

## PERIOPERATIVE DISORDERS OF COAGULATION AND FIBRINOLYSIS IN PATIENTS SUBJECTED TO COLORECTAL CANCER RESECTION

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### ABSTRACT

**Introduction.** Venous thromboembolism and disseminated intravascular coagulation are frequent complications of malignant neoplasia. Abnormally high coagulation activity and fibrinolytic inhibition induced by surgery are suggested to be responsible for frequent occurrences of coagulative disorders.

**Aim.** The aim of this work was to assess the influence of surgery on coagulation and fibrinolytic systems during the early postoperative period in the high risk thromboembolism population, receiving heparin prophylaxis.

**Materials and methods.** This study was carried out in a group of 19 patients (12 males and 7 females), ages from 51 to 82 (mean 66.1), all with colorectal adenocarcinoma, who underwent scheduled elective total tumor resection.

**Results and Discussion.** Following surgical procedures the initially elevated D-dimer plasma level increased significantly. Activated partial thromboplastin time and the prothrombin time were prolonged significantly until the end of the observation period. Substantial reduction of initially normal fibrinogen concentration was revealed 6 hours after surgery, with significant increases at the 24<sup>th</sup> hour and then after 48 hours. The platelet count decreased linearly between 6 and 48 hours. The same pattern with nadir values after 48 hours was observed for antithrombin, protein C and the plasminogen plasma levels.

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**Conclusions.** Colorectal cancer and surgery significantly activate the coagulation and fibrinolytic systems, despite prophylaxis with low molecular weight heparin. Elective cancer resection is accompanied by a process resembling consumptive coagulopathy with an impairment of standard coagulation markers as well as significant reduction in natural plasma anticoagulants. Further studies are required to determine whether substitutional administration of natural anticoagulants added to routine heparin treatment in case of prophylaxis failure should be considered.

**Key words:** colorectal neoplasms, venous thrombosis, blood coagulation disorders

## INTRODUCTION

Venous thromboembolism (VT) and disseminated intravascular coagulation (DIC) are both frequent complications of ongoing neoplastic growth and also serve as early indicators of malignant proliferation [3, 15]. The risk of clinically significant VT in patients diagnosed with malignant disease is estimated to be increased up to 4- to 7-fold in comparison to the healthy population [1, 18]. Pathogenesis of developing a hypercoagulable state is multifactorial. Neoplastic cells may directly impact on the coagulation system by platelet activation, increased expression of tissue factor (TF) on cell's surface, release of cancer procoagulant, mucin and factor V receptor, and generation of thrombin [9, 21]. Indirect impact by the stimulation of vascular endothelial growth factor (VEGF) dependent angiogenesis, release of cytokines (e.g., TNF, IL-1) activating monocytes, macrophages and endothelial cells is also considered [9]. This process increases expression of coagulation activators and may suppress fibrinolysis, decreasing the activation of natural anticoagulants. However, their precise roles in this case is unclear. It has been indicated that plasma protein C (PC) levels vary in the course of malignant diseases and do not predict thromboembolic events [9].

Surgery is the next commonly recognized risk factor in developing VT that increases the risk of this complication over 20-fold [17, 18]. It has been proved that cancer patients compared to those without malignancy run a 2- to 3-fold higher perioperative risk of VT [2, 34]. The main reason for coagulation activation is related to direct surgical trauma to the vessels, secondary exposure of subendothelial TF, and release of cytokines. Limited postoperative mobility of patients favors the venous stasis and also results in further damage of the endothelium [9, 16]. Additionally, surgery is associated with hemodilution, which can be recognized as another cause of hypercoagulability [6, 29, 35].

Furthermore, fibrinolytic activity suppression impacts adversely on the pathogenesis of VT. In cancer patients, fibrinolytic inhibition during surgery has been found to be more enhanced in comparison with those patients having nonmalignant tumors [25].

A particularly high activation of coagulation as well as inhibition of the fibrinolytic system have been observed in patients after open colorectal cancer resection [12].

