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Effects of Open vs. Laparoscopic Cholecystectomy on Oxidative Stress

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Bukan, M.H., Bukan, N., Kaymakcioglu, N. and Tufan, T. *The Effects of Open vs. Laparoscopic Cholecystectomy on Oxidative Stress.* Tohoku J. Exp. Med., 2004, **202** (1), 51-56 —— Elective laparoscopic cholecystectomy is established as the treatment of choice for symptomatic cholecystolithiasis and is now proposed for the treatment of acute cholecystitis. The aim of this study is to evaluate biochemical aspects of open (OC) and laparoscopic cholecystectomy (LC). We measured the levels of malondialdehyde (MDA) and the levels of nitrite+nitrate as stable end products of nitric oxide (NO). MDA and nitrite+nitrate levels were increased at both surgical procedures compared to preoperative period, but the rise was more significant in OC than LC. These results showed that both OC and LC caused an increase in oxidative stress. However LC caused significantly less oxidative stress and the changes during surgery returned to preoperative values after LC in a shorter period. The beneficial effects of laparoscopic surgery may be related, partially, to less oxidative stress in the immediate postoperative period. ——— laparoscopic cholecystectomy; open cholecystectomy; oxidative stress

Laparoscopic technique has became standard for cholecystectomy with results comparable to those of open surgery. Most advantages of laparoscopic surgery have been shown in several studies (Araujo-Teixeria et al. 1999; Avrutis et al. 2000; Pessaux et al. 2001; Schietroma et al. 2001).

The pathological increase of oxygen free radical generation has already been recognized in more than one hundred diseases (Kurien and Scofield 2003; Lyamina et al. 2003; Parihar and Pandit 2003; Ryu et al. 2003). A decrease in the production of nitric oxide (NO) due to surgical stress has been reported and it's known that surgical trauma causes an increase in free radical production (Liu et al. 1994; Delogu et al. 2001; Nathens et al. 2002).

NO is an inorganic free radical gas produced in the vascular endothelium by the iso-enzyme nitric oxide synthase (NOS) using L-arginine as a substrate. Two isoforms of NOS have been well characterized. The first one is inducible NOS (iNOS), which is induced in macrophages

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TABLE 1. *Patients characteristics and operative findings of groups*

	OC (Group 1)	LC (Group 2)	p
Number of patients	15	15	NS
Age (years) [a]	48 (41-62)	50 (38-65)	NS
Sex (female/male)	10/5	9/6	NS
Operation time (minutes)[b]	73±24.3	55±15.4	<0.05
Bleeding volume (mililiter) [b]	200±58.7	120±67.4	<0.05
Hospital stay (days) [b]	5±0.4	2±0.2	<0.05
WBC counts (/mm^3) [b] (preoperative)	7900±894	8200±762	NS
CRP values (mg/100 ml) [b] (preoperative)	5.6±2.7	6.2±2.4	NS

[a] Means, range in parentheses, [b] means ± S.D., NS, non-significant.

and liver cells by endotoxin and cytokines. It is independent of calcium concentration in the physiological ranges. The second form is constitutive NOS (cNOS), which is dependent on calcium and calmodulin, and consists of two isoforms isolated from the brain and endothelial cells (Alagöl et al. 1999). Unlike other biological mediators, the chemistry of NO determines its biological properties. NO can undergo numerous reactions, leading to the formation of biologically reactive oxygen species. Nitrosative and oxidative stress are produced by different chemical mechanisms. NO can also interact with reactive oxygen species that mediate oxidative stress (Andreadis et al. 2003; Wei et al. 2003).

We assessed short-term effects of laparoscopic cholecystectomy (LC) on oxidative stress and compared the effects of LC vs. open cholecystectomy (OC) on oxidative stress. We measured the levels of malondialdehyde (MDA) as a marker of free radical-induced lipid peroxidation and the levels of nitrite+nitrate as stable end products of NO.

Material and Methods

We collected the blood samples of patients undergoing elective cholecystectomy for symptomatic cholelithiasis. This is a prospective randomized study. With the approval of the local ethics committee fifteen patients treated with OC (Group 1) and 15 patients that underwent LC (Group 2) at Gülhane Military Medical Academy, Department of Surgery were enrolled in this study. Patients characteristics and operative findings are shown at Table 1. The blood samples of all patients were collected at one day prior to surgery, 45 minutes after surgical incision and on post-operative day number one. After centrifugation, serum samples were frozen at –70°C until used in the study. We evaluated oxidative stress for both surgical procedures. MDA levels were measured by the method using thiobarbituric acid and the results were given as micromoles per liter (μmol/liter) (Yoshioka et al. 1979). Nitrite was determined using Griess reaction (Green et al. 1982). Nitrate was measured using the enzymatic one-step assay with nitrate reductase. This method is based on the reduction of nitrate to nitrite by nitrate reductase in the presence of β-NADPH (Bories and Bories 1995).

