THE BLOOD VISCOSITY IN PATIENTS WITH DEEP VENOUS THROMBOTIC RISK UNDER LOW-MOLECULAR WEIGHT HEPARIN TREATMENT

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Abstract. Prophylaxis of deep venous thrombosis with low molecular weight heparin has been studied in many clinical trials but the effect on the hemorheological parameters is steel uncertain. Our study checks the hemorheologic effects of administration of LMWH in thromboembolism prevention measuring the whole blood viscosity with a cone/plate viscometer at high shear rate ($600 - 1125\ sec^{-1}$). The study was performed on a group of sixteen patients, hospitalized in orthopedic surgery department for hip fractures. Hematocrit, fibrinogen and whole blood viscosity were measured before operation, immediately after it and seven days later. We found that LMWH decrease hematocrit, fibrinogen and whole blood viscosity at a high shear rate. The decrease of blood viscosity could be one of the most important effects of LMWH in deep venous thrombosis prophylaxis.

Key words: blood viscosity, hemorheology, thrombosis, low-molecular weight heparin.

INTRODUCTION

The risk of venous thromboembolism in patients with limb fractures which compulsorily required surgical intervention is known to be high [2]. Thrombosis is a naturally occurring physiologic process. Under normal circumstances, a physiologic balance is present between factors that promote and retard coagulation. A disturbance in this equilibrium may result in the coagulation process occurring at an inopportune time or location or in an excessive manner. Virchow described a triad of factors of venous stasis, endothelial damage, and a hypercoagulable state that are associated with the equilibrium process. Venous stasis can occur as a result of anything that slows or obstructs the flow of venous blood. This results in an increase in viscosity and the formation of microthrombi, which are not washed away by fluid movement; the thrombus that forms may then grow and propagate. Endothelial (intimal) damage within the blood vessel may be

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intrinsic or secondary to external trauma. It may result from accidental injury or surgical insult. A hypercoagulable state can occur due to a biochemical imbalance between circulating factors. However, the optimal duration of prophylaxis with anticoagulant agents in these conditions is unknown. Because low molecular weight heparins (LMWH) derived from heparin by different methods of depolymerization have a better bioavailability at low doses, they become the elective drugs in this treatment [3].

The aim of this study is to check the hemorheologic effects of administration of LMWH in thromboembolism prevention. LMWH belongs to a class of anticoagulants termed glycosaminoglycans. LMWH products are manufactured from unfractionated heparin (UFH) by either chemical or enzymatic depolymerization, consequently their molecular weights are in the range of about 4,000 – 6,000 daltons, one-third the size of UFH. LMWH exhibit a preferential effect on activated factor X with fewer effects on platelets than standard heparin [10, 11]. These compounds are less able to inhibit thrombin formation. A major pharmacological benefit of LMWH is a reduction in anti-factor IIa activity with preservation of anti-factor Xa activity. This preferential effect on factor Xa along with fewer effects on thrombin and platelets were thought to be properties that might lead to less bleeding complications [4, 8].

Whole blood viscosity, hematocrit, and fibrinogen were studied in a group of patients with hip fracture before and during subcutaneous LMWH treatment.

MATERIAL AND METHOD

The study was performed on a group of sixteen patients, hospitalized in the orthopedic surgery department for hip fractures. The blood samples were collected before operation, immediately after it and seven days later. In all this period the patients received subcutaneous treatment with LMWH to prevent the risk of deep venous thrombosis.

Every time, the blood was collected by venipuncture and 4.5 ml of it was drawn and transferred to a polypropylene tube containing EDTA. The following parameters were determined:

- hematocrit – from a sample of blood collected with EDTA anticoagulant using microcentrifugation procedure, five minutes at 10,000 g;
- fibrinogen – from a sample of 5 ml blood collected with sodium citrate anticoagulant using a spectrophotometer at 546 nm;
- whole blood viscosity – from a sample of 4.5 ml blood collected with EDTA anticoagulant using a DV-II+ Brookfield Cone/Plate viscometer. The blood viscosity was measured at a different shear rate in a range of 600 – 1125 sec^{-1}.

The DV-II+ Brookfield viscometer was connected to a warm bath keeping the temperature constant at 37 °C (Fig. 1). The Brookfield Cone/Plate Viscometer is a precise torque meter which is driven at discrete rotational speeds. The torque measuring system, which consists of a calibrated beryllium-copper spring connecting the drive mechanism to a rotating cone, senses the resistance to rotation caused by the presence of sample fluid between the cone and a stationary flat plate.

