Original Article

Impact of Pneumoperitoneum on Hepatic Functions after Laparoscopic Cholecystectomy (LC)

Fakhar Hameed, Bashir Ahmed, Asrar Ahmed khan, Riaz Hussain Dab

ABSTRACT

Objective: To find out the alterations in hepatic functions after laparoscopic cholecystectomy and the possible mechanisms behind such effect. **Study Design:** A prospective analytic study. **Place and Duration of Study:** The study was conducted in surgical unit-1; Allied Hospital Faisalabad, from January 1st, 2009 to June 30th, 2009. **Patients and Methods:** With approval from the institutional ethical committee and informed consent, as per inclusion and exclusion criteria, 100 patients for laparoscopic cholecystectomy were included in the study. The blood samples of the patients were collected to test liver enzymes; bilirubin, alanine aminotransferase (ALT) aspartate aminotransferase (AST) and alkaline phosphatase (ALP) once pre-operatively and then on 2nd and 10th post operative days. The preoperative values were compared with that of postoperative values. During LC intra-abdominal pressure for pneumoperitoneum was maintained at 14 mmHg of CO2 and the duration of CO2 insufflation was measured. **Results:** Forty eight hours after LC, levels of ALT, AST and bilirubin were found to be increased (ALT: 51.11 U/L, P<0.001; AST: 53.79 U/L, p<0.001 and Bilirubin: 1.38mg/dl P <0.001which were statistically significant. Moreover, these hepatic enzymes were significantly increased in patients who had longer durations of CO2 insufflations. The changes in alkaline phosphatase measurements were found to be non significant. The levels of hepatic functions returned to normal or near normal values in samples of 10th post operative day. **Conclusion:** Transient alterations in hepatic functions are frequently observed after uneventful laparoscopic cholecystectomy, which clinically appear to be insignificant. CO2 Pneumoperitoneum seems to be the main reason for theses changes but other factors may also contribute. **Key Words**: Laparoscopic Cholecystectomy, Hepatic functions, CO2 pneumoperitoneum

INTRODUCTION

The introduction of laparoscopic surgery has changed dramatically the management of gallstone disease and has established Laparoscopic Cholecystectomy (LC) as the gold standard method to treat uncomplicated cholelithiasis. With experience and training, it is applicable to over 95% cases of symptomatic cholelithiasis[1]. Furthermore, the feasibility and safety of fluoroscopic intraoperative cholangio graphy and the laparoscopic common bile duct exploration have extended the role of laparoscopic techniques in the management of choledocholithiasis as well. [2,3]

Despite its numerous advantages (i.e. a shorter hospital stay, limited postoperative pain, quick recovery, fewer complications), this procedure may impair hepatic functions. The application of Carbon dioxide (CO2) Pneumoperitoneum in high-risk patients may induce undesirable consequences in critically ill patients with cardiovascular, respiratory or renal insufficiency due to either hypercapnia or increased intra abdominal pressure. [4,5,6,7]

Some recent trials have shown that due to high intra abdominal pressure during laparoscopic Cholecystectomy, intra abdominal blood flow compromises which leads to reduction in portal venous flow. [8,9,10,11] On the other hand, there are controversial studies, which show that the intra abdominal pressures ranging between 11 and 13 mm Hg do not compromise splanchnic circulation.[12] Moreover, elevation of serum liver enzymes after uneventful LC has been reported which seems to be attributed to splanchnic ischemia [13,14,15,16,17,18,19]. Due to all these observations, gasless laparoscopy has been proposed by some surgeons. [20]

No such local study has been carried out in our set up uptill now. Hence, this study was conducted to explore the incidence and clinical significance of liver enzyme changes after uneventful laparoscopic cholecystectomy.

PATIENTS AND METHODS

This prospective study was carried out as per inclusion and exclusion criteria for LC on 100 patients who were admitted in Surgical Unit-1, Allied Hospital Faisalabad. The period of study extended from January 1st, 2009 to June 30th, 2009.

INCLUSION CRITERIA

Following patients were included in the study.

Age between 20 to 70 years.

Patients with uncomplicated gall stone disease.

Patients who underwent uneventful laparoscopic cholecystectomy only.

Patients with no pre existing liver functions abnormality.

Exclusion Criteria: Following patients were excluded from the study.