Van Duijnhoven et al. [42] have found that those patients with untreated colon carcinoma show increased activation of coagulation and fibrinolysis. The high tendency for thromboembolic complications results from the abnormal balance between both these processes.

It is estimated that despite introducing heparin prophylaxis in the perioperative period, a significant proportion of up to 41% of the colorectal cancer patients in the metastatic stage, suffer from thromboembolism [20]. Therefore, the standards of deep vein thrombosis prophylaxis are not always effective during this vulnerable period. Recently it has been found that despite prophylaxis with low molecular weight heparin, the frequency rate of pulmonary embolism is the highest during the first 3 postoperative days [37].

However, the question arises as to whether after wide implementation of low molecular weight heparin prophylaxis during the early perioperative period in patients undergoing colon cancer surgery, abnormalities in routine coagulation and fibrinolytic tests indicative of hypercoagulable stage are still present.

## AIM

The aim of this study was to assess the influence of surgery on coagulation and fibrinolytic systems during the early postoperative period in the high risk thromboembolism population, receiving heparin prophylaxis.

## MATERIALS AND METHODS

The study was conducted in conformance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Edinburgh, 2000). All patients signed a written informed consent and agreed to participate in the study. The study was approved by the local Ethics Committee.

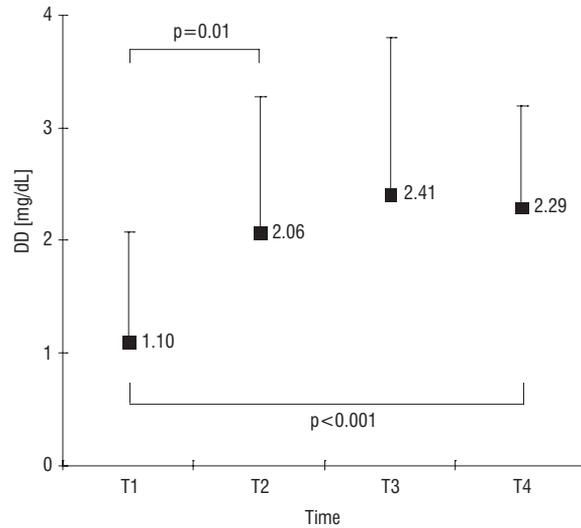
The prospective open study was carried out with a group of 19 patients (7 females and 12 males), aged from 51 to 82 (mean 66.1 years), with histologically confirmed colorectal adenocarcinoma and scheduled for elective total tumor resection. Till the end of the study none of them received chemotherapy. The average time of surgery was 2.5 ( $\pm 0.5$ ) hours. Patients with a history of diabetes, coagulopathy, previous thromboembolic disorders, liver or renal dysfunction and those receiving blood transfusions within 48 hours were excluded from the study. For thromboprophylaxis all patients received Enoxaparin in doses of 40 mg subcutaneously 2 hours before surgery and 40 mg daily thereafter for 4 weeks [19]. Thromboprophylaxis was the only indication for administering low molecular weight heparin and it was not given before the perioperative period. Each patient was premedicated with 7.5–15 mg of Midazolam. The induction of anesthesia included intravenous (IV) bo-