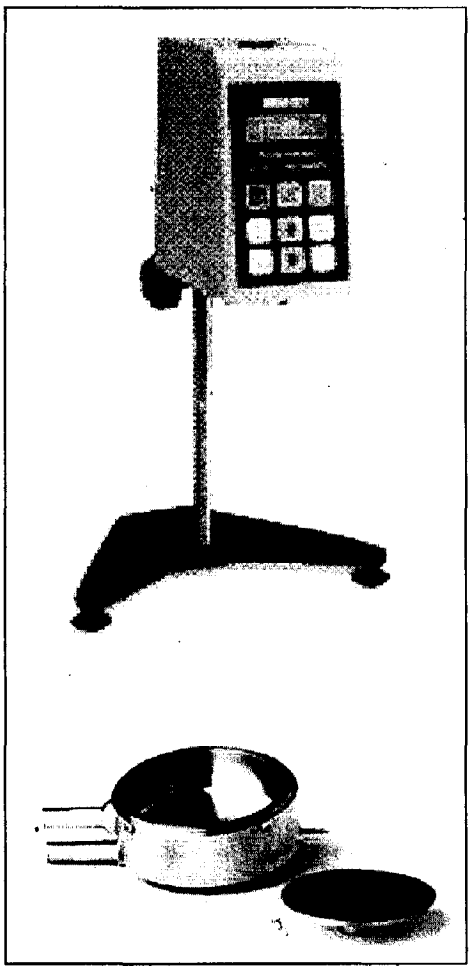

Fig. 1. – The DV-II+ Brookfield Cone/Plate Viscometer.

The resistance to the rotation of the cone produces a torque that is proportional to the shear stress in the fluid. The amount of torque is indicated either on a dial or digital display, depending on the model. This reading is easily converted to absolute centipoise units (mPa·s) from pre-calculated range charts. Alternatively, viscosity can be calculated from the known geometric constants of the cone, the rate of rotation, and the stress related torque.

RESULTS AND DISCUSSIONS

The mean values of hematocrit, fibrinogen and viscosity are presented in the tables and in the figures below.

The whole blood viscosity mean values (Table 1 and Fig. 2) are measured at a high shear rate (600 – 1125 sec^{-1}), which means a range of interval between 80 and 150 rotations per minute.

Table 1

The mean values of whole blood viscosity

	RPM	80	90	100	105	120	135	140	150
Before op.	Average	2.96	2.70	2.43	2.32	2.03	1.81	1.74	1.62
	SD	0.42	0.44	0.40	0.38	0.33	0.29	0.28	0.26
After op.	Average	2.62	2.43	2.17	2.06	1.75	1.50	1.42	1.29
	SD	0.68	0.41	0.25	0.20	0.14	0.18	0.20	0.23
Seven days later	Average	2.61	2.32	1.99	1.84	1.54	1.27	1.17	1.02
	SD	1.34	1.20	1.09	1.04	0.89	0.77	0.73	0.66

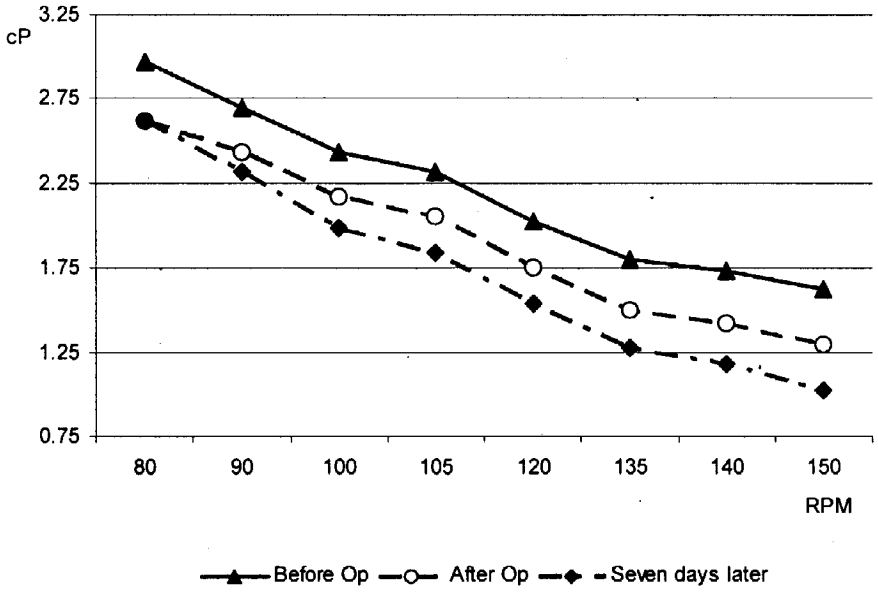

Fig. 2. – The representation of the whole blood viscosity (mean values).

Blood behaves like a non-Newtonian fluid whose viscosity varies with the shear rate. The non-Newtonian characteristics of blood come from the presence of cells (red blood cells), which make blood a suspension of particles [5].

Hemorheological properties of the blood include whole blood viscosity, plasma viscosity, hematocrit, red blood cells deformability and aggregation, and fibrinogen concentration in the plasma. Although a number of parameters such as pressure, lumen diameter, whole blood viscosity, compliance of vessels, peripheral vascular resistance are well-known physiological parameters that affect the blood flow; the whole blood viscosity is also an important key physiological parameter.

