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ORIGINAL STUDY

Monitoring of Heparin Treatment in Patients with Acute Myocardial Infarction

Akut Miyokard İnfarktüslü Hastalarda Heparin Tedavisinin İzlenmesi

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Objectives: We evaluated the effectiveness of monitoring coagulation parameters and plasma heparin levels in patients receiving heparin treatment for acute myocardial infarction (AMI).

Patients and Methods: The study included 30 AMI patients (19 males, 11 females; range 39 to 76 years) who were admitted to the intensive care unit. All patients received standard heparin with a bolus dosage (5,000 IU) followed by continuous intravenous infusion (1,000 IU/h) for 72 hours. Thrombolytic therapy was not applied because of contraindications. Coagulation parameters (aPTT, TT, and AT III) were monitored on coagulometer ACL 2000 at baseline and 24 hours after the initiation of heparin therapy together with plasma heparin levels. Statistical analyses were made using one-sample Kolmogorov-Smirnov test, and paired-samples t-test.

Results: Fifteen patients had below-therapeutic heparin levels during treatment, which were associated with significantly increased aPTT and decreased AT III values ($p<0.001$). The remaining patients with therapeutic heparin levels exhibited the same trend with regard to aPTT and AT III. However, increase in TT values was significant only in the latter group ($p<0.001$).

Conclusion: The two methods, plasma heparin monitoring and standard coagulograms seem to be equally effective for control over heparin therapy, and their combined use enhances the efficacy and safety of heparin treatment.

Key Words: Blood coagulation tests; heparin/blood/administration & dosage; myocardial infarction; partial thromboplastin time; reference values.

Amaç: Akut miyokard infarktüsü (AMİ) nedeniyle heparin tedavisi gören hastalarda koagülasyon parametreleri ve plazma heparin düzeylerinin izlenmesinin etkinliği değerlendirildi.

Hastalar ve Yöntemler: Çalışmaya AMİ nedeniyle yoğun bakım ünitesinde yatan 30 hasta (19 erkek, 11 kadın; dağılım 39-76) alındı. Tüm hastalara bolus dozdan (5000 IU) sonra 72 saat süreyle sürekli intravenöz infüzyonla (1000 IU/saat) standart heparin verildi. Kontrendikasyonlar nedeniyle trombolitik tedavi uygulanmadı. Koagülasyon parametreleri (aPTT, TT ve AT III) tedavi başlangıcında ve 24 saat sonra ACL 2000 koagülometrede ölçüldü, plazma heparin düzeyleri belirlendi. İstatistiksel değerlendirme tek örnekli Kolmogorov-Smirnov testi ve çift örnekli t-testi ile yapıldı.

Bulgular: Heparinin terapötik düzeylerin altında bulunduğu 15 hastada anlamlı derecede artmış aPTT ve anlamlı derecede azalmış AT III değerleri ölçüldü ($p<0.001$). Heparinin terapötik düzeylerde seyrettiği 15 hastada da aPTT ve AT III değerleri aynı özellikleri göstermekteydi. Bununla birlikte, TT değerleri yalnızca ikinci grup hastada anlamlı artış gösterdi ($p<0.001$).

Sonuç: Plazma heparin düzeylerinin izlenmesinin ve koagülasyon parametrelerinin belirlenmesinin heparin tedavisinin kontrolünde eşit derecede etkili olduğu görüldü. Bu iki yöntemin birlikte kullanımı heparin tedavisinin etkinlik ve güvenliğini artırmaktadır.

Anahtar Sözcükler: Kan koagülasyon testleri; heparin/kan/uygulama ve doz; miyokard infarktüsü; kısmi tromboplastin zamanı; referans değeri.

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The current treatment of acute myocardial infarction (AMI) has the aim of eliminating the obstruction in the infarction-related coronary artery. In the therapeutic scheme for patients with AMI, who do not receive thrombolytic drugs, heparin administration is considered to prevent coronary re-thrombosis in cases of spontaneous thrombolysis and after coronary angioplasty, as well as in prophylaxis of thromboembolic events in the acute phase.

Most commonly, the standard heparin is applied as a 5,000 IU bolus followed by continuous intravenous infusion of 1,000 IU/hour for a period of three to five days. However, monitoring of plasma heparin levels is essential both to prevent the occurrence of side effects (hemorrhage, thrombocytopenia, etc.) and to decide whether more heparin is needed due to depletion of antithrombin-III (AT-III)-heparin. In the usual clinical practice, the efficiency of heparin treatment is monitored via standard coagulograms which include activated partial thromboplastin time (aPTT), and thrombin time (TT), the values of which are expected to increase 2-2.5 times than those of their baselines.[1] Because susceptibility to heparin varies among individual patients, a new method has been developed for its direct measurement in the plasma in recent years, whereby control over heparin treatment has improved significantly and heparin administration has become safer.[2]

Literature data show that prophylactic dosages of heparin (200-300 IU/kg/24 hours) are associated with plasma levels varying between 0.15 IU/ml to 0.30 IU/ml, while a more active treatment with dosages 400-800 IU/kg/24 hours corresponds to plasma levels of 0.3-0.6 IU/ml.[3,4]

The aim of this study was to evaluate and compare the reliability of the two methods in the monitoring and control of heparin treatment.

