EVALUATION OF LIVER BIOMARKERS AFTER LAPAROSCOPIC CHOLECYSTECTOMY IN PATIENTS UNDER 60 YEARS

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Keywords: laparoscopic cholecystectomy, pneumoperitoneum, aspartate transaminase (AST), alanine transaminase (ALT), bilirubin.

Abstract: Laparoscopic cholecystectomy (LC) is gold standard treatment for cholelithiasis. This surgical procedure requires insufflation of carbon dioxide into peritoneal cavity. Intra-abdominal pressure increases, causing disturbances on blood flow of the portal vein with secondary liver injury. In this study we evaluated the hepatic function in 147 patients who underwent laparoscopic cholecystectomy. Three liver biomarkers have been measured 24 hours before and 24 hours after the surgery: aspartate transaminase (AST), alanine transaminase (ALT) and total bilirubin. The results show significantly increased levels of all 3 biomarkers, 24 hours after the surgery. We also found a correlation between surgery duration and levels of serum AST, ALT and bilirubin. The highest levels of hepatic enzymes and total bilirubin were recorded in patients with maximal minutes (80-90) under pneumoperitoneum.

INTRODUCTION

Cholelithiasis is one of the most common diseases of digestive tract. In USA it affects more than 20% of the population above 40 years. Early diagnosis and immediate treatment can prevent severe complications such cholecystitis, acute pancreatitis or peritonitis. In the last decades, the gold standard procedure for surgical treatment of cholelithiasis was represented by laparoscopic cholecystectomy (LC) (Torres et al., 2009; Duca S., 2001). Nowadays, almost 90% of all cholecystectomies are performed laparoscopically (Eryilmaz et al., 2012). LC has numerous advantages over classic cholecystectomy like shorter convalescence, rapid recovery, less postoperative pain and less visible scars (Lai H. et al., 2014; Agresta et al., 2014).

Despite all these advantages, numerous complications were reported, some of them related to carbon dioxide pneumoperitoneum (CDP). There are reports about pneumoperitoneum effects on cardiovascular and respiratory system. Several studies have demonstrated the association between carbon dioxide pneumoperitoneum and hepatic injury. Elevated levels of aspartate transaminase (AST) and alanine transaminase (ALT) were noticed in patients who underwent LC (Baris Eryilmaz et al., 2012; Sharma et al., 2015; Krishnegowda et al., 2016). Experimental models have shown that intra-abdominal pressure of 12-14 mmHg of CO₂ can reduce portal blood flow and cause hepatic ischemia. The mechanism of liver ischemia is related by the inflation and deflation of pneumoperitoneum. This ischemia-reperfusion phenomenon cause hepatic injury with release of transaminases. Leukocytes and platelets are permanently adherent to endothelium of hepatic sinusoids which indicate microcirculation abnormalities (Bostanci et al., 2010; Sandhu et al., 2009; Ypsilantis et al., 2016).

The aim of this study is to evaluate the impact of CDP on hepatic injury by comparing preoperative and postoperative levels of serum biomarkers in patients under 60 years old who underwent LC.

PATIENTS AND METHODS

The study was realized in Surgery Department of C. F. Hospital, Iasi. Between 2014 and 2016 a total 306 LC were performed. The inclusion criteria in study were: age (18-59 years), gallbladder disease and normal values of liver biomarkers 24 hours before surgery. Patients with cardiac or hepatic dysfunctions, high levels of preoperative liver enzymes, common bile duct stones, positive serology for hepatitis B or C virus, conversion to open cholecystectomy were excluded. For each patient, the diagnosis was confirmed by a physical examination and abdominal ultrasound. The LC was performed under general anesthesia. All the operations were performed using the standard American technique. The carbon dioxide pneumoperitoneum was installed with Veress needle. During the surgery, 12-14 mmHg pressure of pneumoperitoneum was maintained with an automatic insufflator. The following liver biomarkers were analyzed: total bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT). Blood samples were taken from each patient by peripheral vein with 24 hours before surgery. Another blood sample was taken 24 hours after the surgery. In both cases, all samples were analyzed in hospital laboratory and the levels of AST, ALT and serum bilirubin were recorded. The normal values of hepatic biomarkers used in this study are: for AST, 5-40 U/L; for ALT, 5-35 U/L; for total bilirubin, 0.2-1.1 mg/dL. The duration of surgery was recorded from the installation of pneumoperitoneum to the time of deflation and trocars removal. During the postoperative period no other medication was prescribed, but the intravenous antibiotics and
analgesics. All data were expressed as mean ± standard deviation (SD). We also used paired t-test for levels of liver biomarkers before and after the surgery. A P value of <0.05 was considered statistically significant.

