THROMBELASTOGRAPHY – AN ACCURATE METHOD IN MONITORING THE PATIENTS UNDER ANTICOAGULANT TREATMENT

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Abstract. In patients with limb fractures, in order to prevent venous thrombosis, before and after surgical intervention, anticoagulant substances are usually administered. Because low molecular weight heparins (LMWH) derived from heparin by different depolymerization methods have a better bioavailability at low doses, they become the elective drugs in this treatment. In these cases, laboratory monitoring is not objective enough; therefore, thrombelastography (Teg) has been reported as the best technique for monitoring heparinized patients. Our study was performed on two groups of hospitalized patients in orthopedic surgery and thrombelastogram was recorded before operation, immediately after it and seven days later. The differences between the groups consist in the different types of LMWH administered. Teg was able to emphasize the hypocoagulable status in patients under anticoagulant treatment even in the absence of the clinical signs.

Key words: thrombelastography, low molecular weight heparins, limb fractures.

INTRODUCTION

In order to prevent venous thrombosis in patients with limb fractures which compulsorily required surgical intervention, anticoagulant substances, heparins with small or large molecules are usually administered.

Low molecular weight heparins (LMWH) are derived from heparin by chemical or enzymatic depolymerization, yielding fragments approximately one third the size of heparin. They have a mean molecular weight of 4,500 to 5,000 d. They are prepared by different methods of depolymerization such as: nitrous acid depolymerization, benzylation followed by alkaline depolymerization, enzymatic depolymerization with heparinaze and peroxidative depolymerization.

LMWHs produce their major anticoagulant effect by inactivating factor Xa [2, 4, 7, 9] and activating antithrombin (AT). They have less ability to inactivate thrombin because the smaller fragments cannot bind simultaneously to both AT and thrombin. Also LMWH preparations have a longer plasma half-life and better bioavailability at lower doses than unfractioned heparins, and a more predictable dose response [5].

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In 1976, Johnson et al [6] reported that LMWH fractions had progressively less effect on the APTT activity, as they were reduced in molecular size, while still inhibiting activated factor X.

Because biochemical laboratory monitoring is not objective and even not necessary in LMWH therapy, thrombelastgraphy (Teg) has been reported as an excellent technique for monitoring heparinized patients. By this method all phases of coagulation-fibrinolytic system are recorded and at the same time the different components involved in the clot formation are evaluated.

MATERIAL AND METHOD

The study was performed on two groups (A and B) of 9 and respectively 7 patients, hospitalized in orthopedic surgery for hip fractures. Thrombelastogram was recorded before operation, immediately after it and seven days later. In all these periods the patients of A and B groups received two different LMWH substances by depolymerization technique.

Every time, the blood was collected by venipuncture and 4.5 ml of it was drawn and transferred to a polypropylene tube containing 0.5 ml of 0.109 M sodium citrate (pH 7.4). In this way the citrated whole blood (CWB) was obtained. For each sample 330 µl CWB were put in a cup and then 30 µl of 0.2 M $CaCl_2$ were added. After this, the thrombelastogram was recorded on the printing paper and on the computer analyzer as well.

In our research, we used thrombelastograph coagulation analyzer model 3000C type Haemoscope. The instrument diagram shows the sample cup and measurement pin that is attached to a calibrated torsion wire (Fig. 1). Whole blood (or recalcified/citrated blood) is placed in the space between the cup and pin and allowed to clot. Fibers composed of fibrin and platelets attach to the cup and pin, increasing the elastic shear modulus of the sample.

The cylindrical cup is maintained at a temperature of 37 °C, it holds the blood and is oscillated through an angle of 4°45'. Each rotation cycle lasts 10 seconds including a one second rest period at the end of the excursion (to prevent viscosity errors). The pin is suspended in the blood by a torsion wire and is monitored for motion. The torque of the rotating cup only affects the immersed pin after fibrin-platelet bonding has linked the cup and pin together. The strength of these fibrin-platelet bonds affects the magnitude of the pin motion, such that strong clots move the pin directly in phase with the cup motion. Thus, the magnitude of the output is directly related to the strength of the formed clot. As the clot retracts or lyses, these bonds are broken and the transfer of cup motion is diminished.

The rotation movement of the pin is converted by a mechanical/electrical transducer to an electrical signal, which can be monitored by a computer.

