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EFFECTS OF FRAXIPARINE THERAPY AND D-DIMER LEVELS DURING TREATMENT OF DEEP VEIN THROMBOSIS AND THROMBOEMBOLISM IN CANCER PATIENTS

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Summary

Thrombosis is a common complication in cancer patients. It often occurs as the first sign suggestive of a malignancy, and also during the treatment since surgery, chemotherapy and radiation therapy present an additional trigger for the development of thrombosis and/or thromboembolism. In the last five years at the University Hospital for Tumors, Zagreb, Croatia, 31 cancer patients, 12 males and 19 females, aged 41-80 years, were monitored and treated for deep vein thrombosis (DVT) and pulmonary embolism (PE). The patients were admitted for renal cancer 2, pancreatic cancer 2, colon cancer 4, thyroid cancer 1, ovarian cancer 3, breast cancer 7, melanoma 2, brain cancer 2, sarcoma 1, gastric cancer 1, cervical cancer 1, non-Hodgkin's lymphoma 1 and esophageal cancer 4. DVT and PE were diagnosed preoperatively, during radiation therapy and in the course of chemotherapy in 7, 6 and 18 patients, respectively. To confirm the DVT diagnosis and suspected PE, Doppler US of the veins and spiral CT were performed, respectively. Samples of venous blood were collected from all patients into vacuteiner tubes coated with anticoagulant. Hemostasis tests were done on day 1, 3 and 7 of low-molecular-weight heparin (LMWH) therapy (Fraxiparine). Fraxiparine in the dose of 0.8 ml sc (20000 ICUAXa) was administered every eight hours for DVT, or every six hours for PE. The paper presents D-dimer (DD) values measured on the Behring BCS using reagents of the same brand. A significant decrease of DD levels during Fraxiparine therapy was compared with the patients' clinical recovery. After administration of LMWH, initially high DD levels decreased for 30% and 64% on day 3 and 7, respectively. The decrease of DD levels was accompanied with clinical recovery of the patients.

KEY WORDS: *Fraxiparine, D – dimers (DD), deep vein thrombosis (DVT) , thromboembolism (TE) , cancer*

TERAPIJSKI EFEKT FRAXIPARINA I VRIJEDNOSTI D–DIMERA TIJEKOM LIJEČENJA DVT I TE U BOLESNIKA S KARCINOMOM

Sažetak

Tromboza je učestala komplikacija u bolesnika s karcinomom. Nastaje često kao prvi znak maligne bolesti, ali i u tijeku liječenja jer su operacija, kemoterapija i zračenje dodatni otponac za razvoj tromboze i/ili tromboembolije. U Klinici za tumore je unazad pet godina zbog duboke venske tromboze (DVT) i plućne embolije (PE) praćen i liječen 31 bolesnik (12 muškaraca i 19 žena) u dobi od 41–80 godina, s karcinomom bubrega 2, gušterače 2, crijeva 4, štitnjače 1, jajnika 3, dojke 7, melanomom 2, rakom mozga 2, sarkomom, rakom želuca, ušća maternice i ne-Hodgkinovim limfomom po 1 i 4 bolesnika s tumorima ždrijela. Preoperativno su DVT i PE dijagnosticirane u 7 bolesnika, 6 u vrijeme zračenja i 18 tijekom kemoterapije. Radi potvrde dijagnoze DVT napravljen je ultrazvučni dopler vena, a kod sumnje na PE, spiralni CT. Svim bolesnicima uzeti su uzorci venske krvi u *vacuteiner* epruvete s antikoagulansom. Testovi hemostaze napravljeni su prvog, trećeg i sedmog dana terapije heparinom male molekularne mase (Fraxiparine). Fraxiparine je primijenjen u dozi od 0,8 ml sc (20000 ICUAXa) svakih osam sati kod DVT, odnosno svakih šest sati kod PE. U radu su prikazane vrijednosti DD mjerene uređajem Behring BCS s reagensima istog proizvođača. Znatan pad vrijednosti DD tijekom terapije Fraxiparinom uspoređen je s kliničkim oporavkom bolesnika. Visoke početne vrijednosti DD nakon primjene LMWH pale su trećega dana za 30%, a sedmoga dana za 64%. Klinički oporavak bolesnika pratio je smanjenje vrijednosti DD.

