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ORIGINAL PAPER

D-DIMER AS A PARAMETER OF HYPERCOAGULABILITY IN LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Introduction: Laparoscopic cholecystectomy is a method of choice in the treatment of calculous gallbladder. There is a clear evidence of changes in hemostatic parameters during this surgical procedure, which can result in thromboembolic complications. The aim of the study was to evaluate changes in D-dimer values, as a marker of hypercoagulability in patients treated with laparoscopic cholecystectomy.
Patients and methods: The study included total of 60 patients, divided into two groups, one treated with classic (open) and other with laparoscopic method. Blood samples were taken from all patients before, during the surgery and 24 hours and 5 days after the procedure with consequent determination of D-dimer levels.
Results: Blood samples of patients in both groups manifested higher values of D-dimer during the operation, 24 hours and 5 days after the procedure. We have found elevated values of D-dimer 5 days after the surgery in the group of patients treated with laparoscopic cholecystectomy with 2.5 times higher levels compared to values measured preoperatively.
Conclusion: Our results suggest that there is an increased fibrinolytic activity after laparoscopic cholecystectomy, which demands more detailed and complete study on tromboembolism prophylaxis.

Keywords: *hemostasis, laparoscopic cholecystectomy, D-dimer, thromboembolism prevention*

INTRODUCTION

Hemostasis is a very important mechanism with two primary functions: to provide liquid state of blood in circulation and prevent bleeding (hemorrhage) at the site of damaged blood vessels.[1] Disorders of the hemostasis are a result of a deficit or a changed function of one or more factors of hemostasis. Clinical manifestations of hemostasis disorders are bleeding (hemorrhagic syndrome) and thrombosis. Hemorrhagic syndromes are the result of blood vessels disorders and changes in the flow and composition of blood.[2]

Human body responds to every surgical intervention, as well as to any other trauma. Systemic and local response is coordinated on the metabolic, immunological and neurovegetative level. Surgical trauma induces activation of defensive mechanisms leading to the systemic response to tissue damage, which may result in hemodynamic and biochemical disorders, that can be proved by objective methods.[3,4]

In the course of a surgery and particularly after it, significant changes in blood flow and blood composition occur and levels of proteins involved in the

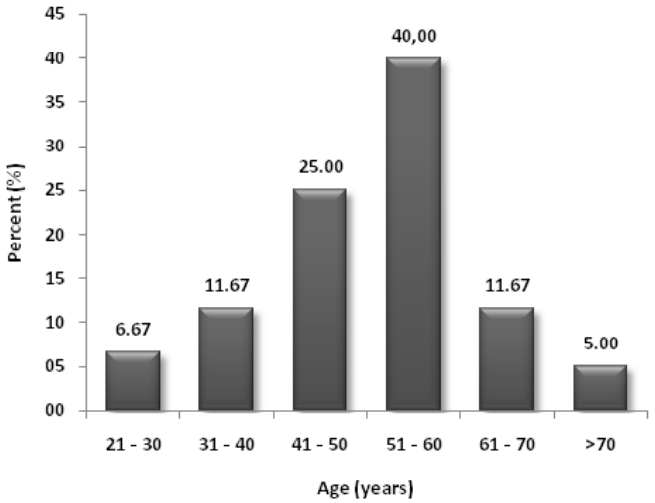

Figure 1. *Age distribution within complete sample*

coagulation process are essentially changed. These changes physiologically decrease risk of blood loss, particularly during the surgery, but also significantly increase a risk of thromboembolic complications. Depending on capacity and invasiveness of a surgery, these changes are of different intensity.

Thrombosis as a multi factorial disease is a serious health problem, particularly if it occurs during or immediately after the surgical treatment, and one of the most significant warnings indicating thrombosis are changes in the coagulation system.[5,6]