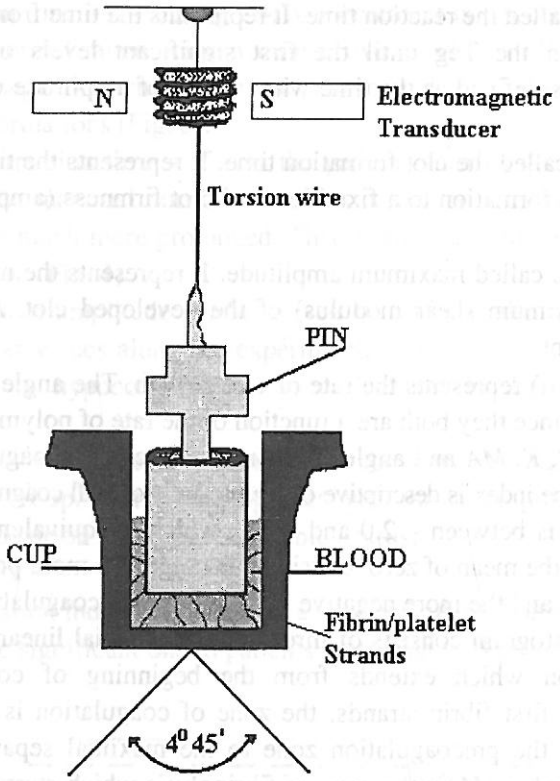

Fig. 1. – The thrombelastograph diagram.

Thrombelastography (Teg) is an accurate test for a global study of coagulation, which it displays from the beginning of clot formation to fibrinolysis. Thromboelastographic information is obtained from an uninterrupted recorded tracing, called the thrombelastogram, which looks like a graphic representation of a burst of sound or diapason, and consists of the following parts (Fig. 2):

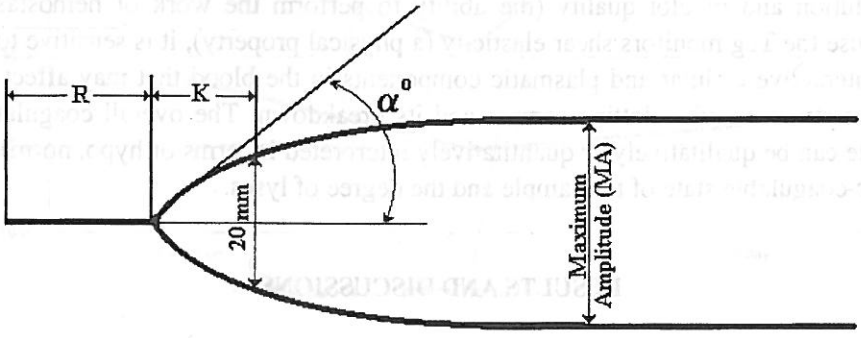

Fig. 2. – Trombelastogram tracing.

- *R* – is called the reaction time. It represents the time from the moment the sample is put on the Teg until the first significant levels of detectable clot formation. This is defined as the time when 2 mm of amplitude of clot strength is detectable.
- *K* – is called the clot formation time. It represents the time from the *R* or beginning of clot formation to a fixed level of clot firmness (amplitude of 20 mm) is reached.
- *MA* – is called maximum amplitude. It represents the maximum strength or stiffness (maximum shear modulus) of the developed clot. *MA* measures the strength of the clot.
- Angle (α) represents the rate of clot growth. The angle is closely related to the *K* – time, since they both are a function of the rate of polymerization.

From the *R*, *K*, *MA* and angle (α) of native tracing, a coagulation index (CI) can be derived. The index is descriptive of the patient's overall coagulation. The normal range for the CI is between – 2.0 and + 2.0, which is equivalent to two standard deviations about the mean of zero. Outside this range, the more positive is the more hypercoagulable, and the more negative is the more hypocoagulable status.

Thrombelastogram consists of three zones: an initial linear segment or zone of precoagulation which extends from the beginning of coagulation to the formation of the first fibrin strands; the zone of coagulation is a sector that lies from the end of the precoagulation zone to the maximal separation of the two symmetrical branches (*MA*); the zone of fibrinolysis which starts at the end of the coagulation zone and is reflected by the slow yet progressive approach of the two curved lines (Fig. 2).

