The Effect of CO_2 Pneumoperitoneum on Serum Prostate-Specific Antigen Levels in Patients Undergoing Laparoscopic Cholecystectomy

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Background: Recently, several studies have shown an elevation of serum prostate-specific antigen (PSA) levels after the events associated with presumed pelvic ischemia. Although it has been shown that CO_2 pneumoperitoneum during laparoscopic surgery causes splanchnic ischemia, no study has investigated the PSA levels after this procedure. This study aimed to evaluate the effects of CO_2 pneumoperitoneum on serum total PSA (tPSA) and free PSA (fPSA) levels in patients undergoing laparoscopic cholecystectomy.

Methods: This study involved 30 men who underwent elective laparoscopic cholecystectomy. Serum tPSA and fPSA levels and f/tPSA ratios were determined the day before surgery (baseline), immediately before insufflation, after desufflation, and 24 hours and 7 days after surgery.

Results: Serum tPSA and fPSA values after desufflation and 24 hours after surgery were significantly higher than the values before insufflation and at baseline ($P < 0.01$), whereas the f/tPSA ratio did not change ($P > 0.05$). PSA levels decreased to baseline levels after 7 days.

Conclusions: Our study showed that CO_2 pneumoperitoneum during laparoscopic surgery can cause a rise in serum tPSA and fPSA levels. We think that CO_2 pneumoperitoneum during laparoscopic surgery should be added to list of the events in which PSA measurements must be interpreted with caution.

Key Words: laparoscopy, prostate-specific antigen, pneumoperitoneum, carbon dioxide, ischemia, prostate

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Laparoscopic surgery has many advantages over open surgery and is the procedure of choice for a large number of abdominal operations. The most commonly used gas in laparoscopy is carbon dioxide (CO_2) and the detrimental effects of CO_2 pneumoperitoneum on cardiac, respiratory, renal, and splanchnic functions have been described in many clinical and experimental studies.[1] Induction of pneumoperitoneum during laparoscopic surgery has also been shown to reduce the perfusion of intra-abdominal tissues. It has been suggested that reduced visceral perfusion and its improvement after abdominal CO_2 pneumoperitoneum evacuation may lead to an ischemia-reperfusion injury in the organs.[2]

Prostate-specific antigen (PSA) is a kallikrein-like serine protease produced exclusively by the epithelial cells of the prostate. Elevated serum PSA levels are seen in inflammatory and neoplastic diseases of the prostate.[3] PSA is used as a biochemical marker in the diagnosis and follow-up of patients with prostate cancer. For practical purposes, it is organ-specific but not cancer-specific, and serum levels may be elevated in the presence of benign prostatic hyperplasia, prostatitis, prostatic trauma, and prostatic infarction.[3–5]

Recently, several studies have shown elevation of serum PSA levels after the events associated with presumed pelvic ischemia, such as prolonged cardiopulmonary resuscitation, cardiac surgery, and extracorporeal cardiopulmonary bypass.[6,7] Decreased pelvic blood flow during CO_2 pneumoperitoneum may reduce supply to the prostate gland and no study has investigated PSA levels after laparoscopic surgery. The aim of this study was to investigate the effects of CO_2 pneumoperitoneum during laparoscopic surgery on serum total PSA (tPSA) and free PSA (fPSA) levels.

MATERIALS AND METHODS

Thirty male patients with American Society of Anesthesiology status I and II, who underwent elective laparoscopic cholecystectomy for symptomatic cholecystolithiasis, were enrolled in the study. The institutional ethics committee approved this study, and all study participants read and signed an informed consent form. Preoperative assessment and anesthesia were carried out according to a uniform protocol and under monitoring of blood pressure, pulse, pulse oxymetry, end-tidal CO_2, etc. The patients were operated upon using a standard technique with 4 trocars and a CO_2 pneumoperitoneum of 12 mm Hg. Serum tPSA and fPSA levels and f/tPSA ratios were determined the day before surgery (baseline), immediately before insufflation, after desufflation, and 24 hours and 7 days after the surgery. None of the patients had a urinary catheter during the study period. Serum tPSA and fPSA were measured with the electrochemiluminescence immunoassay (Hitachi Modular Analytics E170, Roche Diagnostic GmbH, Mannheim, Germany).

