ARTICLE Libri Oncol., Vol. 39 (2011), No 1-3, 7 – 10

D-DIMER LEVELS IN PATIENTS WITH METASTATIC LIVER CANCER BEFORE AND AFTER SURGERY

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Summary

Vein thrombosis is a common complication in patients with cancer. Tumor cells produce or have expressed on their surface many procoagulant factors such as tissue factor and cancer procoagulant. Besides procoagulant activity of the tumor cells, surgical procedure, chemotherapy treatment, immobility and disease stage are additional factors for thrombosis development. Laboratory test used in diagnosis of thrombosis is D-dimer level measurement. Because of its high negative predictive value it has been used to exclude deep vein thrombosis in patients presented with deep vein thrombosis symptoms. Since its levels could be increased in patients with cancer, using this test in cancer population should be taken with caution. The aim of this study was to asses D-dimer levels in a specific group of patients with metastatic liver cancer before and after surgery, and determine the difference between these two measurements.

The study included 43 patients of both sexes, average age 68 (46 – 80) years, with metastatic liver carcinoma. Concentrations of D-dimer after surgery were higher than before surgery accounting for 2851 (617 – 3650) μg/L and 364 (229-615) μg/L, respectively, $P < 0.001$. The lowest difference between measurements was 51 μg/L and the highest one was 10644 μg/L.

We confirmed the trend in D-dimer levels before and after surgery reported in the literature and showed that these values can vary in a wide range.

KEYWORDS: *D-dimer, liver carcinoma, surgery*

VRIJEDNOSTI D-DIMERA U BOLESNIKA S METASTATSKIM KARCINOMOM JETRE PRIJE I POSLIJE KIRURŠKOG ZAHVATA

Sažetak

Venska tromboza česta je komplikacija u bolesnika s karcinomom. Tumorske stanice proizvode ili su im na površini izraženi brojni prokoagulcijski faktori poput tkivnog faktora i tumorskog prokoagulanta. Uz prokoagualcijsku aktivnost tumorskih stanica, kirurški zahvat, kemoterapija, nepokretnost i stadij bolesti dodatni su faktori koji utječu na nastanak tromboze. Mjerenje koncentracije D-dimera laboratorijska je pretraga koja se provodi u dijagnostici venske tromboze. Zbog svoje visoke negativne prediktivne vrijednosti, primjenjuje se kako bi se isključilo postojanje duboke venske tromboze u bolesnika s tim simptomima. S obzirom na to da vrijednosti D-dimera mogu biti povećane u bolesnika s karcinomom, rezultate ove pretrage u toj populaciji bolesnika valja oprezno razmotriti. Cilj ovog ispitivanja bio je procijeniti vrijednosti D-dimera u određenoj skupini bolesnika s metastatskim karcinomom jetre prije i poslije operacije te utvrditi razliku između ta dva mjerenja.

Ispitivanje je obuhvatilo 43 bolesnika oba spola, prosječne dobi od 68 (46-80) godina, s metastatskim karcinomom jetre. Koncentracija D-dimera nakon operacije bila je veća nego prije operacije, tj. nakon operacije iznosila je 2851 (617 – 3650) μg/L, a prije operacije 364 (229-615) μg/L, $P < 0,001$. Najmanja razlika između dva mjerenja iznosila je 51 μg/L, a najveća 10644 μg/L.

Potvrdili smo kretanje koncentracije D-dimera prije i poslije kirurškog zahvata kao što je opisano u literaturi te pokazali da vrijednosti mogu varirati u velikom rasponu.

KLJUČNE RIJEČI: *D-dimeri, karcinom jetre, kirurški zahvat*

INTRODUCTION

Thrombosis occurs in a situation when normal balance of procoagulant and anticoagulant factors is disturbed. One of the triggers for venous thrombosis is malignancy whose contribution has dual meaning. One observation supports a thesis that thrombosis occurs as a complication of malignant disease, and another that clotting mechanisms during thrombosis are in relation with metastases (1). Abnormalities of the coagulation system in cancer patients are present because of a disturbed balance between the coagulation and fibrinolytic systems. Cancer procoagulant which induces the coagulation process is specific for tumor cells and unlike tissue factor, directly activates factor X (2).

It has been reported that approximately 20% of patients admitted with symptoms of venous thromboembolism is related to malignancy (3). Not all malignant diseases have the same prothrombotic potential, but disease stage, immobility, chemotherapy and surgery are factors that significantly influence the development of thrombosis (2). For instance, it is reported that cancer alone increases the risk of venous thromoembolism four-fold, while chemotherapy increases the risk six-fold. Deep vein thrombosis is associated with incidence of 37% in patients with cancer in contrast to patients without cancer (20%) (4).

Measurement of D-dimer levels is one of laboratory tests used to detect thrombosis. The strength of this test is in its negative predictive value which means that a negative result indicates that it is unlikely that a thrombus is present. Previous research showed that sensitivity of D-dimer testing is approximately 90 - 95%, and its specificity around 55%, which once again proves that the test is more effective for ruling out thrombosis than for confirming the diagnosis (5). Negative predictive value of the D-dimer test was improved in combination with the Wells pretest probability for DVT in symptomatic patients without cancer ranging from 99.1 – 99.6 % (6) Since D-dimer levels are increased in patients with cancer, its clinical utility in ruling out venous thromboembolism is decreased in this group of patients. It has been reported that negative predictive value of the D-dimer test is lower in patients with cancer in contrast to patients without underlying malignancy even in combination with the above mentioned pretest probability (5, 6). Surgery is often part of the treatment of patients with cancer and another factor which is responsible for the increase in D-dimer levels. The kinetics of postoperative D-dimer levels is unknown which decreases its value as a test. In addition, the right time of sampling for retesting to rule out thrombosis remains unknown, too.