Patients who had undergone endoscopic retrogade cholangiopancreaticography and sphincterotomy within10 days before the laparoscopic operation.

Patients who developed complications such as bile duct injury, leakage, obstruction and infection.

Patients with per operative cholangiography.

Patients with coexisting liver disease (e.g.Hepatitis B,C and cirrhosis).

High risk patients with co morbid cardiopulmonary and renal problems.

Although, drugs (anesthetic, antibiotic and analgesic) may affect liver function tests.

But, we could not exclude this factor from our study because it was an unavoidable technical flaw. However, we selected those drugs which have either no effect on liver function tests or they affect only to a minimum extent [21,22].

AGE AND SEX DISTRIBUTION

Number and percentage of female and male patients was calculated for their sex wise distribution but for age wise distribution, they were divided into five groups of twenties (A), thirties (B), forties(C), fifties (D) and sixties (E).

Operative Technique: Laparoscopic cholecystectomy in all the patients was performed by the same team of consultants. The operation was performed under general anesthesia with the patients in slight reverse trendelenberg position and 4-trocars technique. All patients received same anaesthetic drugs (propofol,succinyl asta, isoflurane and vencurronium) that are known either not to affect or interfere as little as possible with the enzymatic activity of the liver (constant anesthetic protocol).The pneumoperitoneum was created by insufflation of CO_2 via Veress needle. Intra abdominal pressure was maintained stable at 14 mm Hg in all cases. Monopolar diathermy was used for hemostasis and to detach the gall bladder from its liver bed.After the extraction of gall bladder, drain was placed in sub hepatic space.

POSTOPERATIVE PERIOD

Postoperatively, same intravenous glucose infusions and electrolytes were given to all the patients for 24 hours. Three doses of prophylactic antibiotic ceftriaxone 1G was given intravenously at the time of induction followed by two doses at 12 hourly interval. For postoperative analgesia, injection nalbuphene 10mg I/V was given at 12 hourly intervals as needed. Twenty four hours after operation, all the patients were reviewed for free residual CO_2 gas under the diaphragm by taking X-ray abdomen standing AP view Sampling Technique for Hepatic Functions:Four liver function parameters; alanine Aminotransferase (ALT), Asparate Aminotransferase (AST), bilirubin and Alkaline phosphatase (ALP) were measured pre operatively, on 2nd post-operative day before their discharge and then on the 10th post operative day when they were called for removal of stitches and follow up. The laboratory tests were carried out at the same laboratory using only one type of instrument. It was ensured that all patients selected for the study had normal serum ALT,AST, bilirubin and ALP values in normal range before surgery. The normal range of these haematological parameters was ALT. 5–42 U/L; AST. 5–42 U/L; bilirubin(total) 0.3–1.2 mg/dl and ALP. 80–306 U/L. Statistical Analysis: Results were expressed as means +/- standard deviation. Data was analyzed to find out the significance of effect of laparoscopy on hepatic functions by using students paired "t" test. Statistical analysis was performed with the statistical package of social sciences (SPSS). P- values <0.005 were considered to be statistically significant

RESULTS

Ratio of female patients in our study was 88% (n=88) while males were 12% (n=12). The age of the patients ranged from 21–70 years with mean age 52 years. Patients were divided into five groups namely A, B,C ,D and E for their age wise distribution (Table-1).

Table-1:
Age-wise Distribution of Patients in Groups

Age Range	Groups	Number of patients	Percentage (%)
21 to 30 Years	A	19	19%
31 to 40 Years	B	38	38%
41 to 50 Years	C	27	27%
51 to 60 Years	D	13	13%
61 to70 Years	E	3	03%

All patients remained stable haemodynamically during the postoperative period and the mortality was nil. A statistically significant increase in the levels of serum ALT, AST and bilirubin was noted in samples of 2nd post-operative day. Pre-operative values of ALT and AST were seen to be doubled in 25% of cases. The levels ALT, AST and bilirubin returned to near pre-operative values in samples of 10th postoperative day. Moreover, the elevations in hepatic enzymes particularly, ALT and AST were more marked in patients who had longer durations of CO2 insufflation (Table-2).

