Protocol - Cardiopulmonary bypass

Heparin induced thrombocytopenia diagnosis in cardiac surgery: is there a role for thromboelastography?†,‡,§

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Summary

The aim of the present protocol is to investigate the potency of thromboelastography (TEG) to screen postcardiac heparin induced thrombocytopenia (HIT) patients suspicious for HIT type II, and to differentiate which of them are subject to suffer thrombotic complications from those who will suffer hemorrhagic complications.

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1. Introduction

It is well established that 25–50% of postcardiac surgery patients develop heparin dependent antibodies, but only 1–3% of these individuals will manifest heparin induced thrombocytopenia (HIT) due to platelet activation [1].

Despite the existence of several functional and antigen assays used for HIT diagnosis, no protocol has studied which of these HIT patients will develop the complications of type II and, moreover, who will suffer the thrombotic and the hemorrhagic complications of type II.

Regarding this query, there is only one previous report of ours which had investigated the role of thromboelastography (TEG) in a single patient with a clinical diagnosis of HIT [2]. We concluded that TEG proved to be a useful method to predict which of the HIT patients may manifest signs of HIT type II and we had also underlined the need for further linkage studies.

Herein, we suggest such a protocol which aims to investigate the potency of TEG to detect which of the HIT patients may develop the complications of type II as well as to classify who will suffer the thrombotic and who the hemorrhagic complications. Such a screening would be of great importance since it would permit us to individualize therapy and drug dosage in each one of them.

2. Study design

2.1. Materials and methods

Our multicenter study includes 800 consecutive HIT patients diagnosed with ELISA or platelet aggregation tests (Fig. 1).

2.1.1. Methodology and design principles of TEG

The TEG analyzer’s approach to the monitoring of patient hemostasis is based on these two facts: a) the end result of the hemostasis process is a single product – the clot; b) the clot’s physical properties (rate, strength, stability) will determine whether the patient will have normal hemostasis, will hemorrhage or will develop thrombosis.

The TEG analyzer measures the clot’s physical property by the use of a special stationary cylindrical cup that holds the blood and is oscillated through an angle of 4°45' (Fig. 2). Each rotation cycle lasts 10 s. A pin is suspended in the blood by a torsion wire and is monitored by motion. The torque of the rotating cup is transmitted to the immersed pin only 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
The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal, which can be monitored by a computer. The resulting hemostasis profile is a measure of the time it takes for the first fibrin stand to be formed, the kinetics of clot formation, the strength of the clot (in shear elasticity of dyn/cm²) and dissolution of the clot (Fig. 3).

To evaluate the graphic information displayed by the TEG analyzer, five main parameters of clot formation and lysis are measured:
- **R**: R time is the period of latency from the time that the blood was placed in the TEG analyzer until the initial fibrin formation. This represents the enzymatic portion of coagulation.
- **K**: K time is a measure of the speed to reach a certain level of clot strength. This represents clot kinetics.
- **α**: α measures the rapidity of fibrin built up and cross-linking (clot strengthening). This represents fibrinogen level.
- **MA**: MA or maximum amplitude, is a direct function of the maximum dynamic properties of the fibrin and platelet bonding via GPIIb/IIIa and represents the ultimate strength of the fibrin clot. This represents platelet function/aggregation.
- **LY30**: LY30 measures the rate of amplitude reduction 30 min after MA. This represents clot lysis.

### 2.1.2. Patient exclusion criteria

Patients with known inherited or acquired disorders of coagulation/under coumarin or any form of unfractionated and fractionated heparin therapy (e.g. AF, mechanical valve, unstable angina)/under GPIIb/IIIa inhibitors or any other drug that promotes coagulation disorders/with abnormal coagulation tests/or those who have not discontinued antiplatelet agents for at least seven days will be excluded from our study.

### 2.1.3. Sample evaluation

**Stage 1**: In this stage we will check the ability of TEG to detect HIT patients with abnormal TEG, suspicious for the development of HIT type II.

Any patient diagnosed for HIT – 30–50% platelet fall with positive ELISA or platelet aggregation test – will undergo an evaluation with thromboelastography (TEG #1) before the administration of any direct thrombin inhibitor. All five basics of clot formation and lysis parameters – R, K, α, MA, LY30 – will be measured and a graphic analysis of these results will be obtained with TEG® Analytical Software.

**Stage 2**: In this stage we will investigate the ability of TEG to confirm the pathologic coagulation profile of the HIT type II patient.