Laparoscopic cholecystectomy (LC) is a minimally invasive method used in surgical practice. Because of its proved advantages, it is nowadays considered as a method of choice in the treatment of calculous gallbladder. Physiological changes which are evident in the body during laparoscopic procedures are consequence of an artificial pneumoperitoneum and also depend on numerous factors. The technique itself includes controlled use of insuflation pressure inside peritoneal cavity. Pneumoperitoneum established in this manner has two very important effects. The first one is the increased intraabdominal pressure which has mechanical impact on all intraabdominal organs. The second, negative effect of pneumoperitoneum, is caused by diffusion of CO^2 to neighboring tissues and blood, which leads to biochemical changes and development of acidosis.[7,8,9] The increased venous stasis in the region of lower limbs and abdomen, which is evident during LC is a good predisposing factor for thromboembolism. Debates on thromboembolism incidence during LC are still present but it is considered that incidence of thromboembolism during LC remains very low. Venous stasis, present during LC is one of the three factors needed for the development of thrombosis, with the other two factors being hypercoagulability and disruptions of blood vessel wall (Virchow's triad).[10] Results of many studies showed decrease in risk of thromboembolism during LC, regardless of emphasized venous stasis and increased intraabdominal pressure.

The aim of the study was to determine changes in levels of D-dimer before, during and after the surgery in patients treated with either classical or laparoscopic cholecystectomy and to compare D-dimer levels between those two types of procedure.

PATIENTS AND METHODS

We prospectively recruited 30 patients treated with classic (open) cholecystectomy and other 30 treated with laparoscopic cholecystectomy due to calculous gallbladder. The study was performed in the time period from February to July 2008. Patients were both male and female aged 18 to 80 years and they all preoperativelly received enoxaparin as a prophylactic treatment. We excluded patients with either acute, malignant or autoimmune disease, patients with affinity to bleeding, coagulopathies, and previously verified thromboembolic states. D-dimer levels were determined in all patients in 4 separate measurements; before the surgery, during the procedure, 24 hours and 5 days after the procedure (most often on 7th day). In all measurements venous blood without signs of haemolysis and lypemic state was used. The determination was performed using citric plasma, and analyses were done using BCT-Behring machine.

Statistical analysis was performed by using the method of descriptive statistics, with representation of measures of central tendency and dispersion. Quantitative variables were compared by using t-test while those that did not have normal distribution by Mann-Withney U test. Univariate logistic regression was used for testing the level of influence of the type of the operative procedure on the presence of increased value of D-dimer in the postoperative period.