The computerized thrombelastograph coagulation analyzer (Teg) automatically records the kinetic changes in a sample of whole blood, plasma or platelet-rich plasma as the sample clots, retracts and/or lyses. The resultant coagulation profile is therefore a measure of the kinetics of clot formation and dissolution and of clot quality (the ability to perform the work of hemostasis). Because the Teg monitors shear elasticity (a physical property), it is sensitive to all the interactive cellular and plasmatic components in the blood that may affect the rate or structure of a clotting sample and its breakdown. The overall coagulation profile can be qualitatively or quantitatively interpreted in terms of hypo, normal or hyper-coagulable state of the sample and the degree of lyses.

RESULTS AND DISCUSSIONS

The mean values of the thrombelastogram parameters of A and B groups patients are presented in the figures below.

The reaction time – *R* – during LMWH treatment in patients from A group is not kept in the normal range being a little above it, while in B group it shows a significant prolongation which can be interpreted as slower thrombin and thromboplastin formations (Fig. 3).

The clot formation time – *K* – in the patients from A group presents small variations over the maximal normal values, as compared with *K* time of B group patients, which is much more prolonged. This means that a longer time is required for fibrin formation (Fig. 4).

The maximum amplitude – *MA* – even if, initially, the patients from both groups had similar values along the experiment, B group patients showed a more severe tendency to hypocoagulability so a decrease in the strength and clot elasticity (Fig. 5)

The angle – α – detects values under the normal range, especially the patients from B group. Its results, together with the corresponding *MA* values, lead to the supposition of hypocoagulable status, under this type of LMWH substance (Fig. 6).

The coagulation index – CI – shows a hypocoagulable status in both A and B groups but a more significant one in patients belonging to B group (Fig. 7).

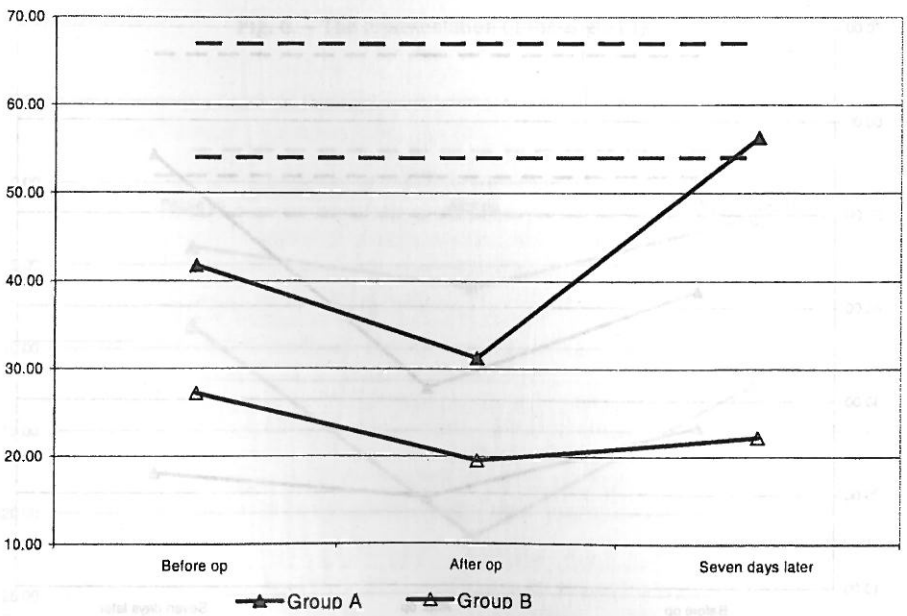

Fig. 3. – The representation of *R* – time.