**RESULTS AND DISCUSSION**

From a total of 306 LC performed, 199 (65.03%) were patients under 60 years old. After we applied the inclusion and exclusion criteria, only 147 patients were included in the study. The age, sex and time of surgery duration are shown in the Table 1 and Table 2.

Table 1. The distribution of sexes

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>124</td>
<td>84,4</td>
<td>84,4</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>15,6</td>
<td>100,0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>147</td>
<td>100,0</td>
<td>100,0</td>
</tr>
</tbody>
</table>

The gender was dominated by female with 84.4% and the mean age of the patients was 46.85 ± 8.85 years. The mean duration of the surgery was 57.57 ± 13.12 minutes. We have chosen patients under 60 years old for a better perspective of the pneumoperitoneum influence on normal hepatic function. The proportion of patients over 60 with comorbidities was much higher than those under 60 years old. This polymorbidity could interfere with the results.

Table 2. Age and surgery duration in minutes

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>147</td>
<td>19,00</td>
<td>59,00</td>
<td>46,8503</td>
<td>8,85140</td>
</tr>
<tr>
<td>Surgery duration</td>
<td>147</td>
<td>40,00</td>
<td>90,00</td>
<td>57,5714</td>
<td>13,12323</td>
</tr>
<tr>
<td>Valid N (listwise)</td>
<td>147</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From fig. 1 we can observe that the mean preoperative AST levels (normal value: 5-40 U/L) were 28.01 ± 3.69 U/L and after the surgery, values have raised to 71.1 ± 12.06 U/L. Similar data are shown for ALT (26 ± 2.67 U/L before and 70.1 ± 11.85 U/L after the surgery) and serum total bilirubin (0.57 ± 0.1 mg/dL preoperative and 1.74 ± 0.12 mg/dL postoperative). Sefik Hasukic, in a prospective study, evaluated the effects of pneumoperitoneum on hepatic function. His data showed that in the first 48 hours postoperatively, levels of AST and ALT were
significantly increased (Hasukic et al., 2005). Rikki Singal et al. found high levels of AST, ALT and bilirubin 24 hours after LC. In their study, the mean postoperative values for AST were 72,9 ± 13,1 and 72,4 ± 12,9 for ALT. They found a significant difference (P=0,0001) between preoperative and postoperative values of hepatic transaminases (Singal et al., 2015).

![Fig. 1. The mean levels of the liver biomarkers 24 hrs. before surgery and 24 hrs. after surgery](image)

The paired \( t \)-test comparison between preoperative and postoperative levels of AST, ALT and serum bilirubin shows that the data are statistically significant (P<0,01). The mean difference between postoperative and preoperative level of AST is 43,08 ± 12,6 U/L. For ALT and serum bilirubin, the mean difference is 44,1 ± 12,09 U/L respectively 1,17 ± 0,17 mg/dL. The confidence interval is similar for AST and ALT (41,03-45,14 and 42,13-46,07)(Table 3).