Table-2:
S/Alkaline Phosphatase(U/L) Means and Standard Deviations

Time of Assessment	Means	Standard Deviations
Pre operative	204.46	43.67
2nd post operative day	184.51	41.80
10th post operative day	203.42	43.04

Table-3:
Correlation of CO2 Insufflation Time with Levels of Serum Liver Enzymes

Percentage of Patients	Duration of CO2 insufflation	Elevations in levels of hepatic enzymes observed on 2nd post operative day		
		ALT	AST	Bilirubin,
15%	Up to 40 minutes	Up to 45%	Up to 40%	Up to 30%
33%	Up to 50 minutes	Up to 70%	Up to 60%	Up to 45%
27%	Up to 60 minutes	Up to 95%	Up to 80%	Up to 70%
20%	Up to 70minutes	100%	Up to 100%	Up to 80%
5%	Above 70 minutes	Above 110%	Above 100%	Up to 100%

For statistical analysis, means and standard deviations were calculated from the results of pre-operative, 2nd and 10th post-operative day samples values (Tables-3). To find out the significance of effect of aparoscopy on hepatic functions, students paired "t" test was used and P-values of ALT, AST and Bilirubin were found to be <0.001.

Table-4:
Means and Standard Deviations of ALT, AST and Bilirubin at Different Time Intervals

Liver Functions	Time of Assessment	Means	Standard Deviations
ALT (U/L)	Pre operative	28.19	5.29
	2nd post operative day	51.11	13.06
	10th post operative day	29.16	5.40
AST (U/L)	Pre operative	31.23	5.51
	2nd post operative day	53.79	12.92
	10th post operative day	31.20	5.75
Bilirubin (mg/dl)	Pre operative	0.8229	0.1378
	2nd post operative day	1.3840	0.2727
	10th post operative day	0.8280	0.1370

We also measured levels of alkaline phosphatase but no significant alterations were noted (Table-4). Free gas under the diaphragm was not detected in any case which showed that the residual CO2 was absorbed completely within 24 hours of operation.

DISCUSSION

Despite numerous clinical advantages, laparoscopic surgery with pneumoperitoneum leads to complex haemodynamic, metabolic, neurologic, and humoral changes [23, 24, 25, 26, 27].

Hepatic hypo-perfusion during LC reported previously has been attributed to combined effects of hypercapnia, elevated intra abdominal pressure and position of the patient.[28,29]

Carbon dioxide is rapidly absorbed across the peritoneal membrane into the circulation.

The rate of CO2 absorption is 20-30ml/hr at flow rates of 200 ml/min [30]. Maximum absorption of CO2 occurs at the beginning of insufflation and at exsufflation due to the difference in pressure gradient[31]. Due to high solubility in the blood, it may cause hypercapnia with respiratory acidosis by the generation of carbonic acid, resulting in increased heart rate, arterial pressure and systemic peripheral resistances [7]. Body buffers, the largest reserve of which lies in bone, absorb CO2 (upto120 L) and minimize the development of hypercarbia or respiratory acidosis during brief endoscopic procedures. Once the body buffers are saturated, respiratory acidosis develops rapidly and the respiratory system takes the burden of absorbing CO2 and its release from the buffers [32]

The increased intra abdominal pressure on the other hand, affects the cardiovascular system by compressing inferior vena cava and pericardium, and thus decreasing directly the venous blood return to the right atrium and the cardiac output [33]. The usual level of intra abdominal pressure (12-14 mm Hg) is higher than that of portal venous system (7-10 mm Hg). Consequently, it may lead to reduction in portal blood flow and changes in liver perfusion. Experimental data has shown decrease in hepatic perfusion when intra abdominal pressure increases over 6 mm Hg[5]. Portal blood flow decreases as much as 53% when the intra abdominal pressure reaches 14 mm Hg. A significant decrease the hepatic microcirculation has been proved at the pressure of 12 mm Hg [8,9].

Finally,potential causes of splanchnic ischemia during pneumoperitoneum are direct vessel compression, release of vasoactive substances such as angiotensin, and hypercapnia. The deflation of the pneumoperitoneum restores the reduced splanchnic blood flow. Thus, laparoscopy is considered a reperfusion phenomenon model and the disturbances of liver function tests could be attributed to free radical-induced lipid per oxidation seen at the end of the procedure[34]. These free radicals generated at the end of a laparoscopic procedure, possibly as a result of an ischaemia-reperfusion phenomenon induced by the inflation and deflation of the pneumoperitoneum can damage the tissues and organs, especially the Kupffer and the endothelial cells of the hepatic sinusoids[35,36]. Therefore, the elevated intra abdominal pressure due to carbon dioxide pneumoperitoneum may be responsible for the increase of liver enzymes after LC.