lus consisting of 100 µg of fentanyl, 0.1 mg kg<sup>-1</sup> of norcuron, 1.5 mg kg<sup>-1</sup> of propofol, and 0.5–1 mg kg<sup>-1</sup> of chlorsuccillin. During general anesthesia norcuron 60 µg kg<sup>-1</sup> per hour, fentanyl 20–60 µg kg<sup>-1</sup> per hour, propofol 3–6 mg kg<sup>-1</sup> per hour were administered together with ventilation with oxygen and nitrous oxide mixture in a ratio of 1:2. The blood samples were taken immediately before surgery (T1) – these served as control values for assessing surgery's impact on the coagulation system. Next, samples were taken 6 (T2), 24 (T3) and 48 (T4) hours after surgery completion. Three different peripheral blood samples were obtained. One was collected into 3.8% trisodium citrate in 9:1 volume, centrifuged at 2 500 g for 15 minutes at 4°C. Separated plasma samples were stored at -70°C until used for the analytical tests. These included antithrombin (AT), PC and plasminogen (PG), which were determined by chromogenic substrate tests (Diagnostica Stago). From the second sample plasma fibrinogen (FG) levels were assessed by the Clauss method. D-dimer (DD) plasma levels were determined by STA Liatest DDI optical density method, activated partial thromboplastin time (APTT), and prothrombin time (PT) estimated as international normalized ratio (INR) were determined using standard kits manufactured by Diagnostica Stago. Additionally, platelet count, hemoglobin concentration, and hematocrit values were measured from the third sample.

The hypothesis of normal distribution of analyzed variables was verified and confirmed by the Kolmogorov–Smirnov test. Statistical analysis was performed using a SPSS software (V6.0 SPSS PC, Inc. Chicago, USA). Statistical significances of differences between means for continuous parameters of normal distribution were tested with Student's t-test.

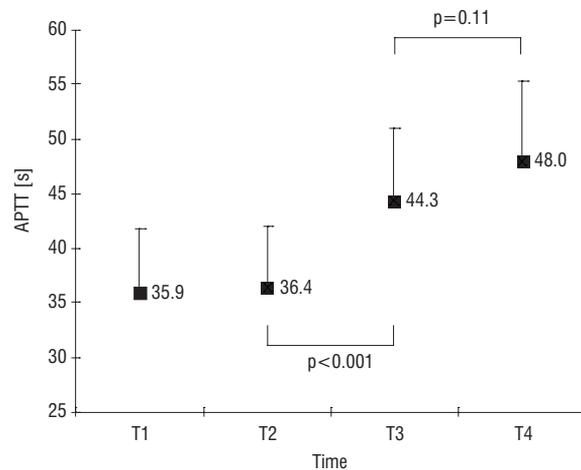
## RESULTS

Before surgery the plasma DD level exceeded the upper limit of reference value (0.5 mg/dL) more than 2-fold and increased significantly 6 hours following surgery. Maximal values were found after 24 hours with an insignificant decrease on the next day (Fig. 1).



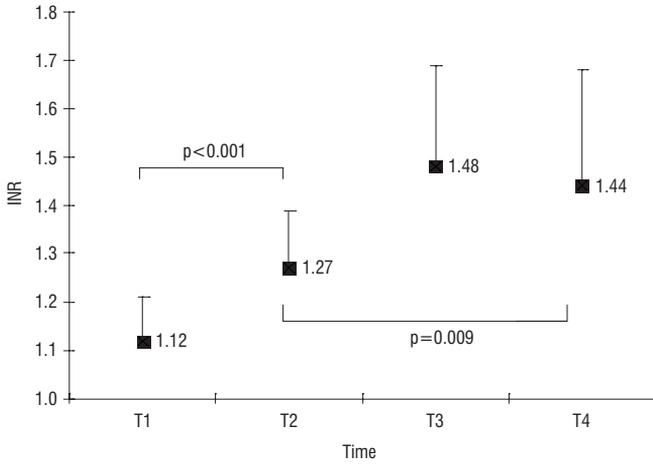
**Fig. 1.** DD plasma levels after colorectal cancer resection. Comments:  $p < 0.01$  for T2 value compared to T1 (control sample). Values expressed as mean  $\pm$ SD

APTT results, presented in Fig. 2, did not change during the initial 6 hours after surgery, but then lengthened significantly after 24 and 48 hours.