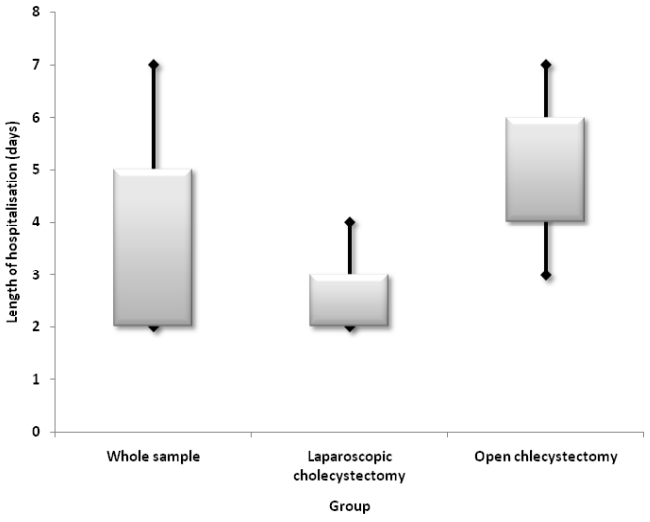

Figure 2. *Comparative view of duration of hospitalization (in days of stay)*

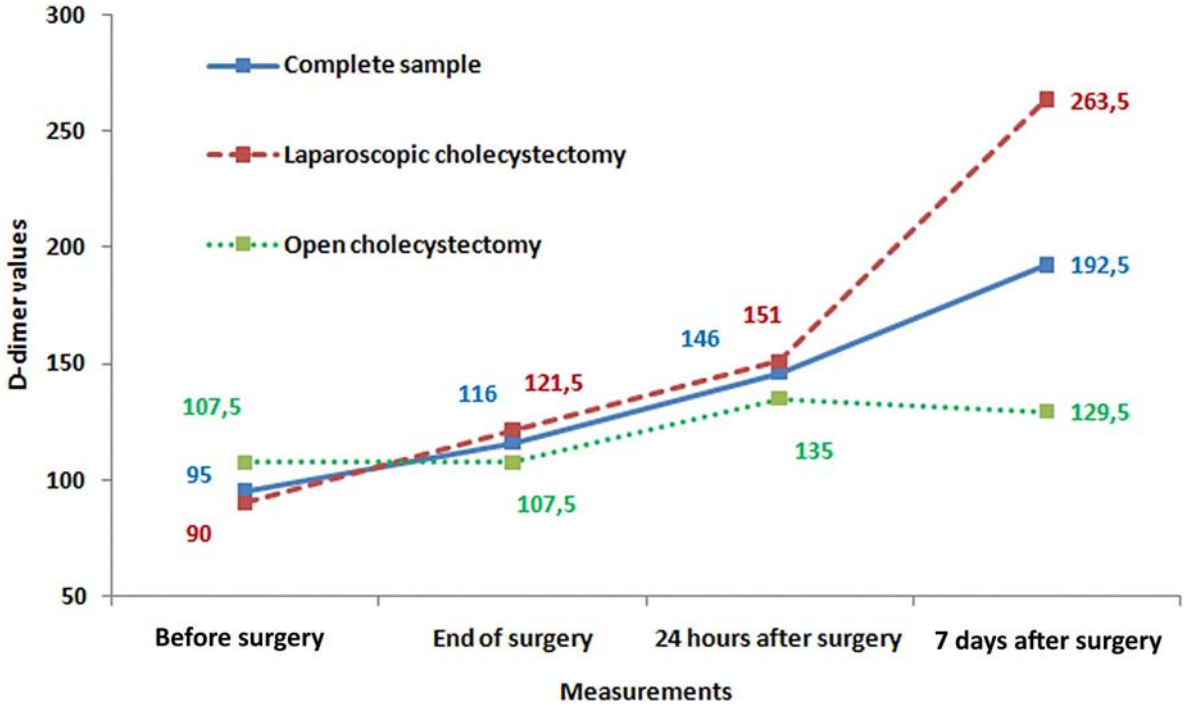

Figure 3. *Dynamics of D-dimer during the observed period (median values)*

RESULTS

The mean age of patients in the complete sample (±SD) was 50±11 years, with minimum of 23 and maximum of 80 years. The age distribution of patients is presented in Figure 1. There was 45/60 (75%) of female patients, and 15/60 (25%) of male patients in the whole sample. There was no significant difference (p=0.55) in sex ratio between the patients treated with laparoscopic cholecystectomy (21/30; 70% female) and the group treated with classical cholecystectomy (24/39; 80% female).

The median duration of hospitalization in the patients treated laparoscopicaly was 2 days (25-75 percentiles: 2-3 days), while patients treated with open cholecystectomy had median value of 5 days of hospitalization (25-75 percentils:4-6 days). This change was statistically significant (p<0.001) as is demonstrated in Figure 2.

The dynamics of D-dimer is presented in Figure 3. Values of D-dimer were significantly higher in patients who underwent laparoscopic cholecystectomy, compared to patients operated classically (p<0.001). However, in comparison with the initial values, each subsequent measurement revealed higher levels of D-dimer, which is especially evident in the laparoscopic group of patients.

Using the D-dimer threshold value of 228 μg/l, we compared proportions of patients with values of D-dimer >228 μg/l in both patient groups. The graphical view of this comparison is presented in Figure 4. Although there was a tendency for elevation of D-dimer values in patients treated with classical cholecystectomy in the first three measurements, this was not statistically significant (p>0.05). However, in measurements performed few days after the surgery we found more patients with the increased values of D-dimer in the group treated laparoscopicaly, when compared to those treated with classical cholecystectomy (p<0.001).

Univariate logistic regression analysis showed that the type of surgical procedure had significant influence on the presence of increased values of D-dimer (>228 μg/l), and that the patients treated laparoscopicaly have 11.77 times greater chances (OR=11.77; 95%CI=2.92-47.46; p=0.001) for increased D-dimer in comparison with the patients treated in classical manner.

