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

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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 maxim of 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 penumoperitoneum and hepatic injury. Elevated levels of aspartate transaminase (AST) and alanine transaminase (ALT) were noticed in patients who underwent LC (Baris Eryilmaz et. all, 2012 ; Sharma et al., 2015 ; Krishnegowda et al., 2016). Experimental models have shown that intra-abdominal pressure of 12-14 mmHg of CO_2 can reduce portal blood flow and cause hepatic ischemia. The mechanism of liver ischemia is related by the inflation and deflation of penumoperitoneum. 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 in patients under 60 years old who underwent LC.

PATIENTS AND METHODS

The study was realized in Surgery Departament 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 the 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 penumoperitoneum 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 penumoperitoneum to the time of desufflation 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 1					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	124	84,4	84,4	84,4
	Male	23	15,6	15,6	100,0
	Total	147	100,0	100,0	

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 2					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	147	19,00	59,00	46,8503	8,85140
Surgery duration	147	40,00	90,00	57,5714	13,12323
Valid N (listwise)	147				

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 at 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).

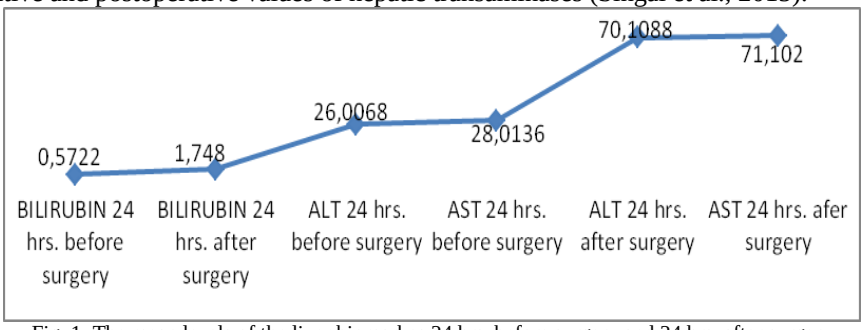

Fig. 1. The mean levels of the liver biomarkes 24 hrs. before surgery and 24 hrs. after surgery

The paired *t*-test comparation 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. Comparation between preoperative and postoperative levels of AST,ALT,bilirubin

Table 3

		Paired Differences					t	df	P value
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Postoperative AST – Preoperative AST	43,08844	12,61111	1,04015	41,03275	45,14412	41,425	146	0,000
Pair 2	Postoperative ALT – Preoperative ALT	44,10204	12,09593	0,99766	42,13033	46,07375	44,206	146	0,000
Pair 3	Postoperative BILIRUBIN – Preoperative BILIRUBIN	1,17626	,17612	0,01453	1,14755	1,20497	80,977	146	0,000

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.

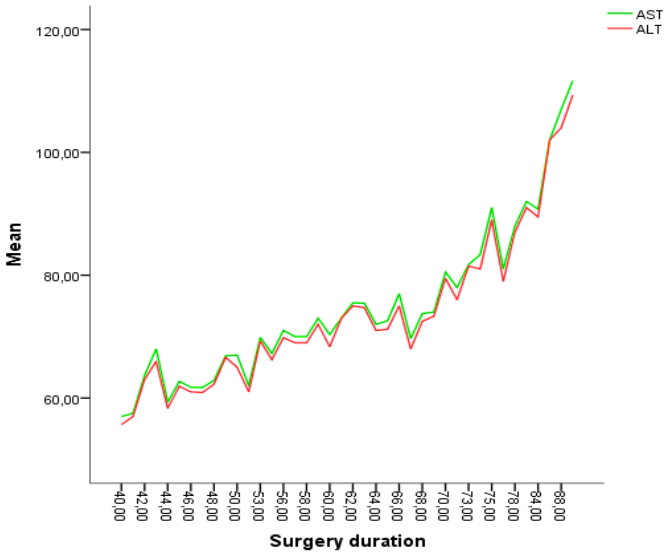

Fig. 2.The correlation between surgery duration and postoperative AST,ALT levels

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 CO_2 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 penumoperitoneum. 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).