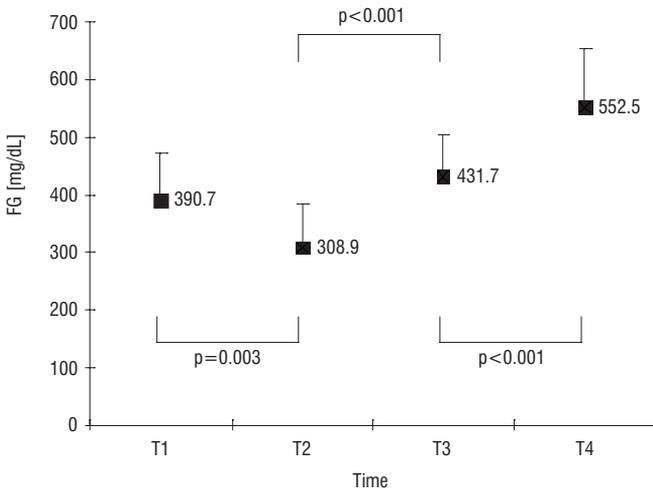
**Fig. 2.** APTT after colorectal cancer resection. Comments:  $p < 0.001$  for T3 and T4 values compared to T1 and for T2 compared to T3 and T4 values. Values expressed as mean  $\pm$ SD

PT defined as INR increased significantly 6 hours after surgery, reaching maximal value after 24 hours, with subsequent insignificant diminishing after 48 hours (Fig. 3).



**Fig. 3.** INR levels after colorectal cancer resection. Comments:  $p < 0.001$  for T2, T3, T4 values compared to T1;  $p < 0.001$  for T2 compared to T3 value and  $p = 0.009$  for T2 compared to T4 value. Values expressed as mean  $\pm$ SD

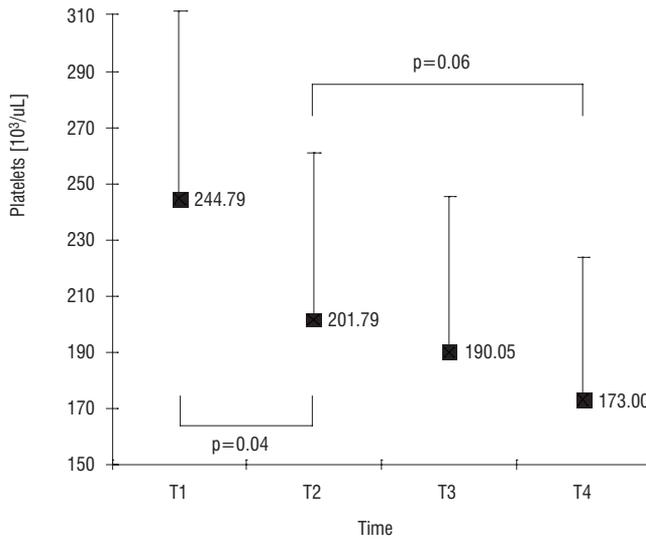
FG plasma levels in perioperative period are summarized in Fig. 4.



**Fig. 4.** FG levels after colorectal cancer resection. Comments:  $p < 0.001$  for T2 value compared to T1. Linear increase of T3 and T4 values ( $p < 0.001$ ) compared to T2 value. Values expressed as mean  $\pm$ SD

A substantial reduction of initially normal FG concentration was revealed 6 hours after surgery. However, FG plasma level significantly increased after 24 hours compared to the lowest detected value and exceeded the upper reference limit. On the next day, the FG concentration plasma level showed a further significant increase.