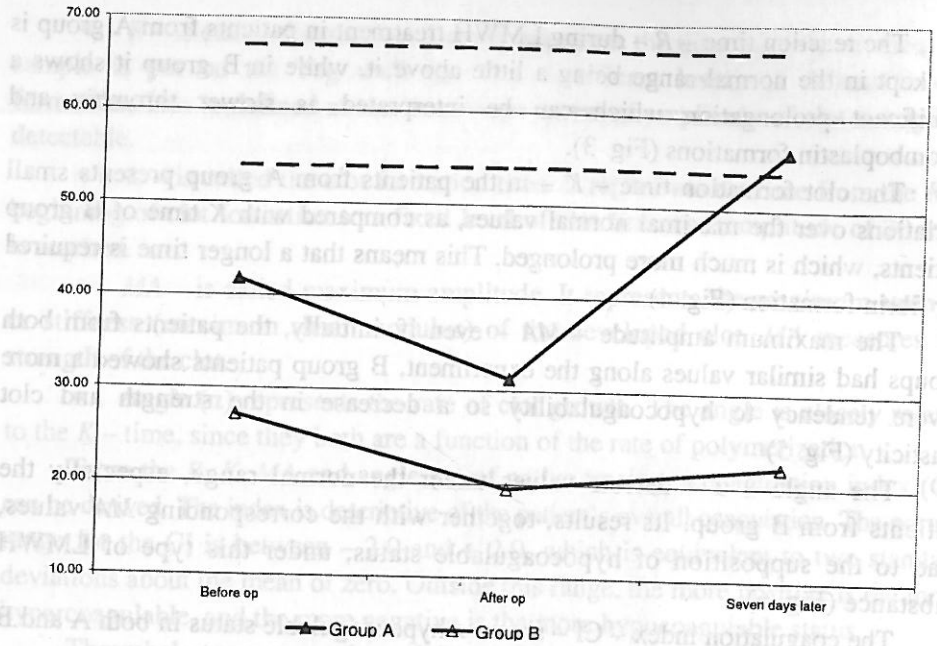

Fig. 4. – The representation of K – time.

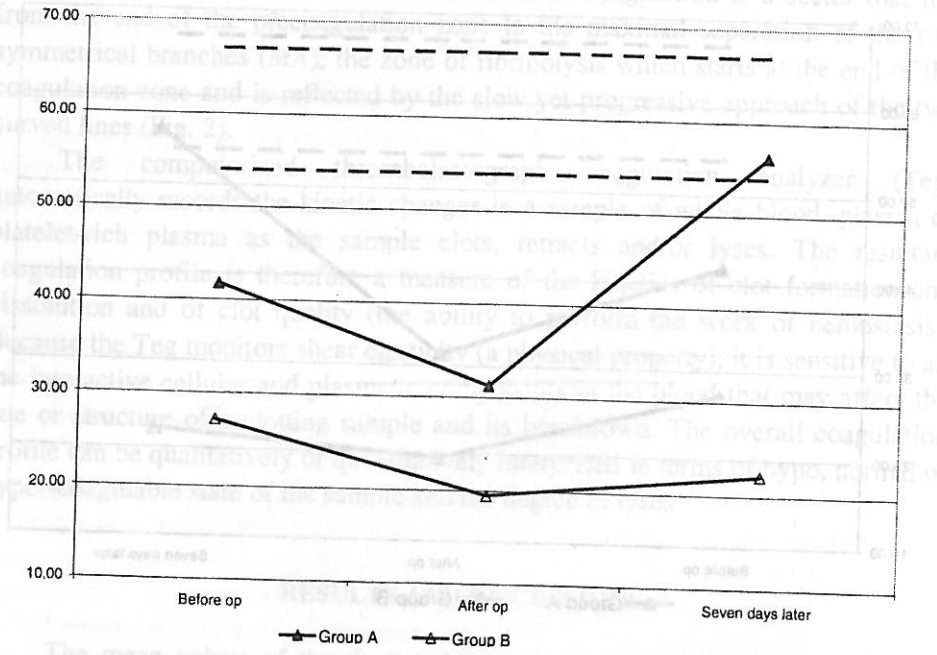

Fig. 5. – The representation of the maximum amplitude (*MA*).