DISCUSSION

During the surgical treatment and especially afterwards, several very important changes take place in the coagulation system. The process of coagulation, once initiated by surgical trauma or by other causes, could uncontrollably lead to undesired consequences. One of the most used surgical procedures is cholecystectomy which is a method of choice in the treatment of calculous gallbladder.[11] When compared with classical cholecystectomy, LC as a minimally invasive method is a method with decreased systemic response, due to the lesser degree of trauma and fewer intraoperative complications.[12,13] Especially important advantages

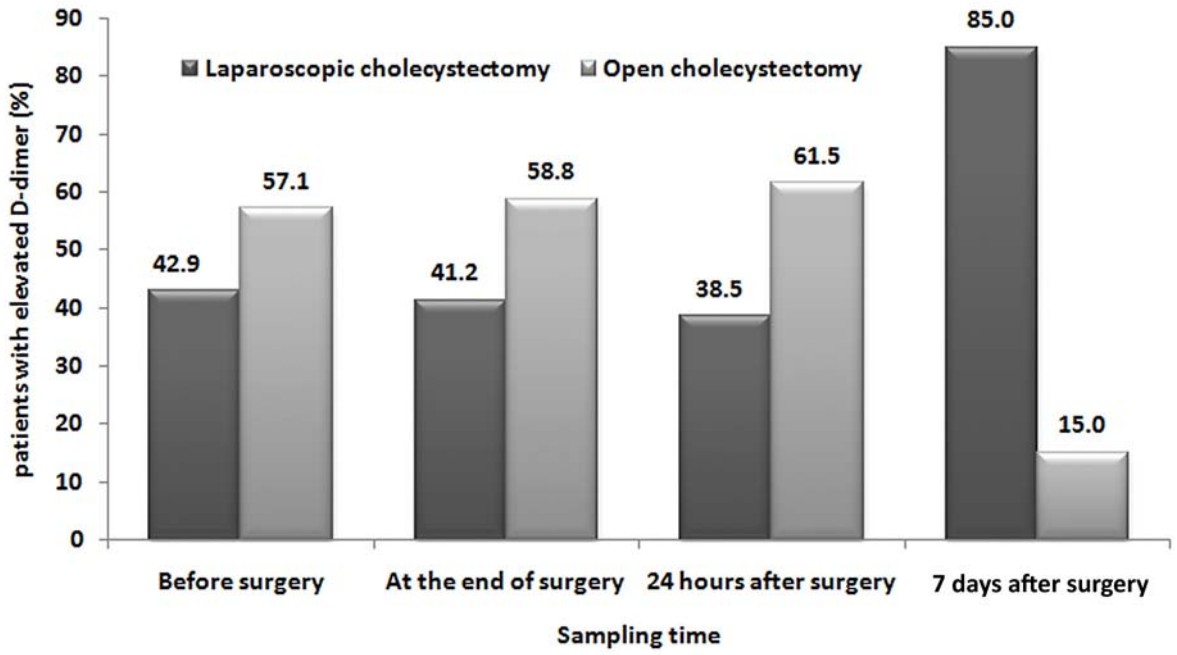

Figure 4. *Comparative view of ratios of patients with the increased D-dimer, according to operative method and time of sampling*

of LC are the shorter recovery and sooner return to work, lower incidence of postoperative pain and better economic effects.[14,15,16] It is a method that ensures a shorter duration of hospitalization, faster functional rehabilitation of the body and the aesthetic benefit, as well.[17,18,19]

Two groups of our patients were similar according to age and sex, while within every group we found a larger percentage of female patients, which confirms the already known fact that diseases of gallbladder are more often present in women.[20] The hospital stay after LC was 2-3 days and after open cholecystectomy 4 to 6 days. According to other reports most patients have hospital stay between 0.89 and 1.6 days.[21] Our results demonstrated somewhat longer period of hospitalization.