The aim of this retrospective study was to asses D-dimer levels in a specific group of patients with metastatic liver cancer before and after surgery, and determine the difference between these two measurements.

MATERIALS AND METHODS

This was a retrospective study in which we included 43 patients based on data from their hospital charts at the Department of Transfusion Medicine and Hemostasis, University Hospital for Tumors, 'Sestre milosrdnice' UHC, Zagreb, Croatia. Characteristics of the selected patients were as follows: average age of 68 (46 – 80) years, both sexes, metastatic liver carcinoma surgically treated at the University Hospital for Tumors, Zagreb. Data are shown in Table 1. All patients had D-dimer levels measured before surgery and within 8 hours after the procedure. After D-dimer testing they received LMWH therapy according to the standard protocol. Patients who had low molecular weight heparin (LMWH) therapy or oral anti-

Table 1

GENERAL CHARACTERISTICS OF THE PATIENTS

Number of patients (n)	43
Male (n)	30
Female (n)	13
Age median (min – max)	68 (46 - 80)

coagulant therapy on record before surgery were not included into this study. D-dimer levels were measured by the commercially available D-dimer Innovance kit provided by Siemens Diagnostics using an analyzer provided by the same manufacturer. We accepted the cut-off value recommended by the manufacturer which was 500 μg/L.

Deviations of our data from a normal distribution were tested by the D'Agostino-Pearson test. Parameters in our study did not follow normal distribution. The data were presented as median and interquartile range and compared by the non-parametric Wilcoxon test for paired samples. $P<0.05$ was considered as statistically significant. Statistical analysis was performed using the MedCalc statistical software, Mairiakere, Belgium.

RESULTS

There were 43 patients with metastatic liver carcinoma aged 46 to 80. Thrombosis was excluded by preoperative clinical examination. The concentration of D-dimers presented as median and interquartile range was 364 (229-615) μg/L before surgery, and 2851 (617 – 3650) μg/L after surgery. Thirteen out of 43 patients had D-dimer values higher than 500 before surgery. There was a statistically significant difference between D-dimer concentrations before and after surgery ($P <0.001$). D-dimer values increased in every patient after surgery (change in one direction). The lowest change was 51 μg/L and the highest one was 10644 μg/L, median and interquartile range: 2445 (900 - 4404) μg/L.

DISCUSSION

D-dimer values are an indicator of fibrin turnover. In their study, Wells et al. reported that it is safe to omit ultrasound testing in patients who are clinically judged unlikely to have deep vein thrombosis, and negative D-dimer test (7). As it was described earlier, cancer presents a risk factor in violation of the hemostatic system, Suega et al. reported positive correlation between D-dimer levels and clinical stage of solid cancer (8). Since thrombosis is a frequent complication in cancer patients, and D-dimer with its high negative predictive value is a valuable test for excluding deep vein thrombosis, the question of its utility in cancer patients with suspected thrombosis remains unanswered. In our study, 13 out of 43 patients without clinical signs of thrombosis before surgery had D-dimer values above the cut-off. Higher values are expected because cancer is a trigger for systematic activation of hemostasis and D-dimers are an indicator of this process (9). Another factor for the thrombosis development is surgery. Our group of patients had significantly higher D-dimer values after surgery. A wide range of difference between two measurements can be explained by different strategies in surgical procedure and clinical stage of the disease. Selected patients underwent abdominal surgery, but we lack information on the type and extent of the surgical procedure performed. Considering D-dimer values in diagnosis of a thrombotic event, it would be interesting to know how does certain surgical procedure relate to D-dimer values in this specific population.

In their study, Dindo et al. reported the kinetics of D-dimers after abdominal surgery in average surgical population. According to their research, D-dimer levels reach their peek value after the 7th postoperative day and fall to normal after 25 to 38 days depending on the severity of the procedure. D-dimer levels did not exceeded the cut off value after superficial surgery without opening the abdominal cavity (10). In population which they call average surgical population, authors included patients with cancer and reported that some of them had increased D-dimer levels before surgery, like in our study group. Exclusion criteria for the mentioned study were pregnancy, history of former VTE and preoperative concomitant diseases (sepsis, pneumonia), which are conditions that might increase D-dimer levels. Since these exclusion criteria were applied, we think that patients with cancer should have been excluded as well. As it has already been described, D-dimer levels are increased because malignancy is a trigger for activation of hemostasis. Patients with cancer are a specific group and we think they should be studied separately in order to understand the kinetics of D-dimers in this population.

Diagnosis of venous thromboembolism in patients with cancer is complicated and often asymptomatic and it is, therefore, important to apply prophylaxis. D-dimer levels seem to be a good predictor of venous thromboembolism in some stratification models which might be useful in

therapy application (11). Considering higher recurrence rates and higher incidence of bleeding complications, low molecular weight heparin therapy is better for patients undergoing major abdominal surgery (4). To assess the diagnostic value of D-dimer testing in patients with cancer undergoing abdominal surgery, a larger prospective study should be preformed.

CONCLUSION

With our study we confirmed the trend in D-dimer levels in cancer patients before and after surgery. We also demonstrated that the difference between measurements can vary in a wide range which might be associated with the type and extent of surgical procedure.

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