Comparison of aPTT and CT Parameter of the ROTEM Test to Monitor Heparin Anti-Coagulation Effect in ICU Patients: an Observational Study

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Abstract- Heparin is frequently used in different clinical settings to reduce the coagulating ability of the blood. Because of probable adverse effects owing to heparin therapy and regarding variability of patients' responses to heparin, which make it very unreliable, it seems prudent to monitor meticulously its effects on the human body. There are a lot of laboratory tests to watch its effects on the body for example; aPTT and ROTEM are the most widely used tests that are performed today. We aimed to compare the aPTT test results against changes of CT parameter of the ROTEM test due to heparin administration. This study was conducted on 45 critically ill patients who needed to receive heparin according to their clinical status. All patients received 550 to 1500 unit heparin per hour (on average 17.5 unit heparin per kilogram weight). While the patients were under infusion of heparin, two blood samples (5 ml) were taken from a newly established cubital vein, just five hours after commencement of heparin therapy. One sample was used for aPTT and the other one for ROTEM. The correlation between aPTT and the changes of CT parameter of the ROTEM with heparin dosage and infusion was the primary outcome. The correlation between heparin therapy and the changes of other parameters like MCF, CFT, and a number of platelets were the secondary outcome of the study. The only significant correlation was between changes of CT and aPTT (P=0.000). The other variables were not correlated. Changes of CT parameter of ROTEM test can be used for monitoring of reduced coagulability during heparin infusion instead of aPTT test.

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Introduction

High-molecular-weight heparin is an anticoagulant that is used in many clinical cases to reduce the coagulability of the patients' blood (1). The dosage of heparin is usually adjusted by the clinician, and it depends on the clinical setting that is to be corrected. It should be mentioned that patients respond differently to the same prescribed dosage of the heparin, and its pharmacodynamic behavior is not very predictable. Moreover, because of the different serious side effects of heparin therapy, especially the most common ones (bleeding and thrombocytopenia), accurate monitoring of its anticoagulant effects along with its potential side-effects seems to be very prudent (1).

Several methods have been proposed to monitor the coagulation process during the heparin therapy including aPTT, PT, ACT, anti-Factor Xa, TEG, Sono Clot and ROTEM. Many of the coagulation tests are done in a laboratory far from the site of care, and so they take too much time to be performed. Thus, it is very difficult to decide in an emergency situation how to improve coagulation state, which is very important in patients admitted to the ICU (2). Moreover, through in vitro studies, it has been shown that PT, aPTT and fibrinogen tests are not applicable for blood samples containing high amounts of heparin. Besides, ACT test is not sensitive enough to detect low concentrations of heparin (3-5).

According to some studies, TEG and ROTEM are more sensitive and more reliable than aPTT, PT, ACT and anti-factor Xa to the changes of the anti-clotting effects of heparin (3,5-8). Benefits of the ROTEM test are quicker test results, its reduced sensitivity to mechanical stress, vibration and motion, and also its repeatability by different people (9). Given all the above

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facts, we decided to design this study to compare the effects of therapeutic doses of heparin on the aPTT test results versus the changes of ROTEM test results under the influence of heparin.

Materials and Methods

After getting the approval from Ethics committee of the Tehran University of Medical Sciences, and obtaining the informed consent from all allocated patients, this study was conducted on 45 critically ill patients who needed to receive heparin according to their clinical status. Patients with known coagulopathy, severe thrombocytopenia (platelets less than 50,000), patients who have already received any anticoagulant (oral, intravenous, and subcutaneous), patients over the age of 80 years and less than 20 years were also excluded. While the patients were under infusion of heparin, two blood samples (5 ml) were taken from a newly established cubital vein, just five hours after the commencement of heparin therapy.

It is important to say that no drug or crystalloid solutions have been already administered through that catheter. One of the two obtained samples was used for assessment of aPTT, and the other one was used for ROTEM test. Samples for ROTEM were placed in citrated tube after mixing with device Reagent in accordance with manufacturer's instructions. Graph and Charts of the parameters were recorded as well. The primary outcome defined as a comparison of aPTT test with changes of one parameter of ROTEM test (CT) using statistical methods. The percentages of change in MCF, CFT, CT were calculated through three equations:

CT change = 100 × (CTinTEM-CThepTEM)/ CTinTEM

CFT change = 100 × (CFTinTEM-CFThepTEM)/ CFTinTEM

MCF change = 100 × (MCFinTEM-MCFhepTEM)/ MCFinTEM

The secondary outcome was evaluating the relationship of CFT and MCF changes with aPTT. In addition, the association of platelet number with the changes of CT test results was also evaluated. We have also noted the INR ratio of all patients who were under heparin therapy on the same day of assessments.

Results

In this study, 45 patients who were admitted to the ICU of Sina hospital between December 2013 and March 2014 were allocated. A total of 29 of patients were males. Characteristics of the patients, including age, weight, heparin dosage, aPTT, changes of MCF, CFT, CT, and the mean platelet numbers are presented in Table 1. The correlation between the amount of received heparin and also heparin infusion rate with aPTT, changes in CT, CFT, and MCF are shown in (Tables 2 and 3), respectively.