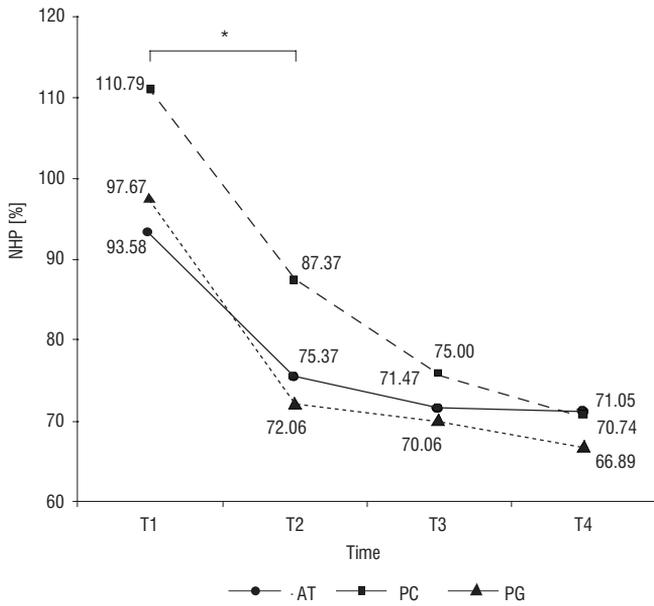
Platelet count diminished significantly after 6 hours, showing a further linear decline up to 48 hours. At that time the mean value was the lowest one. Results are presented in Fig. 5.



**Fig. 5.** Platelets count after colorectal cancer resection. Comments:  $p=0.04$  for T2 value compared to T1. Linear decrease of all subsequent values (T3, T4);  $p=0.009$  for T1 compared to T3 value and  $p<0.001$  for T1 compared to T4 value. Values expressed as mean  $\pm$ SD

The mean AT plasma level before surgery was within normal limits. At 6 hours after surgery a significant drop was noted and lasted up to 48 hours (Fig. 6).

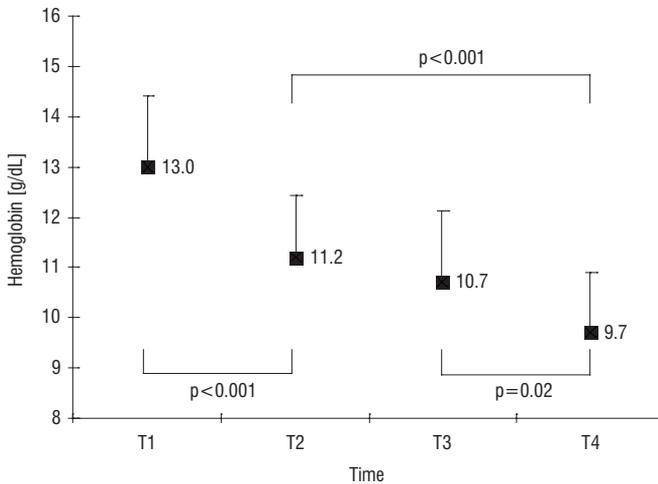
PC plasma level before surgery reached a level of 110.79%. All the subsequent mean postoperative values were significantly and progressively decreased. The lowest value was observed 48 hours after surgery. PG plasma level before surgery amounted to 97.67% and a substantial decrease was detected up to 48 hours (Fig. 6).



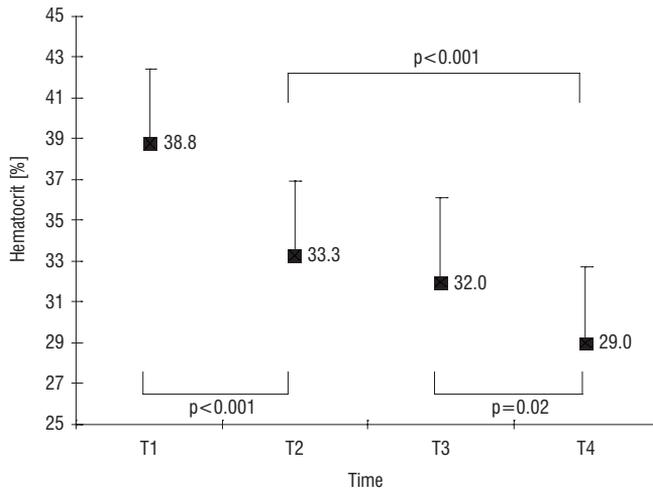
**Fig. 6.** AT, PC and PG levels expressed as the percentage of normal human plasma (NHP) after colorectal cancer resection.