KLJUČNE RIJEČI: *Fraxiparine, D–dimeri (DD), duboka venska tromboza (DVT), tromboembolija (TE), karcinom*

INTRODUCTION

Deep vein thrombosis (DVT) and thromboembolism (TE) are a frequent occurrence in patients with cancer (1). Idiopathic DVT and TE are often the first sign of malignancy, and may also occur as complications of antitumor treatment (2). Measurement of DD values, along with other diagnostic parameters, is a confirmative test for fibrinolysis activation, and an indirect indicator of fibrin formation (3). Low molecular weight heparins (LMWH) are shown to be effective in both prevention and treatment of DVT and TE (4).

PATIENTS AND METHODS

In the last five years at the University Hospital for Tumors, Zagreb, Croatia, 31 cancer patients, 12 males and 19 females, aged 41-80 years, were monitored and treated for deep vein thrombosis (DVT) and pulmonary embolism (PE) (Table 1).

Among them, there were 2 patients with renal cancer, 2 with pancreatic cancer, 4 with colon cancer 4, 1 with thyroid cancer, 3 with ovarian cancer, 7 with breast cancer, 2 with melanoma, 2 with brain cancer , 1 each with sarcoma, gastric cancer, cervical cancer and non-Hodgkin's lymphoma and 4 with esophageal cancer.

DVT and PE were diagnosed preoperatively, during radiation therapy and in the course of chemotherapy in 7, 6 and 18 patients, respectively. To confirm the DVT diagnosis and suspected PE, Doppler US of the veins and spiral CT were performed, respectively (Fig. 1 and 2)

The patients then underwent therapy with LMWH (Fraxiparine) at a dose of 0.8 ml sc administered every eight hours during 7-9 days, and in case of microembolism, 0.8 ml sc of Fraxiparine was given every six hours during 10 days along with 500 units of ATIII concentrate i.v. once a day during 3 days.

Table 1.

PATIENT AGE

Age	No. of patients
41 – 50	2
51 – 60	7
61 – 70	11
71 – 80	11
Total	**31**

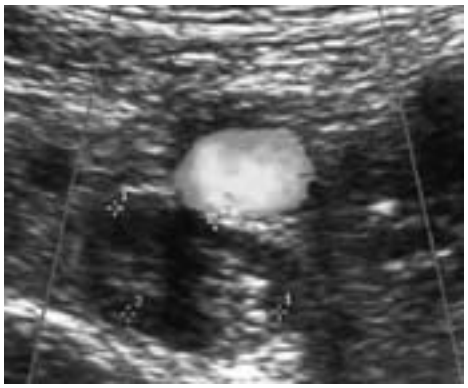

Figure 1. Ultrasound image of DVT

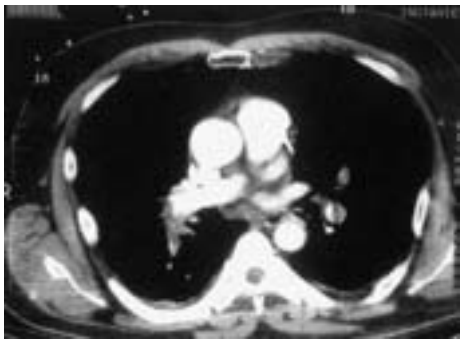

Figure 2. Spiral CT – bilateral PE

Fraxiparine is a low molecular weight heparin (2,400-7,200 daltons) occurring since 1980 under the name of nadroparin calcium (INN, Cy 216). It was extracted from pig intestinal mucosa and then, by fermentation, a chemical structure of high biological potential was obtained. For prophylaxis, it is administered in a dose of 0.2-0.4 ml sc (or 5000-10000 ICUAXa) once a day, and in therapy, a dose of 0.6-0.8 ml sc. (or 15000-20000 ICUAXa) is administered 2-3 times a day.

