Comparison of Two Nomograms of Unfractionated Heparin in Patients with Acute Coronary Syndrome

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Abstract- Heparin has an unpredictable pharmacokinetics and the responses of individuals may vary distinctly. Therefore, different dosing nomograms have been proposed. The aim of this study was to compare two prevalent nomograms to adjust heparin doses in hospitalized patients with acute coronary syndrome. One hundred and forty patients received heparin infusions based on one of two nomograms. Group 1 received a bolus of 80 U/Kg/h and an initial infusion rate of 17 U/Kg/h. In the second group, a bolus of 60 U/Kg (maximum of 4000 U) and an initial infusion rate of 12 U/Kg/h (maximum of 900U/h) was given. Activated partial thromboplastin time (aPTT) was measured at the beginning and every 6 h for 48 hours. The rate of heparin was changed according to each nomogram in order to maintain aPTT in the therapeutic level of 46-70 s. The time to pass threshold was on average 7.63±3.95 h for nomogram 1 and 11.05±4.41 h for the second nomogram (P<0.001). At 48 hours, the proportion of patients in the therapeutic range in group 1 was higher (72.86% vs 45.71%). The time patients stayed at the desired levels was significantly higher in nomogram 1 and they also required fewer heparin rate adjustments (3.41±1.55 vs 4.53±1.63). This study indicated that using nomogram 1 facilitated a more rapid achievement of the therapeutic threshold, higher proportion of patients in the therapeutic range for a longer time, and fewer changes of in the heparin rate.

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Keywords: Acute coronary syndrome; Nomogram; Unfractionated heparin

Introduction

Since it was found that anticoagulation can reduce mortality in patients with pulmonary embolism, heparin has been used significantly in the treatment of thromboembolic diseases (1). Despite the striking developments in antithrombotic therapy, unfractionated heparin (UFH) retains a pivotal role in the prophylactic treatment of many thrombotic disorders (2). In fact, appropriate administration of UFH yields results that are comparable to treatment with heparin derivatives in terms of efficacy and safety (3). However, UFH has a variable pharmacokinetics due in part to its tendency to bind to endothelial cells, platelet factor 4, and platelets, leading to unpredictable pharmacokinetic and pharmacodynamic properties (4,5).

Because of variability in the responses of patients, frequent monitoring is suggested during the course of therapy. UFH therapy is most commonly monitored by the activated partial thromboplastin time (aPTT), an assay which reflects the ability of the heparin-antithrombin complex to inhibit thrombin, factor X_a, and other coagulation enzymes in the intrinsic coagulation pathway (2). The advantages of this test include its relative inexpensiveness, wide availability, simple performance, and rapid results (2).

Clinical experiences have revealed that patients with subtherapeutic aPTT levels for more than 24 hours are more likely to develop recurrent thromboembolism (6). Also, it has been reported that patients with therapeutic aPTT at 12 hours had the lowest rate of mortality at 30 days (7). In GUSTO IIb experience, patients with higher aPTTs at 6 and 12 hours had higher rates of events such as hemorrhage, re-infarction, and death (7). Nonetheless, adequate anticoagulation is frequently not achieved, either as a result of applying empirical dosing that does not take heparin kinetics into account or because of clinicians' wariness of possible hemorrhagic side effects associated with elevated aPTT.

Since weight is the most important factor in

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determining the anticoagulant effect of heparin (8), several different weight-based dosing nomograms have been developed. It has been demonstrated that these nomograms are safer than empirical dosing, and implementing them causes patients to reach therapeutic levels faster and with fewer rate adjustments (9,10). Therefore, the standard of practice for administering heparin is currently to employ a weight-based nomogram which assures that patients will promptly attain optimal levels of anticoagulation, thus decreasing the probability of recurrent venous thromboembolism without extra bleeding-risk (3).

Several different nomograms have been proposed to achieve the therapeutic phase in a shorter period of time (1,9). The aim of this study was to compare the efficacy of two nomograms used widely in western hospitals to adjust heparin doses in patients with acute coronary syndrome (ACS) receiving a heparin infusion in the Cardiac Care Unit (CCU).

Materials and Methods

After approval of the proposal by the ethical committee of Shahid Sadoughi University of Medical Sciences, all patients hospitalized in the CCU of a referral teaching hospital requiring continuous intravenous infusion of UFH for ACS were enrolled in this study. Written informed consent was obtained from each patient prior to initiation of heparin infusion and personal information regarding patients remained confidential. The exclusion criteria were age under 18, receiving thrombolytic therapy in the past 7 days, active bleeding, a history of heparin induced thrombocytopenia (HIT), and platelet count less than 100 x 10^9/l. Patients who received heparin for at least 48 hours and in whom the dosing nomogram was followed closely were qualified for inclusion in the analysis.