Table 3. Comparison between preoperative and postoperative levels of AST, ALT, bilirubin

<table>
<thead>
<tr>
<th>Paired Differences</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
<th>95% Confidence Interval of the Difference</th>
<th>t</th>
<th>df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative AST Preoperative AST</td>
<td>43,088</td>
<td>12,61</td>
<td>1,0401</td>
<td>41,03-45,144</td>
<td>41,4</td>
<td>14</td>
<td>0,0</td>
</tr>
<tr>
<td>ALT</td>
<td>44</td>
<td>111</td>
<td>5</td>
<td>275-12</td>
<td>25</td>
<td>6</td>
<td>0,0</td>
</tr>
<tr>
<td>Postoperative ALT Preoperative ALT</td>
<td>44,102</td>
<td>12,09</td>
<td>0,9976</td>
<td>42,13-46,073</td>
<td>44,2</td>
<td>14</td>
<td>0,0</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>04</td>
<td>593</td>
<td>6</td>
<td>033-75</td>
<td>06</td>
<td>6</td>
<td>0,0</td>
</tr>
<tr>
<td>Postoperative Bilirubin Preoperative Bilirubin</td>
<td>1,1762</td>
<td>1,1761</td>
<td>0,0145</td>
<td>1,147-1,2049</td>
<td>80,9</td>
<td>14</td>
<td>0,0</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>55-7</td>
<td>77</td>
<td>6</td>
<td>0,0</td>
</tr>
</tbody>
</table>

From Fig. 2 and Fig. 3 we can observe the correlation between duration of surgery (in minutes) and levels of serum AST, ALT and bilirubin. Patients with minimum of minutes (40 min.) under the pneumoperitoneum have lower values of hepatic enzymes and bilirubin. The highest levels of hepatic biomarkers were recorded at the patients with surgery duration between 80-90 minutes.

In our study, the mean levels of AST, ALT and bilirubin for patients with 40 minutes under pneumoperitoneum were: for AST 57 ± 1,73 U/L, for ALT 55,66 ± 1,52 U/L and for bilirubin 1,57 ± 0,07 mg/dL. On the contrary, the mean levels of the patients with 90 minutes under...
penumoperitoneum are much higher: for AST 111.66 ± 3.78 U/L, for ALT 109.33 ± 4.04 U/L and for bilirubin 2.03 ± 06 mg/dL.

The duration of surgery, in our study, has a clear correlation with levels of hepatic biomarkers. Hao Lai has concluded in a meta-analysis on 11 comparative studies, that the duration of CO2 penumoperitoneum may be associated with hepatic injury (Lai et al., 2014).

From this study, it is clear that liver biomarkers are elevated after the laparoscopic surgery. Our data show that the level of pneumoperitoneum pressure at 12-14 mmHg may have a significant impact in levels of hepatic enzymes and bilirubin. A study conducted by Makoto Yoshida on a porcine pneumoperitoneum model, showed that the portal vein pressure increased to 15 mmHg for the pneumoperitoneum group, but no significant difference in the levels of serum aminotransferase were recorded (Yoshida et al., 2010). Erdal Birol Bostanci has conducted in 2009 an experimental study in a rat model. He applied carbon dioxide pneumoperitoneum to a number of rats. The results showed that the insufflation of CO2 in the peritoneal cavity to create pneumoperitoneum deteriorates hepatic cell integrity, with an increase in liver enzymes and alteration of the hepatic microcirculation. Levels of AST recorded in their study were 347.4 ± 48 and 67.6 ± 8 for ALT (Bostanci et al., 2009). Due to this postoperative complication of LC, surgeons have developed new methods with low pressure pneumoperitoneum. In this way, Barczynski and Herman compared low pressure (7mmHg) and standard pressure (12mmHg) pneumoperitoneum in laparoscopic cholecystectomy. They concluded that a low pressure peritoneum is superior to standard pressure in terms of the quality of life within 5 days after the operation (Barczynski, 2003).
There are also described methods without pneumoperitoneum. Daijo Hashimoto has developed a model of LC by traction on the abdominal wall with a hanger lifting method. (Hashimoto et. al., 1993).

**CONCLUSIONS**

The pneumoperitoneum seems to have an important role in increasing postoperative levels of serum AST, ALT and bilirubin. The 12-14 mmHg standard pneumoperitoneum pressure is not the ideal pressure to perform LC. The duration of surgery alongside high levels of pneumoperitoneum pressure may affects liver functions. Alternatives methods of laparoscopic surgery, with low pressure peritoneum should be developed.

**REFERENCES**


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