Heparin therapy was administered for 7-9 days, and then the treatment was switched to peroral anticoagulant – cumarin (Marivarin) (PV 25 – 35%, INR 3.0).

On days 1, 3 and 7, a sample of venous blood were collected from all patients into vacuteiner tubes coated with anticoagulant and hemostasis tests (prothrombin time– PT, activated partial thromboplastin time – APTT, fibrinogen – F1, thrombin time – TT, fibrinolysis, antithrombin III – ATIII, and D–dimers – DD), were performed on the Behring BCS using reagents of the same brand. DDs are produced as a result of plasmin activity on cross-linked fibrin (Figure 3).

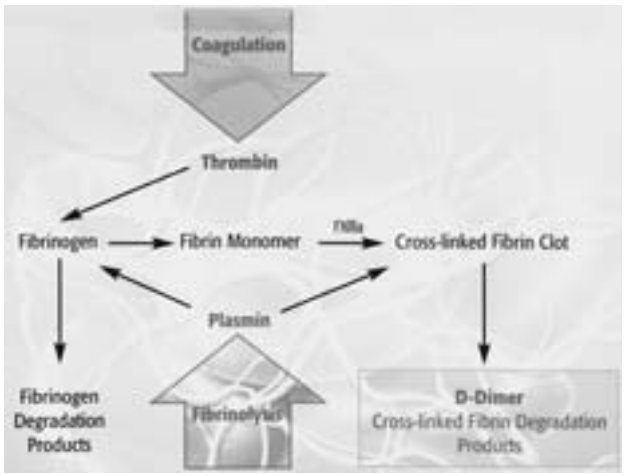

Figure 3. Schematic representation of DD development pattern

The patients'clinical status (scores 1–3) including data on basic symptomatolgy of pathological events in DVT and PE, was assessed on days 1, 3 and 7 of hemostasis testing. In this paper, the decrease of plasma DD levels was monitored in relation to Fraxiparine therapy doses and patients' clinical recovery.

RESULTS

Measurements of DD levels were performed in patients undergoing Fraxiparine therapy on days 1, 3 and 7 of the treatment (Table 2)

Mean DD values measured before heparin therapy with Fraxiparine (I) were markedly high (1130 μ/L) corresponding to the clinical picture of DVT established in 30 patients, and PE which was documented in one patient.

Measurements of DD levels (III) obtained on day 3 and 7 of Fraxiparine therapy showed a significant dose-related decrease of 30% and 64%, respectively, compared to the first measurement.

Table 2.

MEAN DD VALUES IN μ/L MEASURED ON DAY 1, 3 AND 7 OF DVT AND TE THERAPY WITH FRAXIPARINE

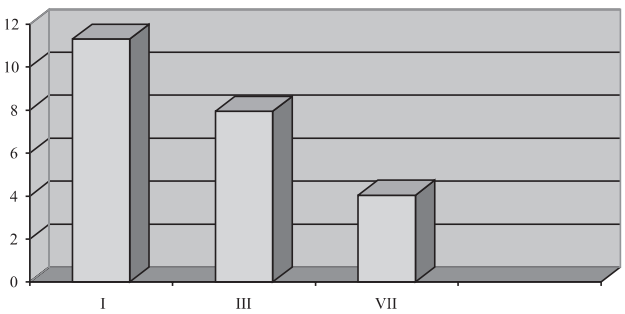

Table 3.

ASSESSMENT OF THE CLINICAL STATUS OF DVT PATIENT

Symptoms	1	2	3
Extremity swelling	++	+ -	-
H sign	+++	+	-
Pain upon movement	++	+	-
Livid skin	++	-	-
Taut skin	++	+ -	-

Table 4.