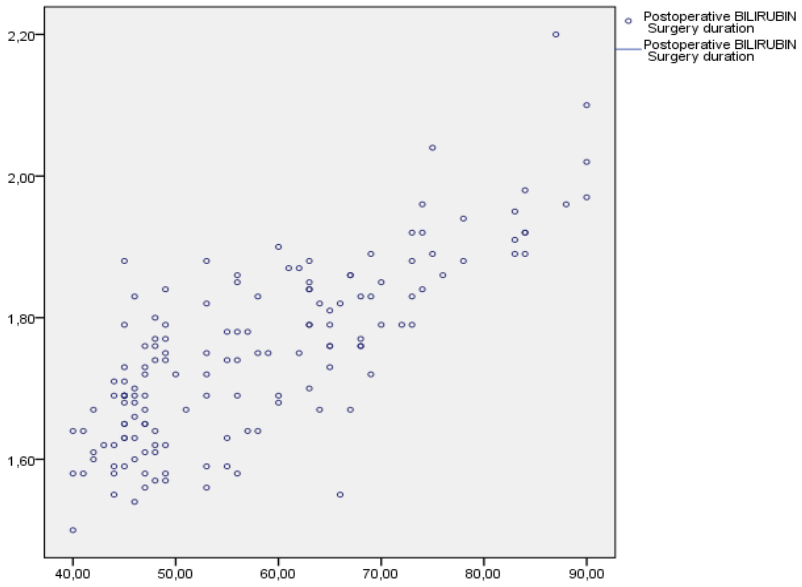

Fig. 3. The correlation between surgery duration and postoperative bilirubin levels

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

Agresta F.,Campanile F. C.,Vettoretto N. (2014). *Laparoscopic cholecystectomy an evidence-based guide.* Springer Cham Heidelberg New York Dordrecht London, pp. 159-167.

Barczynski M.,Herman R. M. (2003). *A prospective randomized trial on comparison of low-pressure(LP) and standard-pressure (SP) pneumoperitoneum for laparoscopic cholecystectomy.* Surg Endosc, 17: 533–538.

Bostanci E. B.,Yol S.,Teke Z.,Kayaalp C. et al. (2010). *Effects of carbon dioxide pneumoperitoneum on hepatic function in obstructive jaundice: an experimental study in a rat model*. Langenbecks Arch Surg , 395:667–676.

Duca S. (2001): *Chirurgia Laparoscopica*,Editia a 2-a, Editura Paralela 45, pp. 68-70, 93-96

Eryılmaz B. H.,Memis D.,Sezer A.,Inal M. T. (2012). *The effects of different insufflation pressures on liver functions assessed with LiMON on patients undergoing laparoscopic cholecystectomy.* The Scientific World Journal Volume 2012, Article ID 172575.

Hashimoto D.,Nayeem S. A.,Kajiwara S.,Hoshino T. (1993). *Laparoscopic cholecystectomy: an approach without pneumoperitoneum.* Surg Endosc, 7:54-56.

Hasukic S.,Kosuta D.,Muminhodzic K. (2005). *Comparison of postoperative hepatic function between laparoscopic and open cholecystectomy.* Med Princ Pract, 14:147–150.

Krishnegowda U.,Gupta A.,Sharma R.,Gupta N.,Durga C. K. (2016). A *comparative study between low and normal pressure pneumoperitoneum in laparoscopic cholecystectomy with special reference to shoulder tip pain.* Hellenic Journal of Surgery, 88:1, 13-17.
Lai H.,Mo X.,Yang Y.,Xiao J. et al. (2014). *Association between duration of carbon dioxide pneumoperitoneum during laparoscopic abdominal surgery and hepatic injury: a meta-analysis*. PLoS ONE, 9(8): e104067.
Negură A., *Introducere în biochimia clinică*, Editura TEHNOPRESS, Iași, 2008. ISBN 978-973-702-527-2
Sandhu T,Yamada S.,Ariyakachon V.,Chakrabandhu T.,Chongruksut W.,Ko-iam W. (2009). *Low-pressure pneumoperitoneum versus standard pneumoperitoneum in laparoscopic cholecystectomy,a prospective randomized clinical trial*. Surg Endosc, 23:1044–1047.
Sharma A.,Dahiya D.,Kaman L.,Saini V.,Behera A. (2016). *Effect of various pneumoperitoneum pressures on femoral vein hemodynamics during laparoscopic cholecystectomy*.Updates Surg, DOI 10.1007/s13304-015-0344-x.
Singal R.,Singal R. P.,Sandhu K.,Singh B. et al. (2015). *Evaluation and comparison of postoperative levels of serum bilirubin, serum transaminases and alkaline phosphatase in laparoscopic cholecystectomy versus open cholecystectomy.* Gastrointest Oncol, 6(5):479-486.
Torres K.,Torres A.,Staskiewicz G. J.,Chroscicki A.,Łos T.,Maciejewski R. (2009). *A comparative study of angiogenic and cytokine responses after laparoscopic cholecystectomy performed with standardand low-pressure pneumoperitoneum.* Surg Endosc, 23:2117–2123.
Yoshida M.,Ikeda S.,Sumitani D.,Takakura Y. et al. (2010). *Alterations in portal vein blood pH, hepatic functions, and hepatic histology in a porcine carbon dioxide pneumoperitoneum model*. Surg Endosc, 24:1693–1700.
Ypsilantis P.,Lambropoulou M.,Tentes I.,Chryssidou M.,Georgantas T.,Simopoulos C. (2016). *Room air versus carbon dioxide pneumoperitoneum: effects on oxidative state, apoptosis and histology of splanchnic organs.* Surg Endosc, 30:1388–1395.

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