Patients were excluded from the study if they had a history of earlier prostate biopsy, malignancy of prostate, medical or surgical treatment of benign prostatic hyperplasia, urethral catheterization or instrumentation, prostatitis or a documented urinary tract infection, and had PSA

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TABLE 1. Patient Characteristics

Age (y)	53.90 ± 6.19
Residual urine volume (mL)	35.62 ± 15.21
Prostate volume (mL)	40.33 ± 18.45
Transition zone volume (mL)	20.45 ± 11.85
Operating time (min)	62.4 ± 19.7

Data presented as mean ± standard deviation.

levels greater than 2.5 ng/mL and f/tPSA less than %25 before the procedure. Patients with additional health problems, such as diabetes mellitus, renal failure, hypertension, cardiac failure, etc, were excluded.

Statistics

All data are expressed as mean ± SD. Statistical analyses were carried out using the paired *t* test to compare the PSA values. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics are summarized in Table 1. Serum tPSA and fPSA values after desufflation and 24 hours after surgery were significantly higher than the values before insufflation and at baseline ($P < 0.01$), whereas f/tPSA ratio did not change ($P > 0.05$) (Table 2). Compared with the baseline, there was no statistically significantly difference in the PSA values before insufflation and 7 days after the surgery ($P > 0.05$).

DISCUSSION

To our knowledge, this is the first study that has been focused on the effect of CO_2 pneumoperitoneum during laparoscopic surgery on serum PSA levels. Our study shows that CO_2 pneumoperitoneum leads to a significant increase in serum levels of tPSA and fPSA. In contrast, we showed that serum tPSA and fPSA values decreased to baseline after 7 days of the laparoscopic procedure. However, we found that CO_2 pneumoperitoneum did not affect the f/tPSA ratio. Although PSA is not a parameter routinely measured in patients undergoing laparoscopic surgery, our study implies that any PSA elevation after CO_2 pneumoperitoneum in laparoscopic surgery might be re-controlled and prostate biopsy should not be performed based on this measurement only.

Several factors can contribute to elevated PSA levels and evidence suggests that prostatic ischemia damages the epithelial cells of the prostate gland, leading to increased serum PSA.[8] It has been shown that laparoscopy itself is an ischemia-reperfusion phenomenon that causes splanchnic ischemia and related adverse alterations in intra-abdominal organs.[9] CO_2 pneumoperitoneum is usually used for the visualization of the operative field. During this period, the production of the oxygen-derived free radicals after the ischemia-reperfusion period caused oxidative injury.[2] However, not only pneumoperitoneum itself, but the deflation phase as well carries the risk of ischemic potential for intra-abdominal organs. Pelvic ischemia because of cross clamping of the aorta during coronary artery bypass grafting, aortic and iliac arterial surgery, hypotensive shock, and acute myocardial infarction is presumed to be the reason for prostatic ischemia and/or infarction leading to elevation of serum PSA levels.[10] Although the exact mechanism has not been clearly understood, our study showed that PSA elavation after laparoscopic surgery may be related to pelvic ischemia because of CO_2 pneumoperitoneum. However, the alteration in splanchnic perfusion is proportional to increased intra-abdominal pressure.

In this study, we showed an elevation of serum PSA levels after laparoscopic cholecystectomy at a pressure of 12 mm Hg. The increased pressure during laparoscopy also leads to a mechanical impairment of the venous blood return leading to an increase in venous pressure of the pelvic organs. Schilling et al[11] showed that reduction of organ perfusion is pressure dependent by studying the effect of different insufflation pressures in laparoscopic cholecystectomy using a laser Doppler flow probe to measure organ perfusion. An increase of 5 mm Hg, from 10 to 15 mm Hg, of the intra-abdominal pressure resulted in a blood flow decrease by 40% to 54% to the stomach, by 32% to the jejenum, by 44% to the colon, by 39% to the liver, and by 60% to the peritoneum.