ASSESSMENT OF THE CLINICAL STATUS OF PE PATIENT

SYMPTOMS	1	2	3
Hemoptysis	+	-	-
Dyspnea	++	+ -	-
Chest pain	+++	+ -	-
Irritable cough	++	-	-

DD levels measured in the course of Fraxiparine therapy showed the efficaciousness of the administered therapy dose.

According to the assigned scores ranging from 1-3 (Tables 3, 4) the patients' clinical status was assessed. The patients' recovery overlapped with the decrease of DD levels, or the effects of Fraxiparine therapy.

DISCUSSION

In 1895 already, Trousseau pointed to the frequent occurrence of migrating thrombophlebitis in cancer patients (5).

In their studies, Achkar et al. confirmed the Trousseau's observations, while Gouin-Thibault and Samama pointed at the occurrence of cancer in patients with idiopathic DVT established 6-12 months earlier. In 90% of cancer patients, the same group documented an enhanced activation of coagulation from hemostasis testing (6, 7).

Numerous factors are held responsible for the activation of the coagulation system in patients with cancer (8, 9). The body responds to a new growth by a wide range of activations and suppressions (inflammatory condition, necrosis, disproteinemia, hemodynamic disorders). Under the influence of tumor cells and macrophages, both the coagulation system and the fibrinolytic system become activated, and the interreaction of endothelium, platelets and macrophages devel-

ops (10-12). Venous stasis and an increase in blood viscosity enhance the risk of venous thrombosis (13,14). A tumor procoagulation factor - cancer procoagulant (CP), 68-kd cysteine proteinase without carbohydrate, isolated as early as 1975 by the Gordon's group, directly activates factor X. The activation was experimentally demonstrated upon incubation of purified bovine factor X with the Russell's viper venom on one hand, and CP on the other. FX cleaving was achieved using either of the two activators, and after the 15-hour incubation, the electrophoresis image in both cases showed FX beta as the final product (15, 16).

This paper reports 7 solid malignoma patients with preoperatively detected DVT.

Cancer treatment presents an additional trigger for the development of thromboembolism. Chemotherapy becomes more and more aggressive treatment, causing endothelial lesions and desquamation of leukocytes, and secretion of cytokines and thromboplastins that, through F VII, activate the coagulation system. Lee and Fuktuomi describe cases of acquired thrombophilia caused by chemotherapy (17-19).

The administration of methotrexate in children with osteogenic sarcoma caused DIC. In melanoma patients, dacarbazin caused thrombosis of the vena hepatica. Pulmonary vein occlusion developed in patients receiving treatment with bleomycin and mytomycinom C (20, 21). In our study, DVT developed in 18 patients receiving chemotherapy for breast cancer, melanoma, thyroid cancer, ovarian cancer, colon cancer and non-Hodgkin's lymphoma.

During radiation therapy, vacuoalization and sclerosation of small blood vessels occur. In our study, activation of the anticoagulation system and depletion of fibrinolytic activity in the middle of radiotherapy sessions were demonstrated. Five-year follow-up of patients treated with high-dose preoperative irradiation for cancer of the rectum, showed an increased risk for thromboembolism in comparison with the group not receiving radiation treatment (7.5% : 3.6%). According to the studies of Graf et al (22-25), radiotherapy in gynecological cancer patients increases the risk of developing TE.

DVT developed in 6 of the patients presented in this study undergoing radiotherapy, for esophageal cancer – 4 and for malignant brain tumor – 2.

DVT is defined as a complete or partial obstruction of deep veins due to a fibrin clot (26). The clinical picture is characterized by: edema, taut skin, pain on toe flexion (Homan's sign), and confirmed by color Doppler technique and/or phlebography (27). Hemostasis tests show hypercoagulability with secondary activated fibrinolysis and elevated plasma levels of DD (28). In our study, the initial mean plasma levels of DD were markedly high by five times exceeding the normal range.