Fibrinolysis, as the strongest physiological mechanism of fibrin degradation enables recanalisation of the blood vessel in which blood cloth is positioned, whether it is a hemostatic plug at the place of the vessel defect or pathological thrombosis.[22,23] D-dimer appears as a result of degradation of stabilized fibrin under the influence of plasmin and is a firm sign of fibrin plaques or thrombus somewhere in the circulation. This test presents a marker of hypercoagulability of blood and is an important factor in genesis of thrombosis.[2] In both patient groups in our study, values of D-dimer from the initial to final measurement and 24 hours afterwards showed ascending path and mildly descending path during the operative treatment and 24 hours afterwards. In measurements performed between 5th and 10th day after the operation in the group of patients that underwent open cholecystectomy, values were 2,5 times higher compared to the preoperative measurements and were above reference values. In the group of patients who underwent open cholecystectomy, there was an evident increase of D-dimer value during the surgery and 24 hours afterwards, but in the final measurement it was within reference range. Similar results were published by Prisco et al[24] and Dexter et al[25] where D-dimer values during the operation, 6 and 24 hours afterwards also showed ascending trend. Compared to laparoscopic method, values in the group of patients that underwent classical method of operation were much higher. Martinez-Zamos et al[26] evaluated values of D-dimer directly after the surgery, after 24 hours and on the 7th day. They reported increased values of D-dimer, with the domination in the group of patients treated with LC. Report by Milic et al,[27] involved patients without thromboembolic prophylaxis; in both groups they described elevated values of D-dimer during the operation, 24 and 72 hours afterwards and it was more evidently elevated in the group treated by classical cholecystectomy. Regardless of the type of data, the final conclusion suggested that laparoscopy even with slight change in coagulation status does bear the risk of thromboembolism, and that prophylaxis should become a routine part of the procedure. In a report from Serbia, Vodnik et al[2] demonstrated increased values of D-dimer in both groups, with more pronounced elevation in the group treated classical cholecystectomy in measurements just after the surgery and 24 hours afterwards. D-dimer values normalized within three days from surgery in patients treated with LC. Therefore, judging by the results of numerous studies, including ours as well, there is an

evidence of fibrinolytic activity, even with administered prophylaxis. As a result of shorter hospitalization period, studied groups were not treated equally in terms of the use of antithrombotic prophylaxis. Patients treated laparoscopicaly spent shorter period of time in the hospital, which resulted in at most, two days of antithrombotic prophylaxis. On the other side, patients who had classical cholecystectomy remained longer in hospital (five days in average) and received continuous prophylactic therapy. Increased D-dimer levels in patients treated by LC was much more evident postoperatively in the period after the 5th day from the operation when prophylaxis was not administered while during the operation and 24 hours afterwards in the period of active prevention this increase was not significant.

It still remains an open question whether observed changes were consequence of a longer prophylaxis in patients treated with classic cholecystectomy or perhaps they are result of negative effects of laparoscopy (pneumoperitoneum, adverse Trendelenburg's position). But, taking into account that D-dimer is a parameter of hypercoagulability and a marker of fibrinolytic activity it could be prudent to administer longer antithrombotic prophylaxis in patients undergoing laparoscopic treatment.