Before operation and without any LMWH treatment, the values are significantly higher than immediately after it and seven days after operations. In all this time, patients were treated with a single subcutaneous dose of LMWH as prevention for deep venous thrombosis. LMWH led to a significant reduction in whole blood viscosity. This reduction is concordant with hematocrit decreased values and fibrinogen values. No bleeding accident was reported during all this period.

Table 2

The mean values of fibrinogen and hematocrit

	Fibrinogen (mg/%)			Ht (%)		
	Before op.	After op.	Seven days later	Before op.	After op.	Seven days later
Average	418.71	407.43	381.14	36.67	31.51	30.94
Sd	37.36	64.47	64.04	5.30	2.87	1.68
Pt		0.7	0.2		0.05	0.03

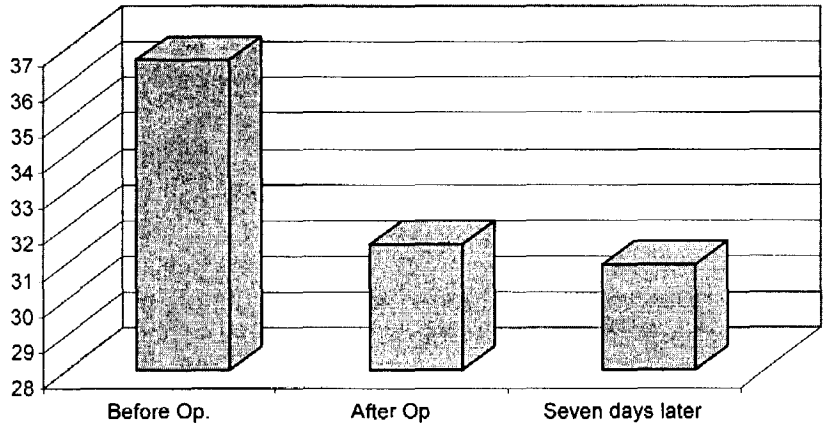

Fig. 3. – The representation of the hematocrit (mean values).

The hematocrit mean values (Table 2 and Fig. 3) are decreased from the beginning at the lower rate of the normal range. After operations and seven days later the values present a slower tendency to decrease but with no significant

statistic values. Hematocrit is the most important determinant of the whole blood viscosity [6]. The effect of hematocrit on the blood viscosity has been well documented. All studies have shown that the viscosity of whole blood varies directly with the hematocrit at cell concentration above 10% [7].

The fibrinogen mean values (Table 1 and Fig. 4) are increased before operations and after as a consequence of trauma and the associated inflammatory process. Seven days after operations the fibrinogen values became normal, but at the highest values of the normal range. Our result is concordant with recent studies [1], which show decreased values of fibrinogen and blood viscosity six weeks after acute phase of a deep venous thrombosis.

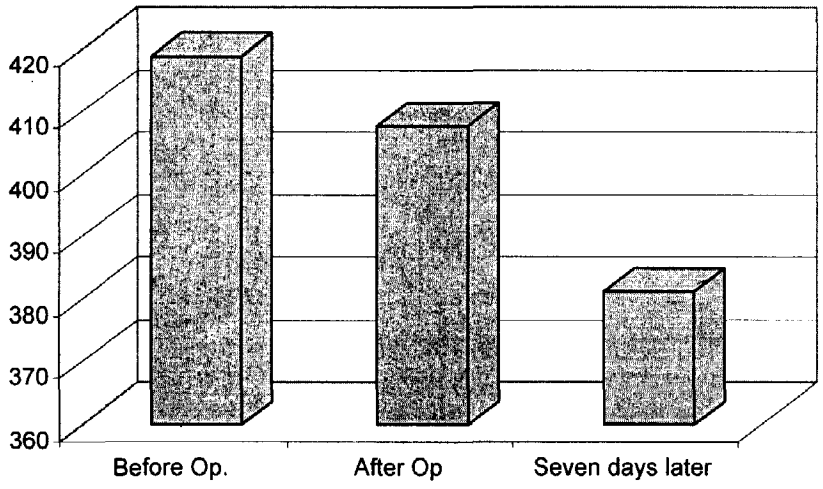

Fig. 4. – The representation of fibrinogen (mean values).

CONCLUSIONS

We found that LMWH decreases the hematocrit, fibrinogen and whole blood viscosity at a high shear rate. The decrease of blood viscosity due to LMWH is one of its most important effects in deep venous thrombosis prophylaxis.

LMWH, which selectively inhibit the Xa factor [9] with minimal risk of hemorrhage, seems to offer new possibilities in the prevention and treatment of deep venous thrombosis having also an antithrombotic effect.

The LMWH are highly effective, with a good safety profile, and require no blood test monitoring. This, together with their ease of administration, means that the majority of deep venous thrombosis patients can now be treated on an ambulatory basis, without the need for hospital.

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