PE is defined as a sudden partial or total obliteration of the pulmonary artery or one of its branches by a fibrin clot. The diagnosis is made from the clinical picture evidence of dyspnea, chest pain, irritable cough, hemoptysis, syncope, tachypnea, cyanosis, and from the ECG evidence for right heart strain. The partial pressure of oxygen decreases, and the carbon dioxide pressure increases. The method of choice for diagnosis is either lung scintigraphy or spiral CT (29). Hemostasis test results reveal hypercoagulability, secondary activated fibrinolysis with markedly increased plasma DD levels (30).

In our study, spiral CT, along with the clinical picture and assessed coagulation parameters, proved to be an appropriate choice to confirm the PE diagnosis.

In the University Hospital for Tumors, Zagreb, Croatia, the administration of LMWH-Fraxiparine for the prevention of TE and DVT started in 1992. In the first five years, Fraxiparine for the prevention of TE was given in a dose of 0.3 ml or 0.4 ml sc, depending on the patient's body weight, two hours before abdominal surgery.

Since 2000, the administration of Fraxiparine for the prevention of TE has been extended to a selected group of high-risk patients (with a history of myocardial infarction or atrial fibrillation, brain insult, varicose syndrome) receiving chemotherapy with 5-FU and leucovorin or radiation therapy for prostate and intestinal cancer.

In Libri Oncologici of 2000, we published a paper on hemostasis test results in patients receiving therapy doses of Fraxiparine, by which we confirmed literature citations that LMWH therapy does not alter APTT and TT. According to literature citations, the therapy dose of LMWH can be controlled by measuring the FX activity, but the method and the reagents are too expensive. Our study from 2000 showed the positive ef-

fect of Fraxiparine on natural coagulation inhibitors, ATIII and C protein (PC), confirming a statistically significant increase in their levels parallel to the patients' clinical recovery (31-34).

In 2001, we reported a case of successful Fraxiparine treatment stressing the validity of DD measurement as an indicator of LMWH therapeutic effect. The patient weighed 85 kg, and was administered 0.8 ml Fraxiparine three times a day, during 11 days. Her DD level dropped from 1014 µ/L to 306 µ/L, and the patient made a full clinical recovery (35, 36).

D-dimer is a direct indicator of fibrinolytic activity and an indirect market of clot formation. Plasmin not only degrades fibrin, but it also lyses fibrinogen. Fibrinogen degradation results in fibrinogen degradation products not containing D-dimer fragments, and therefore not detected by DD testing unlike plasmin-mediated fibrin degradation and positive plasma DD values (37).

An increase of fibrin concentration accompanies many diseases such as malignomas, heart disease, liver disease, inflammatory conditions, rheumatic diseases, as well as major surgeries and physiological conditions (older age, pregnancy). D-dimers are therefore not an absolutely safe marker of DVT and/or PE, however, along with other diagnostic indicators (US Doppler, scintigraphy, phlebography, spiral CT) and clinical picture, they are reliable for the diagnosis of DVT and PE (38-40).

It is a well-known fact that LMWH therapy should not be monitored by hemostasis tests as they change after the administration of heparin (41). The DVTENOX study group in 1993 and Schrecengost et al in 2003 report a significant decrease of DD levels immediately after the administration of heparin (42).

In our study we demonstrated a decrease of DD levels by 30% from day 1 to day 3 of Fraxiparine treatment. At the end of the treatment, DD levels decreased by even 64% in relation to the first measurement, to be considered as statistically significant and in accordance with other studies in the literature.

CONCLUSION

In the 31 malignant solid tumor patients undergoing Fraxiparine therapy for DVT and PE, Fraxiparine was shown to be both efficacious and safe.

During Fraxiparine therapy, DD levels decreased to almost normal values.

Clinical recovery of the patients was accompanied by a decrease of DD values.

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