Several studies support the hypothesis that alterations in hepatic function after LC may be caused by the local effect of prolonged use of diathermy to the liver surface and subsequent spread to the hepatic parenchyma.[37,38,39,40] However, changes in the level of serum liver enzymes have also been observed after laparoscopic colectomy where the focus is far from the liver.[41].

In our study, there was a significant rise in the levels of serum ALT, AST and bilirubin ($p<0.001$) in immediate post operative period when compared to pre operative values and that of 10th post operative day. While mean values of serum ALP showed no significance alteration in immediate post operative period when compared with means of pre operative and that of 10th post operative day. Moreover, the levels of serum ALT and AST in up to 25% cases and that of serum bilirubin in 5% of patients were doubled on 2nd post operative day. These increased levels were seen in those patients who had a prolonged period of CO2 pneumoperitoneum when compared to others. Ten days after operation, liver enzymes values returned to near normal pre-operative levels in almost all the patients. None of the patient reported any apparent clinical hepatic dysfunction after surgery in their follow up feedback.

Tauro LF, Sheethal CM, et al conducted a study to check and compare the mean pre- operative levels of serum bilirubin, ALT, AST and ALP with that of 1st and 7th post operative days, showed transient increases in these hepatic functions on 1st post operative day. The increased levels were particularly seen in those patients who had prolonged periods of CO2 pneumoperitoneum when compared to others. All the patients in their study, there was a transient rise in the enzymes levels and the values returned to near pre operative levels with in one week after surgery.[42] Similar findings have also been revealed in different series of international literature. [13,14,16,17,18]

The results of our study showed transient increases in serum aminotransferases and bilirubin in all the cases after LC, but, no significant alteration in the levels of ALP.

The alterations in hepatic enzymes of our study are comparable with the observations given in literature. But, in order to ensure accurate conclusions, it was necessary to rule out all other possible reasons of hepatic enzymes abnormalities such as those related to gallstone disease itself and its complications, or any pre-existing chronic liver disease. So, a strict exclusion criteria was set in this study by excluding the patients with known liver function test abnormality, conditions which could affect hepatic enzymes per-operatively i.e. conversion to open cholecystectomy or any other post-operative complications.

Keeping in view the results of international literature and our study, it is concluded that transient elevation of hepatic enzymes occur after un-eventful laparoscopic cholecystectomy without any apparent clinical implications. These transient alterations return to normal levels within 10 days after operation. Major causative factor seems to be the CO2 pneumoperitoneum and increased intra abdominal pressure.

CONCLUSION

Transient elevation in liver function tests is a usual finding after un-eventful LC with out any significant clinical consequences and it is mainly attributed to the high intra- abdominal pressure of CO2 pneumoperitoneum but other factors such as surgical manipulation, diathermy etc may contribute.

RECOMMENDATIONS

Due to paucity of research work on this topic in our clinical set up, further research and studies are suggested to probe our point of view.