Friedman's non-parametric test was used for the statistical analysis and p<0.05 was considered significant. The statistical differences of patient characteristics and operative findings between the patients groups were analyzed with Mann-Whitney's U-test. p<0.05 was accepted significant.

Results

In the serum of the patients who underwent OC (Group 1), both MDA and nitrite+nitrate levels increased during surgery (perop.) compared to those of the preoperative visit (preop.) (p< 0.05) and this increase reverts to normal on the first postoperative day (postop.). On the other hand,

TABLE 2. *Nitrite+nitrate levels (μmol/liter) of the patients (results are expressed as mean±S.D.) (preop.: preoperative values, perop.: peroperative values during surgery, postop.: postoperative values)*

Groups	Preop.	Perop.	Postop.
OC (group 1)	48.64±14.1	84.10±17.5[a]	55.69±12.8[b]
LC (group 2)	44.52±11.9	68.6±13.4[a]	43.56±9.8

[a] $p<0.05$ compared to preop. and postop., [b] $p<0.05$ compared to LC group.

TABLE 3. *MDA levels (μmol/liter) of the patients (results are expressed as mean±S.D.) (preop.: preoperative values, perop.: peroperative values during surgery, postop.: postoperative values)*

Groups	Preop.	Perop.	Postop.
OC (group 1)	24.6±7.1	39.2±5.6[a]	25.1±3.2
LC (group 2)	26.2±5.1	29.3±4.3	12.6±2.4[b]

[a] $p<0.05$ compared to preop. and postop., [b] $p<0.01$ compared to preop. and perop.

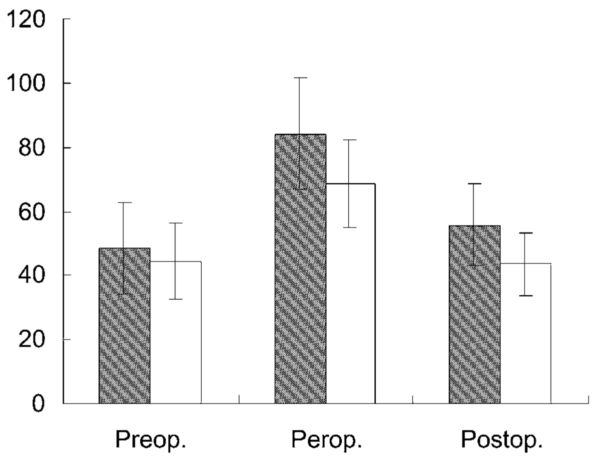

Fig. 1. Nitrite+nitrate levels (μmol/liter) of the patients. (preop.: preoperative values, perop.: peroperative values during surgery, postop.: postoperative values).
■, OC; □, LC.

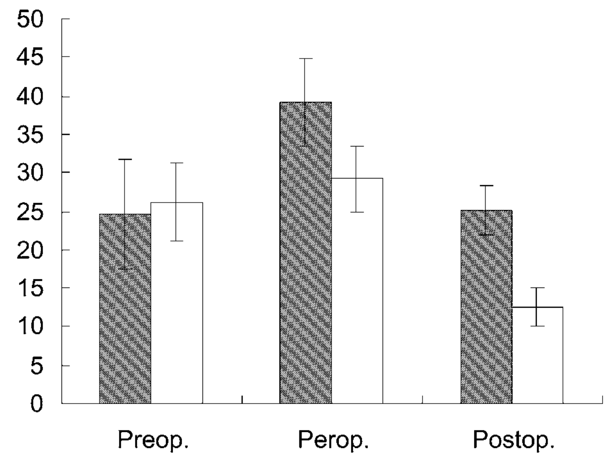

Fig. 2. MDA levels (μmol/liter) of the patients. (preop.: preoperative values, perop.: peroperative values during surgery, postop.: postoperative values).
■, OC; □, LC.

MDA levels increased slightly, but not significantly, during surgery in group 2 ($p>0.05$). On the first postoperative day, it decreased significantly compared to the preoperative value ($p<0.01$). Nitrite+nitrate levels of group 2 increased during surgery compared to the preoperative value ($p<0.05$) but it returned to preoperative levels on postoperation day number one ($p<0.05$). In the peroperative and postoperative samples MDA and nitrite+nitrate levels in group 1 were found higher than those in group 2 ($p< 0.05$). But there was no difference between the groups in the preoperative day. The results are shown at the Tables 2 and 3 and Figs. 1 and 2.