Comments: \*  $p < 0.001$  for T1 value compared to all subsequent values for PC and PG;  $p = 0.002$  for T2 value compared to T1 for AT. Values expressed as mean  $\pm$ SD

Significant decreases in the hemoglobin (Fig. 7) and hematocrit levels (Fig. 8) were detected after 6 hours with further significant reductions 48 hours following surgery.



**Fig. 7.** Hemoglobin levels after colorectal cancer resection. Comments:  $p < 0.001$  for T2, T3, T4 values compared to T1 and for T2 value compared to T4;  $p = 0.02$  for T3 compared to T4 value. Values expressed as mean  $\pm$ SD



**Fig. 8.** Hematocrit levels after colorectal cancer resection. Comments:  $p < 0.001$  for T2, T3, T4 values compared to T1 and for T2 value compared to T4;  $p = 0.02$  for T3 compared to T4 value. Values expressed as mean  $\pm$ SD

## DISCUSSION

In the studied group of patients, DD plasma levels before surgery increased over 2-fold compared to the upper reference value. DD value is considered to be an indicator of coagulation activation, secondary clot proteolysis and correlates with colorectal cancer progression [5, 12, 19, 20, 38]. A high plasma DD level before surgery confirms numerous, already published, conclusions concerning preoperative activation of coagulation and fibrinolytic systems in patients with colorectal cancer [12, 13, 19, 42].

It seems that increased DD plasma concentration in the studied group of patients with the highest level at 24 hours after surgery was caused mostly by the compensatory fibrinolysis process. Galster et al. [12] have found that in the patients who underwent gastrointestinal cancer resection in comparison to those operated on due to non-malignant disease, fibrinolysis assessed by DD plasma level was more intense, and lasted longer, until the 14<sup>th</sup> day of the postoperative follow-up. The mean values of the DD increased up to 48 hours, and were similar to those in the study group. However, these authors observed a decrease of fibrinolytic processes known as fibrinolytic shutdown assessed after 24 hours, which was not observed in our study.

Postoperative fibrinolysis is crucial for fibrin degradation rate and protects against the new thrombotic incidents. Its activity depends on t-PA activity and PAI-1 activity. Neudecker et al. [28] have found that patients who have undergone colorectal cancer resections regardless of the operation type – conventional or laparoscopic, have had increased t-PA activity without an increase in PAI-1 activity during per-

formed procedures. A significant decrease of t-PA activity was observed 8 hours after surgery, and a moderate increase was found again after subsequent 16 hours. PAI-1 activity was increasing since the 8<sup>th</sup> hour to the end of the 24-hour observation period [28]. Fibrinolytic shutdown was found in over 60% of patients in whom elected abdominal surgery was performed and is considered to be an important reason for developing perioperative VT complications [8, 24]. Persistently elevated DD level indicates that this process has not occurred in our study despite an accompanying hemodilution process.

In addition, from the 24<sup>th</sup> hour till the end of the observation period, APTT statistically prolonged and reached therapeutic values. INR was significantly increased since the 6<sup>th</sup> hour, with its maximal value after 24 hours, whereas platelet count was significantly decreased until the end of the study period.

Boldt et al. [7] have noticed a non-significant prolongation of APTT in the 1<sup>st</sup> day after abdominal surgery. Usuba et al. [41] have observed a significant prolongation of APTT accompanied by decreased platelet count in patients operated on due to esophageal cancer. Similar coagulative disturbances in patients have been reported also by Samama et al. [36]

Detected impairment of coagulative activity in the study group probably resulted from consumption of coagulation factors and significant hemodilution, which were manifested by decreased hemoglobin and hematocrit values. Increasing DD plasma level, accompanied by the prolongation of APTT, increased INR and decreased platelet counts 48 hours after surgery may be interpreted as a surgery triggered activation of consumptive coagulopathy despite prophylaxis with low molecular weight heparin. Results from other studies concerning a similar population confirm such interpretation [23, 32]. Galster et al. [12] have noted that differences in the activation of coagulation depend on the operated cancer type, which suggests that this process is mainly related to procoagulants released from the neoplastic cells [22].