REFERENCES

1. Sir Alfred Cusheiri;Robert J.C. Abdool Rahim Moosa; Essential Surgical Practice. Disorders of biliary tract; Ed.4th Vol II, Page. 412
2. Griniatsos J, Karvounis E, Isla AM. Limitations of fluoroscopic intraoperative cholangiography in cases suggestive of choledocholithiasis. J Laparoendosc Adv Surg Tech A 2005; 15: 312-317.
3. Lein HH, Huang CC, Huang CS, Shi MY, Chen DF, Wang NY, Tai FC. Laparoscopic common bile duct exploration with T-tube choledochotomy for the management of choledocholithiasis. J Laparoendosc Adv Surg Tech A 2005; 15: 298-302.
4. Koivusalo AM, Lindgren L. Effects of carbon dioxide pneumoperitoneum for laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2000; 44: 834-841.
5. Hashikura Y, Kawasaki S, Munakata Y, Hashimoto S, Hayashi K, Makuuchi M. Effects of peritoneal insufflation on hepatic and renal blood flow. Surg Endosc 1994; 8: 759-761.
6. Elefteriadis E, Kotzampassi K, Papanotas K, Heliadis N, Sarris K. Gut ischemia, oxidative stress, and bacterial translocation in elevated abdominal pressure in rats. World J Surg 1996; 20: 11-16.
7. Gutt CN, Oniu T, Schemmer P, Kashfi A, Kraus T, Büchler MW. Circulatory and respiratory complications of carbon dioxide insufflation. Dig Surg 2004; 21: 95-105.
8. Elefteriadis E, Kotzampassi K, Botsios D, Tzartinoglou E, Farmakis H, Dadoukis J. Splanchnic ischemia during laparoscopic cholecystectomy. Surg Endosc 1996; 10: 324-326.
9. Jakimowicz J, Stultiëns G, Smulders F. Laparoscopic insufflation of the abdomen reduces portal venous flow. Surg Endosc 1998; 12: 129-132.
10. Schäfer M, Krähenbühl L. Effect of laparoscopy on intra-abdominal blood flow. Surgery 2001; 129: 385-389.
11. Schäfer M, Sägesser H, Reichen J, Krähenbühl L. Alterations in hemodynamics and hepatic and splanchnic circulation during laparoscopy in rats. Surg Endosc 2001; 15: 1197-1201.
12. Odeberg S, Ljungqvist O, Sollevi A. Pneumoperitoneum for laparoscopic cholecystectomy is not associated with compromised splanchnic circulation. Eur J Surg 1998; 164: 843-848.
13. Sakorafas G, Anagnostopoulos G, Stafyla V, Koletis T, Kotsifopoulos N, Tsiakos S, Kassaras G. Elevation of serum liver enzymes after laparoscopic cholecystectomy. N Z Med J 2005; 118: U 1317.
14. Al-Jaberi TM, Tolba MF, Dwaba M, Hafiz M. Liver function disturbances following laparoscopic cholecystectomy: incidence and