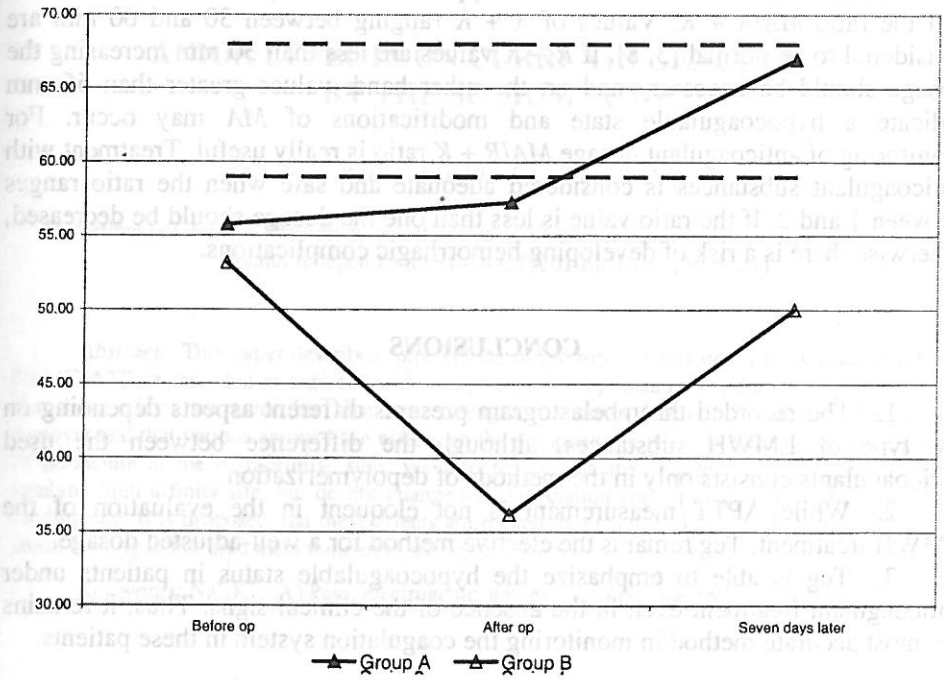

Fig. 6. – The representation of the angle (α).

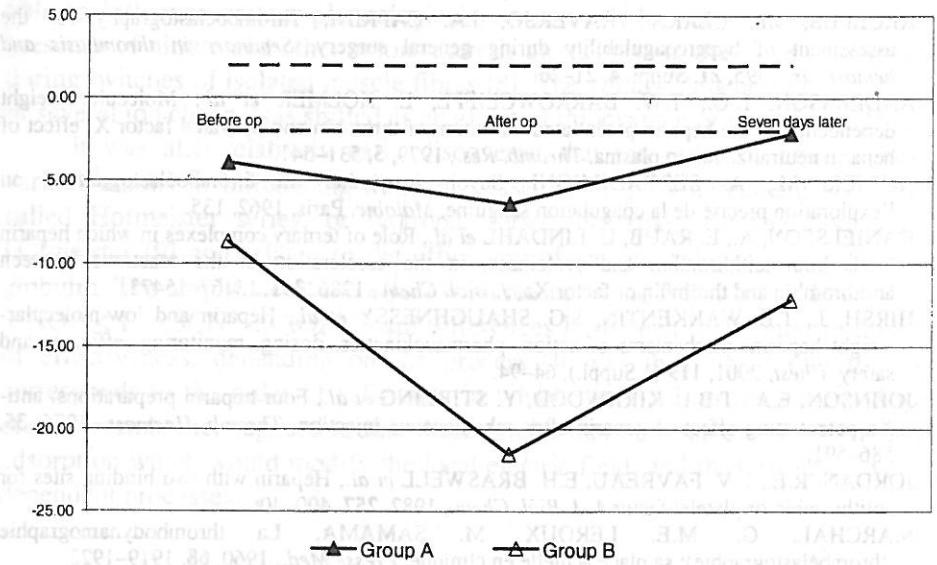

Fig. 7. – The representation of coagulation index (CI).

There are some criteria that can be applied in clinical practices such as $R + K$ and the ratio $MA/R + K$. Values of $R + K$ ranging between 30 and 60 mm are considered to be normal [3, 8]. If $R + K$ values are less than 30 mm increasing the dosage should be necessary and on the other hand, values greater than 55 mm indicate a hypocoagulable state and modifications of *MA* may occur. For monitoring of anticoagulant dosage $MA/R + K$ ratio is really useful. Treatment with anticoagulant substances is considered adequate and safe when the ratio ranges between 1 and 2. If the ratio value is less than one the dosage should be decreased, otherwise there is a risk of developing hemorrhagic complications.

CONCLUSIONS

1. The recorded thrombelastogram presents different aspects depending on the type of LMWH substances, although the difference between the used anticoagulants consists only in the methods of depolymerization.
2. While APTT measurement is not eloquent in the evaluation of the LMWH treatment, Teg remains the elective method for a well-adjusted dosage.
3. Teg is able to emphasize the hypocoagulable status in patients under anticoagulant treatment even in the absence of the clinical signs. Thus, it remains the most accurate method in monitoring the coagulation system in these patients.

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