In each of the HIT patients who may develop the thrombotic or hemorrhagic complications of type II, we will perform a second thromboelastography (TEG #2) in order to study its potency to confirm the expressed clinical thrombotic or hemorrhagic coagulation profile.

All collective data from TEG #1 and TEG #2 concerning the R, K, α, MA, LY30 parameters will be subject to quantitative analysis. A qualitative analysis of graphics obtained with TEG #1 and #2 will be studied as well.

### 2.1.4. Determination of sample size

For the determination of the sample size, the sensitivity of TEG #1 was considered as the main measurement-determinant. Adopting an a priori assumption (point estimate assumption) of acceptable sensitivity equal to 90%, a ±15% range in the respective 95% confidence interval (95% CI) was thought of as satisfactory. For the purpose of calculation, it should be kept in mind that the proportion expressing sensitivity follows the binomial distribution.

The minimum number of HIT-type II patients for the achievement of the ±15% range is approximately 40 patients (the lower, more skewed confidence limit principally determined the minimum number). Forty patients would yield a (76.3–97.2%) 95% CI for sensitivity (90%, 36 true-positive/40 HIT-type II patients).
Given that the frequency of HIT-type II is nearly equal to 5%, 800 HIT patients should be included in the study. Assuming a 100% specificity of TEG#1 (800–40 = 760 true-negative/760 non-type 2 patients), the respective one-sided 97.5% CI would be equal to 99.5–100%. Accordingly, under the above assumptions for sensitivity and specificity, the positive predictive value (true positive results/positive results) would be equal to 100% (36/36, 97.5% one-sided CI: 90.3–100%), while the negative prognostic value (true negative results/negative results) would be equal to 99.5% (760/764, 95% CI: 98.7–99.9%).

Eight hundred HIT patients correspond to a reference population of nearly 26,700 procedures, due to the fact that the frequency of HIT is approximately 3%. That points to the need for a multi-center design and a meticulous surveillance system regarding HIT patients.

Given that there are no background data on the putative distribution of the quantitative parameters measured by TEG in the HIT-type II sub-population, and that no pilot study has been conducted, the performance of a power calculation with respect to each parameter has not been possible. Indeed, this would necessitate theoretical means and standard deviations for all quantitative parameters in the HIT-2 sub-population. The variability within the HIT-type II subpopulation is hard to estimate.

The statistical calculations were performed using STATA 8.0 statistical software (Stata Corporation, College Station, TX, USA).

3. Discussion

Heparin induced thrombocytopenia type II presents after an interval of 3–15 days of commencement of heparin therapy and its complications include hemorrhage, thromboembolism and death in 53%, 44% and 33% of patients, respectively [3].

Guidelines clearly state that if the platelet count falls by 50% or more, or falls below the laboratory normal range and/or the patient develops new thrombosis or skin allergy between days 4 and 14 of heparin administration, HIT should be thus considered and a clinical assessment should be performed. If the probability of HIT is high, heparin should be discontinued and an alternative anticoagulant initiated at full dosage, unless there are significant contraindications while laboratory tests are performed [4].

Nevertheless, direct thrombin inhibitors used for the treatment of HIT are not devoid of complications, especially in such high doses, while on the other hand we are not in a position to know the exact coagulation profile thrombotic or hemorrhagic each of HIT patients at the time of diagnosis. HIT type II is an expression of DIC which is a variable condition ranging from hypercoagulation to hypocoagulation and fibrinolysis (Fig. 4f,g). Thus, if for any reason the diagnosis of HIT type II has been delayed and this patient is already in the hypocoagulable state, the risk for clinical thrombosis is minimal. Respectfully, the above suggested administration of full doses of lepirudin or argatropan in accordance with the low number of platelets may not benefit but, on the contrary, result in a hemorrhagic complication [2].

Thromboelastography, like other non-invasive diagnostic methods [5–8], is able to monitor and analyze quantitatively and qualitatively the exact coagulation state of all postcardiac HIT patients. It can differentiate the patient with normal coagulation (Fig. 4a) from those with hypercoagulation (Fig. 4e), DIC (Fig. 4f,g), or fibrinolysis (Fig. 4d). In this way, it may permit us to adjust and individualize the dosage of our therapy, and thus to minimise the risk of hemorrhagic complications instead of administrating blindly full doses of direct thrombin inhibitors.

From a technical point of view, thromboelastography is easy to apply, it requires only 0.36 ml of whole blood samples and it takes only a few minutes. The cost of the equipment is approximately €20,000, while each examination costs <€20.

References