significance. J Laparoendosc Adv Surg Tech A 2002; 12: 407-410.
15. Nesek-Adam V, Rasic Z, Kos J, Vnuk D. Aminotransferases after experimental pneumoperitoneum in dogs. Acta Anaesthesiol Scand 2004; 48: 862-866.
16. Halevy A, Gold-Deutch R, Negri M, Lin G, Shlamkovich N, Evans S, Cotariu D, Scapa E, Bahar M, Sackier JM. Are elevated liver enzymes and bilirubin levels significant after laparoscopic cholecystectomy in the absence of bile duct injury? Ann Surg 1994: 219: 362-364.
17. Saber AA, Laraja RD, Nalbandian HI, Pablos-Mendez A, Hanna K. Changes in liver function tests after laparoscopic cholecystectomy: not so rare, not always ominous. Am Surg 2000; 66: 699-702.
18. Andrei VE, Schein M, Margolis M, Rucinski JC, Wise L. Liver enzymes are commonly elevated following laparoscopic cholecystectomy: is elevated intra-abdominal pressure the cause? Dig Surg 1998; 15: 256-259.
19. Morino M, Giraudo G, Festa V. Alterations in hepatic function during laparoscopic surgery. An experimental clinical study. Surg Endosc 1998; 12: 968-972.
20. Giraudo G, Brachet Contul R, Caccetta M, Morino M. Gasless laparoscopy could avoid alterations in hepatic function. Surg Endosc 2001; 15: 741-746.
21. Gelman S, Dillard E, Bradley EL. Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane, or fentanyl. Anesth Analg 1987;66:936-43
22. O'Riordan J, O'Beirne A, Young Y, Bellamy M. Effects of desflurane and isoflurane on splanchnic microcirculation during major surgery. Br J Anaesth 1997; 78: 95–6
23. Pavlidis T, Alexiadis D, Papanicolaou C, Kouvelas D. Effect of laparoscopic cholecystectomy on liver function tests. Comparative study. Arch Gastroenterohepatol 1995; 14: 26-27.
24. Campos LI, Mansfield D, Smith A, et al. Carbon dioxide volume and intra-abdominal pressure determination before the creation of a pneumoperitoneum. Surg Laparosc Endosc. 1995;5:100–4.
25. Eleftheriadis E, Kotzampassi K, Botsios D, et al. Splanchnic ischemia during laparoscopic cholecystectomy. Surg Endosc. 1996;10:324–6.
26. Windberger U, Siegl H, Ferguson JG, et al. Hemodynamic effects of prolonged abdominal insufflation for laparoscopic procedures. Gastrointest Endosc. 1996;41:121–9.
27. Westerband A, Van De Water JM, Amzallag M, et al. Cardiovascular changes during laparoscopic cholecystectomy. Surg Gynecol Obstet. 1996;175:535–8
28. Sato K, Kawamura T, Wakusawa R. Hepatic blood flow and function in elderly patients undergoing laparoscopic cholecystectomy. Anesth Analg. 2000;90:1198–1202.
29. Junghans T, Bohm B, Grundel K, et al. Does pneumoperitoneum with different gases, body positions, and intraperitoneal pressures influence renal and hepatic blood flow? Surgery. 1997;121:206–11
30. Cameron AE, Dear GL, Pocock TJ, Tennant RW. Gas exchange in abdominal cavity during laparoscopy. Jr Soc Med 1983;76:1015-8.
31. Baraka A. Cardiovascular collapse after carbondioxide exsufflation in a patient undergoing laparoscopic cholecystectomy. Anesth Analg 1994;78:603
32. Seymour I. Schwartz. John G.Hunter: Principles of Surgery; Laparoscopy in Minimal Invasive Surgery, Ed. 7th Vol-II. P-2147
33. Mullet CE, Viale JP, Sagnard PE, et al. Pulmonary CO2 elimination during surgical procedures using intra- or extraperitoneal CO2 insufflation. Anesth Analg. 1993;76:622–6.
34. Campos LI, Mansfield D, Smith A, Kohli H, Sun D, Espinosa MH, Dy V. Carbon dioxide volume and intra-abdominal pressure determination before the creation of a pneumoperitoneum. Surg Laparosc Endosc 1995; 5: 100-104.
35. Glantzounis GK, Tselepis AD, Tambaki AP, Trikalinos TA, Manataki AD, Galaris DA, Tsimoyiannis EC, Kappas AM. Laparoscopic surgery-induced changes in oxidative stress markers in human plasma. Surg Endosc 2001; 15: 1315-1319.
36. Sare M, Yilmaz I, Hamamci D, Birincioglu M, Ozmen M, Yesilada O: The effect of carbon dioxide pneumoperitoneum on free radicals. Surg Endosc 2000; 14:649-52

37. Tulikangas PK, Smith T, Falcone T, et al. Gross and histologic characteristics of laparoscopic injuries with four different energy sources. Fertil Steril. 2001;75:806–10.
38. Capelluto E, Champault G. Variations in intraperitoneal temperature during laparoscopic cholecystectomy. Ann Chir. 2000;125:259–62.
39. Barrat C, Capelluto E, Champault G. Intraperitoneal thermal variations during laparoscopic surgery. Surg Endosc. 1999;13:136–8.
40. Shamiyeh A, Schrenk P, Tulipan L, et al. A new bipolar feedback-controlled sealing system for closure of the cystic duct and artery. Surg Endosc. 2002;16:812–3.
41. ke Y, Takeda J, Matsumoto M, et al. Subclinical hepatic dysfunction in laparoscopic cholecystectomy and laparoscopic colectomy. Br J Anaesth. 2001;87:774–7.
42. Tauro LF, Sheethal CM, Aithala PSM, Shetty SR, D'souza CS, Rao BSS, et al:Evaluation of effects of laparoscopic surgery on hepatic functions. Journal of Clinical and Diagnostic Research [serial online] 2008 December [cited:2009 Jan 20]; 2; 1155-1162.

AUTHORS

- **Dr. Fakhar Hameed**
  Assistant Prof. Surgery
  PMC/Allied Hospital,
  Faisalabad.
- **Dr. Bashir Ahmed**
  Medical Officer Surgery
  PMC/Allied Hospital
  Faisalabad.
- **Dr. Asrar Ahmed khan**
  Senior Registrar Surgery
  PMC/Allied Hospital
  Faisalabad.
- **Prof. Dr. Riaz Hussain Dab**
  Head of Surgical Departments
  PMC/Allied Hospital,
  Faisalabad.