MATERIALS AND METHODS

The study group consisted of 30 patients with AMI admitted to the intensive care unit of the Cardiology Department of Medical University in Plovdiv. There were 19 males and 11 females, with an age range of 39 to 76 years. Treatment with standard heparin was started with a 5,000 IU bolus followed by continuous intravenous infusion of 1,000 IU/hour for a period of 72 hours. Concomitant medications consisted of aspirin (300 mg/24 hours; n=30), beta-blockers (n=30), and nitroglycerine IV (n=13) for 24-36 hours. Thrombolytic therapy was not applied because of contraindications. The coagulation parameters including aPTT, TT, and AT III were measured at baseline and 24 hours after the initiation of heparin administration together with the plasma heparin level.

Biological material: Blood samples were obtained under standard conditions atraumatically and taken into Sarstedt monovettes (Sarstedt, Nümbrecht, Germany) containing 0.109 ml sodium citrate. The samples were centrifuged at 2,500 rpm for 15 minutes at 4 °C, after which the plasma was separated and frozen at -24 °C until the time of analyses.

Coagulation tests: Screening of aPTT and TT were made using conventional methods with one- and two-step coagulation techniques with Baxter reactives on coagulometer ACL 2000 (Instrumentation Laboratory, Milan Italy). The activity of AT III was determined through chromogenic tests (amidolythic assay) on the same coagulometer. Standard heparin levels were measured by determining its inhibiting influence on factor IIa (thrombin) through adding AT III. The residual activity of thrombin was determined via its influence on a specific synthetic substrate.

Statistical analyses: Data were processed with the use of descriptive statistics, one-sample Kolmogorov-Smirnov test, and paired samples t-test on SPSS statistical package 9.0 for MS Windows 98.

RESULTS

The patients were divided into two groups depending on the plasma heparin levels, namely below- and within-therapeutic ranges. No significant differences were found between these two groups with regard to age and sex. All descriptive coagulation parameters found at

Table 1. Coagulation parameters at baseline and during-treatment in the study group

					Paired-samples t-test	
Parameters		Number	Mean±SD	Range	*t*	*p*
Heparin below-therapeutic range		15	0.00±0.10	0.047 - 0.008		
Heparin within-therapeutic range		15	0.16±0.70	0.343 - 0.14		
aPTT (seconds)	Baseline (sub)	15	25.3±0.86	19 - 30	-4.906	<0.001
	During treatment (sub)	15	30.78±1.25	23.3 - 41.7		
	Baseline normal	15	26.14±0.77	21.9 - 32	-3.346	<0.01
	During treatment normal	15	53.61±8.66	30 - 130		
TT (seconds)	Baseline (sub)	15	18.81±0.61	15.1-22.8	-1.886	>0.05
	During treatment (sub)	15	42.25±13.06	16 - 178		
	Baseline normal	15	20.83±0.88	15.9 - 28	-5.83	<0.001
	During treatment normal	15	119.17±17.1	27 - 189		
AT III (IU)	Baseline (sub)	15	93.07±3.96	76 - 120	6.737	<0.001
	During treatment (sub)	15	83.27±4.52	62 - 115		
	Baseline normal	15	89.67±3.2	72 - 110	8.413	<0.001
	During treatment normal	15	78.27±2.8	58 - 95		

Sub: Plasma heparin level below the therapeutic range; Normal: Plasma heparin level within the therapeutic range.

baseline and during therapy are summarized in Table 1. Patients with low and therapeutic plasma heparin levels during treatment did not show any statistical differences with regard to baseline coagulation parameters.

Upon finding a normal distribution of cases by the one-sample Kolmogorov-Smirnov test, we used paired-samples t-test to define the significance levels of the coagulation changes between each set of patients (Table 1).

In the subgroup of patients with below-therapeutic heparin levels, aPTT values during treatment showed a significant increase ($p<0.001$) and AT III values showed a significant decrease ($p<0.001$), whereas TT values did not differ significantly possibly due to greater standard deviation ($p>0.05$). On the other hand, patients with therapeutic heparin levels during treatment exhibited significantly increased aPTT ($p<0.01$) and TT ($p<0.001$) values and decreased AT III values ($p<0.001$) (Table 1).

DISCUSSION

Our findings suggest that heparin administration of 1,000 IU/hour ensures prolongation of aPTT within a desirable range, together with a significant decrease in AT III levels; however, it is not associated with therapeutic plasma levels in all cases. In half of the cases, therapeutic plasma levels of heparin correlated with significant increases in aPTT and TT and with a significant decrease in AT III. On the other hand, we observed a significant prolongation of aPTT and a significant decrease in AT III in patients with below therapeutic plasma levels, while TT values remained similar.[5]

Insufficient plasma heparin levels during treatment are probably due to differences in individual susceptibilities and the presence of an increased resistance to heparin, a phenomenon observed in the hypercoagulability state.

Concomitant medications did not differ in the patient group, except for intravenous nitroglycerine, which was administered to two patients and to 11 patients who showed within- and below-therapeutic plasma heparin levels, respectively. Intravenous nitroglycerine may play a partial influence on heparin levels through a blockage of AT III activity.

In the absence of intravenous nitroglycerine administration, the two methods, plasma heparin monitoring and standard coagulograms seem to be equally effective for control over heparin therapy, and their combined use seems to enhance the efficacy and safety of heparin treatment.

Nowadays, low molecular weight heparins (LMWH) offer increased treatment opportunities together with a parallel reduction of associated risks owing to their predominant antithrombotic activity.

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