Prior to initiation of the study, the rationale and implementation of the study was explained to the nursing staff. Basic patient data were obtained before infusion of heparin. After informed consent was obtained, patients were randomized into two groups to receive one of the two dosing nomograms. The first nomogram was based on Raschke *et al.'s* (9) nomogram, but considering our experience, we started at an initial infusion rate of 17 U/kg (Table 1). The nomogram proposed by Hochman and his colleagues was used for the second group (Table 2) (10).

Table 1. Weight-based nomogram used for group 1 (9)

aPTT* (sec)	Bolus administration	Change in rate of infusion
<35	80 U/kg	↑4 U/kg/hr
35-45	40 U/kg	↑2 U/kg/hr
46-70	None	No change
71-90	None	↓ 2 U/kg/hr
>90	Hold infusion for 1 hour	↓ 3 U/kg/hr

Initial bolus: 80 U/kg

Initial heparin infusion: 17 U/kg/hr

*aPTT = activated partial thromboplastin time.

Table 2. Weight- based nomogram implemented for group 2 (10).

aPTT* (sec)	Bolus administration	Change in rate of infusion
<35	2000 U	↑2 U/kg/hr
35-45	None	↑2 U/kg/hr
46-70	None	No change
71-80	None	↓1 U/kg/hr
81-90	Hold infusion for 1/2 hour	↓2 U/kg/hr
>90	Hold infusion for 1 hour	↓3 U/kg/hr

Initial bolus: 60 U/kg for patients <70 kg and 4000 U for individuals > 70 kg.

Initial heparin infusion: 12 U/kg/hr for patients <70 kg and 900 U/kg for individuals > 70 kg.

*aPTT = activated partial thromboplastin time.

Since the study was not blind, the dosing nomogram used for each patient was given to the nurses. Dosage adjustment was performed based on a preprinted order form signed by the physician and implemented by attendant nurses. All doses were calculated based on actual body weight. Bolus and infusion doses were rounded off to the nearest 50-100 U. Data were collected by the nursing staff, and each patient was followed for the duration of heparin administration.

APTT values were checked at baseline and every 6 hours through 48 hours and afterward if needed. A popular laboratory method was applied to measure aPTT. The primary goal was to achieve and maintain a target aPTT value of 46 to 70 seconds. Upon obtaining a blood sample, it was transferred immediately to the laboratory. Results were given to nurses and physicians via computer as soon as possible and heparin infusion rates were adjusted accordingly.

These nomograms were compared primarily in terms of time to reach the target aPTT, number of adjustments to achieve therapeutic levels within the first 24 and 48 hours, proportion of patients in subtherapeutic, therapeutic, and supratherapeutic aPTTs, percentage of time in the therapeutic phase, and average rate of heparin in the last 12 hours prior to discontinuation of heparin infusion.

Data were analyzed using paired t-test, ANOVA, and Chi-square with SPSS 10. A *P*-value of less than or equal to 0.05 was considered statistically significant. Data are presented as mean ± standard deviation.

Results

From September 2009 to November 2010, 149 patients requiring continuous intravenous infusion of UFH for ACS were enrolled in this study. Due to failure to comply with the dosing regimen, 4 patients in group 1 and 5 patients in group 2 were excluded.

The two groups were similar in regard to mean age, weight, aPTT, and sex distribution (Table 3). The initial bolus dose and rate of infusion for group 1 were 5460.29±833.24 U and 16.88±3.05 U/kg/hr, respectively. These were significantly higher than initial dose and infusion rate of the second group, which were 3923.71±396.9 U and 11.72±1.52 U/kg/hr, (P<0.001, P<0.001, in order). The rate of infusion and aPTT of patients over 48 hours are illustrated in figures 1 and 2.

Table 3. Patient characteristics.

Characteristics	Group 1	Group 2	*P*-value
Number of patients (n)	70	70	
Sex (n (%))			
Male	45 (64.29)	37 (52.86)	0.17
Female	25 (35.71)	33 (47.14)	
Age (y) (mean ± SD)	58.82±12.81	57.59±1.20	0.54
Weight (kg) (mean ± SD)	69.21±11.94	72.33±13.04	0.14
Baseline aPTT(s) (mean ± SD)	35.50±7.97	37.77±9.40	0.13

