 hours after surgery. Water and moistened dog food were offered 12 hours after surgery.

Oxidative stress parameters

Blood samples (3 ml) were collected via venipuncture from the jugular vein at each designated time. The samples were centrifuged at 3000 rpm for 10 min to separate plasma and the blood samples were stored at −80ºC until analysis. Plasma total oxidant status (TOS) and total antioxidant status (TAS) levels for the evaluation of oxidative stress were determined using a commercially available kit (Mega Tip; REL Assay Diagnostics, Gaziantep, Turkey) developed by Erel [1]. The ratio of the TOS to the TAS gave oxidative stress index (OSI), an indicator of the degree of oxidative stress.

Statistical analysis

Data were expressed as median (inter-quartile range), and Mann-Whitney U-test was used for detection of differences between blood sample. A p-value < 0.05 was considered significant. All statistics were performed using a computer statistical package (Statistics Package for the Social Sciences, version 18.0; SPSS, Chicago, IL, USA).

Results

Total anesthetic time was mean (SD) 110 (20) minutes (ranging from 80 minutes to 110 minutes). Mean operation times of group 1 and group 2 were 48 (11) and 57 (15) minutes, respectively. The differences in the respective mean operation times of two groups were not stiatistically significant. All dogs were hemodynamically stable during experiments. There were no significant worsening in heart rate, mean arterial pressure, end-tidal carbon dioxide, peripheral oxygen saturation, and respiratory rates (data not shown).

The plasma TOS, TAS, and OSI are shown in Table 1. An increase in the plasma TOS levels in both groups after surgery was observed. The TOS level of groups was significantly higher at the end of surgery than before induction of anesthesia. Plasma TAS levels were significantly decreased in both group after surgery. OSI levels increased significantly in the both groups after surgery.

Discussion

Laparoscopic cholecystectomy, a minimally invasive procedure in which the gallbladder is removed, is a common operation and has gained worldwide acceptance as the gold standard surgical method to treat gallstone diseases (3). Laparoscopic, using the pneumoperitoneum or wall-lifting techniques, has become the gold standard for symptomatic

Table 1. Oxidative stress parameters of the dogs

Parameters	Group	Before induction of anesthesia	End of the surgery
TOS ($\mu molH_2O_2/L$)	Group 1	8.44 (1.31)	27.3 (6.15)*
	Group 2	8.70 (2.18)	22.2 (5.26)*
TAS (mmol Trolox equiv/L)	Group 1	1.74 (0.53)	0.70 (0.15)*
	Group 2	1.75 (0.24)	0.78 (0.11)*
OSI (arbitrary unit)	Group 1	5.13 (1.24)	41.25 (16.28)*
	Group 2	5.17 (1.89)	29.08 (9.47)*

The values represent the median (inter-quartile range).
*Statistically difference compared to "before induction of anesthesia." (n = 5).
**Statistically difference compared to thiopental group (n = 5).

cholelithiasis and the first choice for treatment of this disease in recently all surgical clinics (8).

There are several studies that demonstrate the beneficial effects of laparoscopic techniques and the advantages of laparoscopic cholecystectomy. Many of studies have shown that one of the most important benefits of laparoscopic cholecystectomy is a decrease in hospital stay. In the present study, we showed that oxidative stress parameters were found similar in dogs underwent laparoscopic or open cholecystectomy.

The evaluation of oxidative stress can indirectly reflect the changes in microcirculation in the splanchnic area during surgery. Different oxidative stress makers have been investgated, including nitric oxide; levels of tissue and blood malondialdehyde and total antioxidant; and levels of thiobarbituric acid reactive substances to assess lipid peroxidation, protein carbonyl content, and protein sulfydryl. In addition to these methods, TOS, TAS and OSI have been used to reflect oxidative stress and actions against oxidative stress.

Trauma and surgical injury are associated with increased production of ROS, and the use of antioxidant system, in particular when associated with relative tissue ischemia followed by reperfusion, may inhibit ROS production. Oxidative stress results from an imbalance between radical-generating and radical-scavenging systems, which leads to cell membrane impairment (6). In the present study, oxidative stress was multifactorial in origin; the main impacts were from the surgical trauma of both laparoscopic or open surgery, and anesthesia. In addition, oxidative stress was in origin from ischemia-reperfusion events due to viseceral organ manipulation in the open cholecystectomy. TOS levels of both experimental groups were significantly increased after surgery. In a similar manner, a recent study on surgical patients reported that surgical trauma alone raises TOS (4). In a study Zulfikaroglu *et al*., the effect of carbon dioxide insufflations on tissue and blood malondialdehyde, TAS and blood nitric oxide were examined (11). The total operation times for laparoscopic cholecystectomy and open cholecystectomy patients were 46 and 53 minutes, respectively. Blood malondialdehyde levels were higher after surgery. In contrast, TAS levels did not change significantly. However, in the present study, we observed a decrease in TAS from induction of anesthesia to the end of surgery. This change in TAS level was statistically significant in both groups. These results are evidence for changing antioxidant defense systems under surgical condition.

TOS, OSI and TAS levels were significantly changed after surgery in comparison to levels of before anesthesia. There were no significant different between groups. Therefore, the different effect of laparoscopic cholecystectomy in oxidative stress status is not clear in this study.

In conclusion, this study showed that both laparoscopic and open cholecystectomy caused an increase on oxidative stress. In addition, the oxidant-antioxidant status was similar in dogs undergoing open or laparoscopic cholecystectomy. Further studies need to be conducted to demonstrate the exact mechanism of oxidative stress due to anesthesia and surgery in dogs.

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개에서 산화 스트레스 상태에 대한 일반 개복술 대 복강경 수술을 통한 담낭절제술의 영향

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요 약 : 본 연구에서는 개에서 일반 개복술을 통한 담낭절제술과 복강경을 이용한 담낭절제술에서 생체 내 산화-항산화 상태에 미치는 영향을 비교 연구하였다. 10 마리의 비글견을 사용하였고 일반 개복술을 통한 담낭절제술군 (group 1, n = 5)과 복강경을 이용한 담낭절제술군 (group 2, n = 5)으로 분류하였다. 심박수, 혈압, 호기말 이산화탄소 분압, 말초 산소포화도, 호흡수를 측정하였다. 산화 스트레스 평가를 위한 총 산화 상태 (total oxidant status, TOS) 및 총 항산화 상태 (total antioxidant status, TAS) 수준이 측정되었다. TAS에 대한 TOS의 비율로 산화 스트레스 지수 (OSI)를 평가하였다. 수술 후에 두 군 모두 TOS, OSI, TAS의 유의성 있는 변화가 관찰되었으나 군 간의 유의성은 없었다. 본 실험을 통해 개에서 일반 개복술을 통한 담낭절제술과 복강경을 이용한 담낭절제술에서 생체 내 산화스트레스 상태에 미치는 영향은 비슷하게 나타났다.

주요어 : 담낭절제술, 복강경 수술, 산화 스트레스, 개