AT and PC activities were decreasing beginning with the 6<sup>th</sup> hour after surgery and reached nadir values after 48 hours. The decreased AT activity observed immediately after surgery is considered to be a consumption effect [39]. Effectiveness of heparin treatment depends on AT activity, which inhibits activated factors IX, X, XI, XII, FVII-TF complex, and thrombin [40]. The more so, because the compensation of decreased AT activity proceeds faster and is more augmented in patients below 60 years of age [7]. In the studied patient group the average age was more advanced, which can be regarded as the next factor contributing to a reduced AT activity measured until the end of the observation period.

PC is an important natural anticoagulant with an inhibitory effect on coagulation. In its activated form (APC), it decreases thrombin generation by factor V and VIII inhibition [27]. It is believed that APC deficiency results in thrombosis of capillary vessels, leukocytes adhesion, and generation of cytokines [10]. Gouin-Thibault et al.

[15] explain that decreased AT, PC and protein S (PS) activities in cancer patients result from diminished hepatic synthesis and overconsumption. Nguyen et al. [30] found laparoscopic and open gastric bypass surgery to result in a gradual postoperative decrease of initially normal PC and AT plasma levels as we detected in our group of patients [38]. Garcia-Avello et al. [13] found a decreased PC plasma level only in samples taken from the tumor draining vein after colorectal cancer resection. In the study group both the consumption of coagulation factors and postoperative hemodilution can be regarded as contributing to decreased plasma levels of natural anticoagulants. In a large prospective study Folsom et al. [11] concluded that in a population without cancer, a low PC level rather than AT deficiency is responsible for new onsets of thrombotic complications. When comparing patients with thrombosis and cancer to those without malignancy, PC concentration is found to be significantly decreased in the former group [14]. These observations suggest a clinical significance of low PC plasma levels in the development of thromboembolic complications.

Decreased PG values 6 hours after surgery in the study group was accompanied by a rapid increase in FG plasma level. Low PG level may lead to deterioration in plasma fibrinolytic potential. However, isolated congenital PG deficiency was not recognized as a risk factor for VT [31].

Nguyen et al. [30] suggested that a decrease in PG level and a concomitant increased FG concentration may facilitate fibrin generation. This process shifts the coagulation-fibrinolysis balance towards a hypercoagulable state [42].

Before heparin prophylaxis era, it was found that general anesthesia was associated with a statistically significant increase in postoperative thromboembolic complications [33]. Despite the introduction of low molecular weight heparin prophylaxis, it was proved that general anesthetics may still produce more VT complications [26]. There is no doubt that heparin prophylaxis by impairing the coagulation system reduces the risk of thromboembolic complications in patients subjected to open surgery. Nevertheless, the activation of the coagulation system occurs as a result of processes described above, and leads to impairment of intrinsic and extrinsic coagulation pathways, decreased platelet count as well as the lowering of natural anticoagulants. Thus, a question arises: What is the significance of both these processes in pathogenesis of thromboembolic complications? It seems that decreased levels of anticoagulants may be of the greatest importance.

The limitation of this study is the fact that the prothrombotic effect of applied general anesthetics in this research cannot be excluded. Due to the safety reasons, we did not compare our patients with a control group without heparin prophylaxis. It is therefore impossible to establish whether the observed hemostatic disarrangements are related to the applied standard general anesthesia or to what extent they were prevented by the use of prophylaxis with low molecular weight heparin.

## CONCLUSIONS

Colorectal cancer induces a significant activation of coagulation and fibrinolytic systems. Despite prophylaxis with low molecular weight heparin, colorectal cancer resection interferes with hemostasis by induction of a process resembling consumptive coagulopathy with an impairment of standard coagulation laboratory tests and triggers reactions leading to a decreased level of natural anticoagulants. Further studies are required to determine whether substitutional administration of natural anticoagulants added to routine heparin treatment in case of prophylaxis failure should be considered.

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