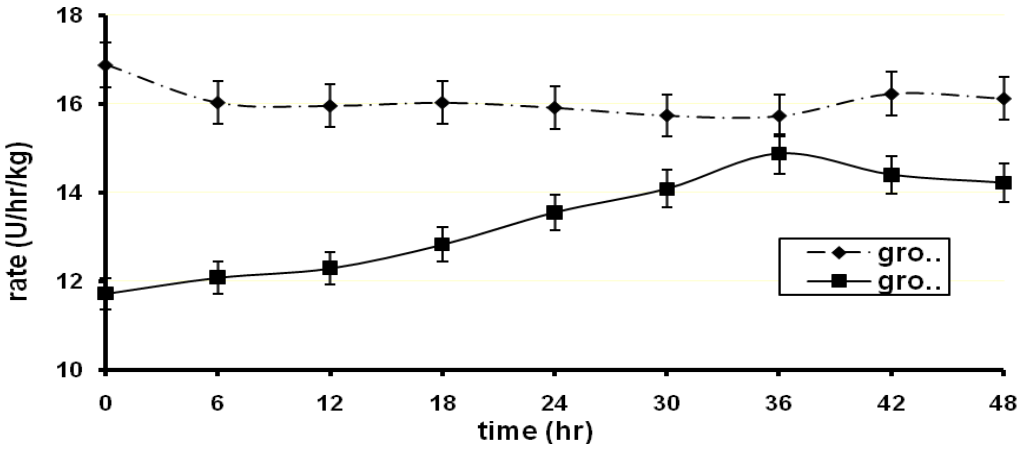

Figure 1. Rate of infusion in 48 hours.

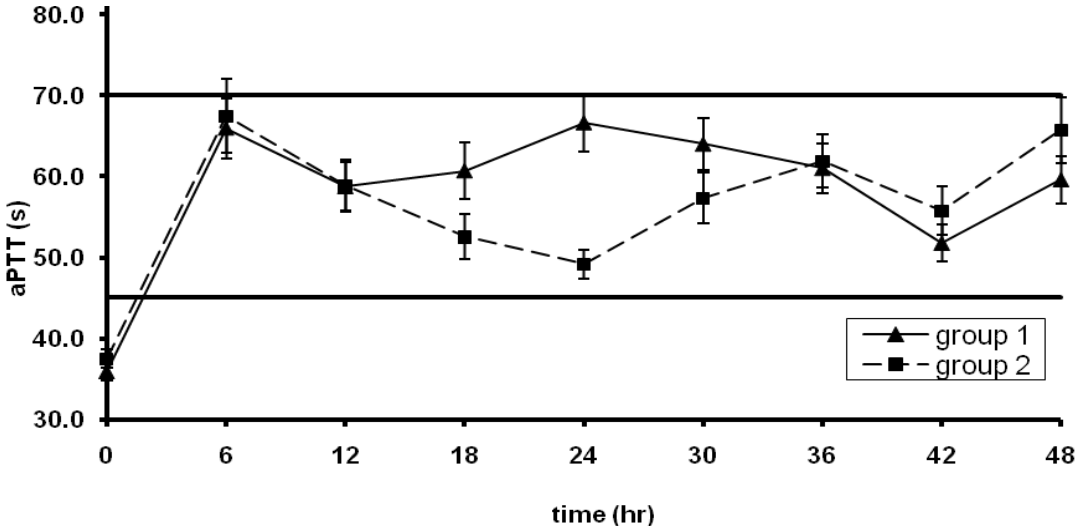

Figure 2. aPTT of patients of two groups in 48 hours*
*therapeutic aPTT= 46-70s

Patients in group 1 passed the therapeutic threshold level (aPTT≥46 s) 7.63±3.95 hours after commencement of heparin infusion, while it took 11.05±4.41 hours for patients in group 2 to pass this level (P<0.001). Six hours after initiating heparin infusion, the proportion of subtherapeutic patients dropped rapidly from 88.57% to 28.57% in group 1 and from 87.14% to 41.43% in group 2. In fact, the aPTT of 38.57% of individuals in the first group and 24.29% of the second group fell to the therapeutic range in 6 hours (P<0.001). Since achieving therapeutic levels in the first 24 hours is critical, the two groups were also compared in this regard. At 24 hours, 15.71%, 60.00%, and 24.29% of patients in group 1 were in the subtherapeutic, therapeutic, and supratherapeutic range, respectively, whereas the percentages of patients in group 2 in these ranges were 42.86%, 48.57%, and 8.57%, in order (P<0.01). During this period, the average rate of heparin for group 1 was 16.15±3.08 U/kg/hr and for group 2 was 13.01±2.09 U/kg/h (P<0.001).