REFERENCES

1. Balint B. *Diagnostics of haemorrhagic syndromes and haemophylia.* [Dijagnoza hemoragijskih sindroma i hemofilije]. In: Miković D, Rakić Lj. (eds.) *Transfusiology.* [Transfuziologija]. Beograd: Zavod za udžbenike i nastavna sredstva, 2004; 295-317.
2. Vodnik T, Vukosavljević D, Kaljević G. *Parameters of haemostasis in cholecystectomy*. [Parametri hemostaze u holecistektomiji]. Journal of Medical Biochemistry 2007; 26: 189-95.
3. Harris BH, Gelfand JA. The immune response to trauma. Semin Pedratr Surg. 1994; 4: 77.
4. Schlag G, Redl H. Mediators of injury and inflammation. World J Surg 1996; 20: 406.
5. Cuschieri A. Laparoscopic cholecystectomy. J.R. Coll. Surg. Edinb. 1999; 44: 187-92.
6. Deveney K. Laparoscopic cholecystectomy. In: Carol EH Scott-Conner. The SAGES Manual: Fudamentals of laparoscopy, thoracoscopy, and GI endoscopy. Second edition, SAGES. Springer Verlag, 2006.
7. Baxter JN, O'Dvyer PJ. Patophysiology of laparoscopy. Br J Surg 1995; 82: 1-2.
8. Nesek-Adam V, Mrsic V, Smiljanic A, Oberhofer D, Grizelj-Stojcic E. Pathophysiologic effects of CO2-pneumoperitoneum in laparoscopic surgery. Acta Med Croatica 2007; 61:165-170.
9. Mouiel J. Principles of safety in laparoscopic cholecystectomy. In: Postgraduate Course. Preventing Complications and Treatment in Minimal Invasive Surgery. 7th International Congress EAES. Linz, Austria, 23-26 June, 1999.
10. Guyton AC, Hall JE. *Haemostasis and coagulation.* [Hemostaza i koagulacija krvi]. *Medical physiology*. [Medicinska fiziologija]. Zagreb: Medicinska naklada, 2007; 419-429.
11. Annonymous. National Institutes of Health. Gallstones and Laparoscopic Cholecystectomy. NIH Consensus Statement 10:1-26. (Cited February 2009). Available from http://consensus.nih. gov/1992/1992Gallstones Laparoscopy 090html.htm.
12. Adachi Y, Shiraishi N, Shiromizu A, Bandoh T, Aramaki M, Kitano S. Laparoscopy-Assisted Billroth i Gastrectomy Compared With Conventional Open Gastrectomy. Arch Surg 2000; 135: 806-10.
13. Fornara P, Doehn C, Gehring H, Jocham D. Klinischer Stellenwert der urologischen Laparoskopie vor dem Hintergrund der Invasivitaet. Minimal Invasive Chirurgie 1999; 8: 65- 80.
14. Aby-Eshy SA, Moosa RA, Al-Rofaidi AA, Al-Faki AS et al. Proinflammatory cytokines in open versus laparoscopic cholecystectomy. Saudi Med J 2002; 23: 436-40.
15. Hannan E, Imperato PJ, Nenner RP, Starr H. Laparoscopic and open cholecystectomy in New York State: Motality, complications, and choice of procedure. Surgery Online 1999; 125: 223-31.
16. Gangly NN. Open cholecystectomy: a dissection technique makes the procedure safer and complication free. Gauhati Medical College & Hospital 2002 - {AUTHOR QUERY!!!}
17. Hasukić Š, Mešić D, Dizdarević E, Keser D, Hadžiselimović S, Bazarđžanović. Pulmonary function after laparoscopic and open cholecystectomy. Surgical Endoscopy 2001; 6:163-5.
18. Gonzales QH, Tishler DS, Plata-Munoz JJ, Bondora A, Vickers SM, Leath T, Clements RH. Incidence of clinically evident deep venous thrombosis after laparoscopic Roux-en gastric bypass. Surg Endosc 2004; 18: 1082-4.
19. Hasukić Š. Postoperative changes in liver function tests: randomized comparison between low-pressure and high-pressure laparoscopic cholecystectomy. Surgical Endoscopy 2005; 19: 1451-5.
20. Lau H, Brooks DC. Transitions in laparoscopic cholecystectomy. Surgical Endoscopy 2001; 16: 323-326.
21. Gadacz TR. U.S. Experience With Laparoscopic Cholecystectomy. Am J Surg 1993; 165: 450-454.
22. Grande M, Tucci GF, Adorisio O, Barini A, Rulli F, Neri A, Franchi F, Farinon AM. Systemic acute-phase response after laparoscopic and open cholecystectomy. Surgical Endoscopy 2001; 16: 313-6.
23. Stefanović S. *Disorders of haemostasis: disorders of blood vesels.* [Poremećaji hemostaze: promene krvnih sudova.] In: Stefanović S. (ed.) *Haemathology.* [Hematologija.] Beograd: Medicinska knjiga, 1989; 1069-88.
24. Prisco D, Guadio AR, Clara R, Gori AM, Fedi S, Cella AP, Gensini GF, Abatte R. Videolaparoscopic cholecystectomy induces a hemostasis activation of lower grade than does open surgery. Surg Endosc 2000; 14:170-4.
25. Dexter SPL, Griffith JP, Grant PJ, McMahon MJ. Activation of coagulation and fibrinolysis in open and laparoscopic cholecystectomy. Surg Endosc 1996; 10: 1069-74.
26. Martinez-Ramos C, Lopez-Pastor A, Pena-Nunez JR, Gopegui M, Sanz-Lopez R, Jorgensen T, Pastor L, Fernandez-Chacon JL, Tamames - Escobar S. Changes in hemostasis after laparoscopic cholecystectomy. Surg Endosc 1998; 13: 476-9.
27. Milić DJ, Pejčić VD, Živčić SS, Jovanović SZ, Stanojković ZA, Janković ID. Coagulation status and presence of postoperative deep vein thrombosis in patients undergoing laparoscopic cholecystectomy. Surg Endosc 2007; 21: 1588-92.