There were no significant changes between age and sex characteristics, white blood cells (WBC) count, CRP levels of patients. However, operation time, bleeding volume and hospital stay were lower in patients treated by LC than those in OC (p<0.05, at all).

Discussion

Laparoscopic surgery showed a dramatic development during the last years of the 20th century. From the beginning, laparoscopic cholecystectomy (LC) has been the pacemaker of this development. Elective LC, using the pneumoperitoneum or wall-lifting techniques, has become the gold standard for symptomatic cholelithiasis and the first choice for treatment of this disease in nearly all surgical clinics (Schirmer et al. 1991; Kitano et al. 1993; Niomiya et al. 1998; Ogawa et al. 2001). Therefore, laparoscopic cholecystectomy is the most common minimally invasive procedure. Open cholecystectomy is left for special indications only (Kraas and Farke 2002).

There are several studies that demonstrate the beneficial effects of laparoscopic techniques and the advantages of LC (Bickel et al. 1996; Eldar et al. 1997; Kiviluoto et al. 1998; Lujan et al. 1998). Researchers have shown that one of the most important benefits of LC is a decrease in hospital stay. In the present study, we showed that operation time, hospital stay and bleeding volume were found lower in patients underwent LC. These are known as the most important advantages of laparoscopic surgery.

Schietroma et al. (2001) evaluated the clinical and financial advantages of LC vs. OC in their study. They observed significant differences concerning the number of days that pain was suffered, the duration of postoperative hospitalization, the extent of postoperative monitoring and the number of days in order to return to normal activity. The results of their study showed , clinically and financially, LC had obvious advantages over OC. In addition to these benefits, they also suggested that LC has less effects on oxidative stress than OC during surgery. Zulfikaroglu et al. (2002) showed that the antioxidant defense system is stimulated less with less oxidative stress, providing further evidence to support the opinion that LC is a safe technique.

On the other hand, Glantzounis et al. (2001) examined the thiobarbituric acid-reactive substances (TBARS), total antioxidant status (TAS) and uric acid (UA) levels in LC and OC groups. They concluded that free radical-induced lipid peroxidation resulted in decreased plasma TAS and UA levels as well as altered hepatic function after deflation of the pneumoperitoneum. These results suggested that free radicals are generated at the end of a laparoscopic procedure, possibly as a result of an ischemia-reperfusion phenomenon induced by the inflation and deflation of the pneumoperitoneum (Glantzounis et al. 2001).

In another study, lipid peroxidation and antioxidant state after laparoscopic and open cholecystectomy were examined and it was shown that LC caused significantly less oxidative stress than the open operation (Seven et al. 1999).

Gal et al. (1998) investigated surgical trauma induced by laparoscopic cholecystectomy and showed both open and laparoscopic procedures induced changes of acute-phase response, free radical mediated reactions, and neutrophil functions. However, LC induced a significantly less intense response in these parameters. These results and data from the literature suggested that surgical injury caused by the LC was less intense than that after OC, which could explain the better clinical outcome following laparoscopic versus open procedure (Gal et al. 1998). Similarly, other studies revealed that LC causes minor changes in activity of antioxidant enzymes and level of MDA compared to OC (Gal et al. 1997; Olakowski et al. 1997).

Our results are similar to studies that suggested LC caused less oxidative stress than OC. There was no difference between the groups during preoperative evaluation. We determined both MDA and nitrite+nitrate levels increased during both open and laparoscopic procedures, compared to those of the preoperative day. This increase may relate to surgical stress, because these parameters revert to normal on the first postoperative day. On the other hand, MDA levels increased slightly during operation at laparoscopic procedure but this increase is not significantly. In the first postoperative day, MDA levels decreased significantly compared to the preoperative value. Nitrite + nitrate levels of LC group increased during surgery compared to preoperative values. On the first postoperative day, these levels decreased under the preoperative values. MDA and nitrite + nitrate levels in OC group were higher than those in LC group during the intraoperative and postoperative period.

Our study showed that both OC and LC caused an increase on oxidative stress. However, LC caused significantly less oxidative stress than the open operation and the changes depending on surgery quickly returned to normal levels after LC. The beneficial effects of laparoscopic surgery may relate,in part, to less oxidative stress in the immediate postoperative period.

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