It is generally accepted that proinflammatory mediators, including cytokines, are to a great extent responsible for the metabolic changes associated with tissue injury and inflammation. Ozmen et al[9] showed that pneumoperitoneum is responsible for ischemia and proinflammatory cytokine response-mediated cell damage during laparoscopic surgery. In contrast, PSA has been identified as a member of the human kallikrein family of serine proteases, and the kallikrein kinin system is also related to inflammation. It has been shown that the inactive precursor form of PSA, proPSA, is converted rapidly to active PSA by human kallikrein 2 (hK2), suggesting an important in vivo regulatory function by human kallikrein 2 on PSA activity.[12] The formation of irreversible PSA complexes also has a significant correlation with the acute-phase proteins. This may be another mechanism of PSA elevation related to CO_2 pneumoperitoneum during laparoscopic surgery.

In conclusion, our results show that CO_2 pneumoperitoneum during laparoscopic surgery is associated with a rise in serum tPSA and fPSA levels after intervention. We also found that increased tPSA and fPSA levels had returned to baseline levels by 7 days after surgery. Although only follow-up measurements and continuous increases

TABLE 2. PSA Values of the Patients

	Baseline	Before Insufflation	After Desufflation	Postoperative 24 h	Postoperative 7 d
tPSA (ng/mL)	1.45 ± 0.42	1.48 ± 0.55	2.95 ± 0.85*	3.25 ± 0.85*	1.42 ± 0.38
fPSA (ng/mL)	0.55 ± 0.23	0.52 ± 0.34	1.15 ± 0.45*	1.22 ± 0.64*	0.57 ± 0.30
f/tPSA (%)	0.40 ± 0.25	0.39 ± 0.22	0.41 ± 0.28	0.38 ± 0.25	0.42 ± 0.20

Data are mean ± standard deviation.
*$P < 0.01$, compared with baseline.

of PSA are valuable for cancer diagnostics, we think that CO_2 pneumoperitoneum must be added to the list of events in which PSA measurements must be interpreted with caution.

REFERENCES

1. Gutt CN, Oniu T, Mehrabi A, et al. Circulatory and respiratory complications of carbon dioxide insufflation. *Dig Surg*. 2004;21:95–105.
2. Sammour T, Mittal A, Loveday BPT, et al. Systematic review of oxidative stress associated with pneumoperitoneum. *Br J Surg*. 2009;96:836–850.
3. Shah JB, Reese AC, McKiernan JM, et al. PSA updated: still relevant in the new millennium? *Eur Urol*. 2005;47:427–432.
4. Oesterling JE, Rice DC, Glenski WJ, et al. Effect of cystoscopy, prostate biopsy and transurethral resection of prostate on serum prostate-specific antigen concentration. *Urology*. 1993;42:276–282.
5. Long RL, Giri S, Diver S, et al. Effect of prostate manipulation on the serum levels of complexed prostate-specific antigen and total prostate-specific antigen. *Int J Urol*. 2006;13:947–950.
6. Koller-Strametz J, Fritzer M, Gwechenberger M, et al. Elevation of prostate-specific markers after cardiopulmonary resuscitation. *Circulation*. 2000;102:290–293.
7. Parlaktas BS, Naseri E, Uluocak N, et al. Comparison of the effects of on-pump versus off-pump coronary artery bypass surgery on serum prostate-specific antigen levels. *Int J Urol*. 2006;13:234–237.
8. Guvel S, Turkoz R, Egilmez T, et al. Does ischemia-induced prostate damage during cardiac surgery involving cardiopulmonary bypass cause bladder outlet obstruction? *Urol Int*. 2005;74:337–340.
9. Ozmen MM, Zulfikaroglu B, Col C, et al. Effect of increased abdominal pressure on cytokines (IL1β, IL6, TNFα), C-reactive protein (CRP), free radicals (NO, MDA), and histology. *Surg Laparosc Endosc Percutan Tech*. 2009;19:142–147.
10. Patané S, Marte F. Prostate-specific antigen kallikrein: from prostate to cardiovascular system. *Eur Heart J*. 2009;30:1169–1170.
11. Schilling MK, Redaelli C, Krahenbuhl L, et al. Splanchnic microcirculatory changes during CO_2 laparoscopy. *J Am Coll Surg*. 1997;184:378–382.
12. Jansen FH, Roobol M, Jenster G, et al. Screening for prostate cancer in 2008 II: the importance of molecular subforms of prostate-specific antigen and tissue kallikreins. *Eur Urol*. 2009;55:563–574.