Table 1. Characteristics of patients

	Mean	Max.	Min.	SD
Age (year)	55	79	26	15
Weight (kg)	56.57	78	42	6.74
Heparin infusion rate (units per hour)	995	1500	500	233
Heparin dose (unit per kg)	17.5	22	10	2.6
Platelet (per ml)	210124	490000	90000	89115
aPTT (second)	52	169	23	39
INR	1.18	1.81	1.00	0.16
CT change	+35%	+89%	+0.5%	16
CFT change	+20%	+95.6%	-55%	3.8
MCF change	-1.2%	+18.6%	-76.9%	1.7

Table 2. Correlation between total dose of injected heparin (bolus dose) and aPTT, CT, CFT and MCF

	aPTT	CT	CFT	MCF
Pearson Correlation	0.236	0.111	-0.122	-0.059
Sig. (2-tailed)	0.118	0.466	0.423	0.699
Sum of Squares and Cross-products	1095.576	364.482	-558.614	-118.526
Covariance	24.899	8.284	-12.696	-2.694
N	45	45	45	45

The correlation between aPTT and the change of percentages in CT is obvious because of the correlation coefficient of 0.52 that was obtained ($P = 0.000$).

The linear regression equation between these two variables is $\Delta CT = 0.35\ aPTT + 16.30$ with a regression coefficient of 0.27 which is shown in Figure1. With respect to the secondary outcome, no association was found in any of the other comparisons.

Table 3. Correlation between heparin infusion rate and aPTT, CT, CFT and MCF

	aPTT	CT	CFT	MCF
Pearson Correlation	0.388**	0.216	0.276	-0.433**
Sig. (2-tailed)	0.008	0.153	0.067	0.003
Sum of Squares and Cross-products	527324.311	207496.206	368690.935	-253949.322
Covariance	11984.643	4715.823	8379.339	-5771.575
N	45	45	45	45

Table 4. Correlation between aPTT and CT changes

		aPTT	CT
Pearson Correlation	**aPTT**	1.000	0.517
	CT	0.517	1.000
Sig. (1-tailed)	**aPTT**	--	0.000
	CT	0.000	--
N	**aPTT**	45	45
	CT	45	45

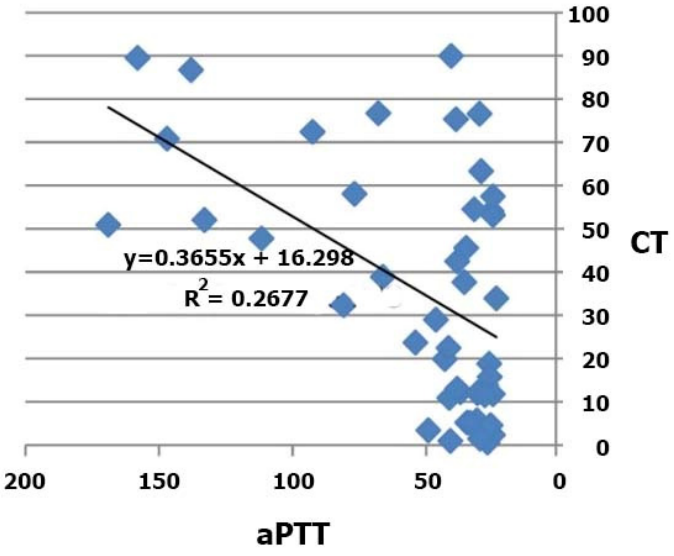

Figure 1. Linear regression graph between aPTT and CT changes in the studied patients

Discussion

In this study, patients who received heparin intravenously were studied in a pilot test. This study was designed to examine the association between the dose of heparin and changes of the ROTEM components because it is faster and more accurate way to adjust the dose of heparin and consequently may prevent complications. Several methods have been proposed to monitor the coagulation process: aPTT,

PT, ACT, anti-factor Xa levels and checking viscoelastic changes associated with fibrinase polymerization as in thrombelastography devices including TEG, Sono Clot and the new generation of them, ROTEM. ICU patients because of different reasons experienced blood coagulation disorders, including fibrinolysis, activation of inflammatory pathways, administration of clotting factors, hypothermia, and surgery or trauma. Furthermore, in some cases, the combined administration of anticoagulants such as warfarin or heparin might have followed by severe coagulation impairments (2). In this study, it has been found that a direct association is between aPTT and total dose of heparin and heparin infusion, there was no significant relationship. It should be noted that the correlation between the desired parameters at heparin infusion versus heparin dose was somewhat higher. It appears that the cause of these differences is the impact of the patient's weight on the desired parameters. This factor is not included in the heparin dose, especially during the initial administration that was the same for everyone. There was a direct association between changes in CT and heparin dose or heparin infusion rate. It should be noted that this correlation is even weaker than the correlation between them and aPTT parameters mentioned above. Another parameter that was examined in this study was the change of percentages of CFT. According to the effect of number and functions of platelets during clot formation (CFT); we evaluated the effects of heparin administration on CFT (10).

In addition, the relationship between CFT changes and the number of platelets in patients was also noted. Statistical analysis showed no significant relation between them. Change of the percentages of MCF was also observed, without finding any significant association between this and heparin dose or infusion rate. The only relatively significant direct relationship that can be seen between the studied parameters is the correlation between aPTT and CT change percentages. Of course, this can be provided to achieve better results in forthcoming studies that are to have a more comprehensive design. It’s recommended to perform studies with larger sample size and adding a time factor for each person during the course of treatment (to eliminate individual differences), and also it is preferable to measure serum concentrations of heparin or factor Xa for further precision.

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