In nomogram 1, at 48 hours, 15.71% were subtherapeutic, 72.86% therapeutic, and 11.43% supratherapeutic. On the other hand, in nomogram 2 at this time, 25.71% were subtherapeutic, 45.71% therapeutic, and 28.57% supratherapeutic, markedly different results from those found in the first group (P<0.01). Figure 3 illustrates the percentages of patients in the two groups in the therapeutic range (aPTT= 46-70 s) at 48 hours. Table 4 shows the period of time that each group had aPTT above 45 s or was in the therapeutic phase at 24 and 48 hours.

The number of changes in the rate of infusion in 24 hours for group 1 was 127 with an average of 1.81±1.01 per person, and for group 2 was 171 and 2.44±1.15 respectively (P=0.002). Likewise, the mean number of changes in the rate at 48 hours for group 1 was 3.41±1.55, versus 4.53±1.63 for group 2 (P<0.001). The mean rate of heparin in the last 12 hours before terminating heparin infusion (regardless of duration of infusion) for group 1 was 15.98±3.72 U/kg/h and for group 2 was 14.70±3.92 U/kg/h (P<0.001). Only one patient in group 2 suffered from major bleeding that had been recovered and none of the individuals in group 1 had adverse bleeding events or thrombotic complications.

Table 4. Comparison of aPTT at different intervals

Time	Group 1 (mean ± SD)	Group 2 (mean ± SD)	*P*-value*
aPTT >46s within 24 hours	18.00 ± 1.64	14.17 ± 1.01	<0.001
aPTT in therapeutic range within 24 hours	12.09 ± 2.19	8.83 ± 2.38	0.003
aPTT>45 s within 48 hours	36.01 ± 3.56	29.49 ± 3.38	<0.001
aPTT in therapeutic range within 48 hours	26.06 ± 4.84	19.11 ± 3.58	0.003

*P value <0.05 is considered significant.

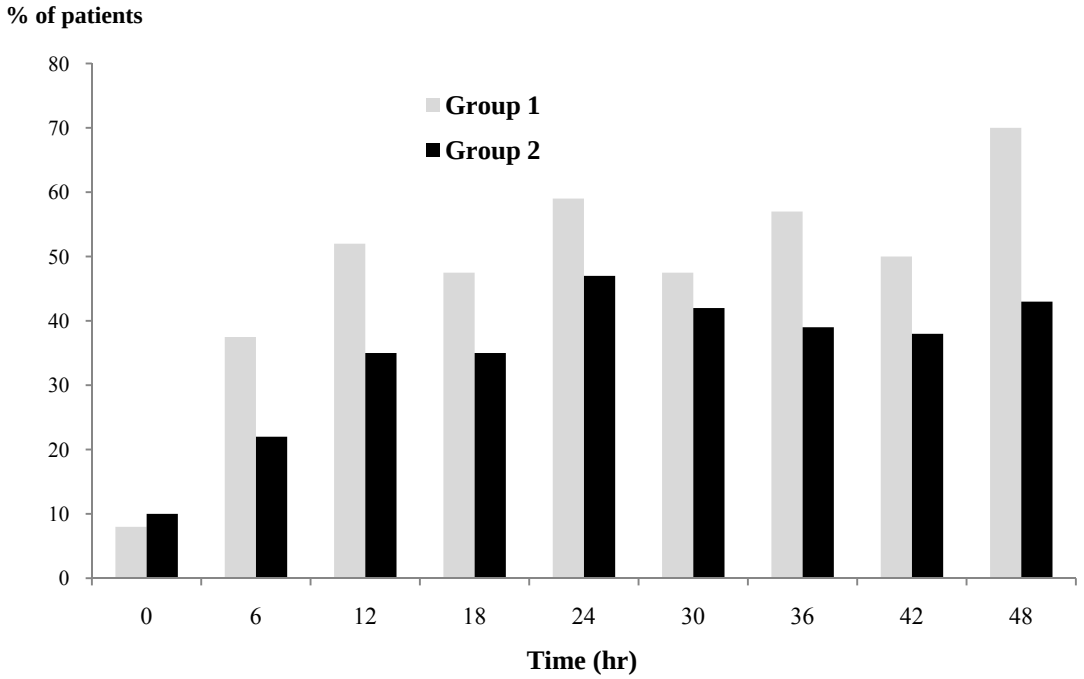

Figure 3. Percentage of patients in the therapeutic level of aPTT (46-70 s).

Discussion

Applying weight-based nomograms considerably improves the ability to treat patients with ACS by UFH. In this study; we compared two prevalent weight-based nomograms to adjust the rate of heparin infusion in patients with ACS hospitalized in the CCU. For optimal results and hindrance of recurrence, rapid attainment of therapeutic aPTT is of the utmost importance (9,12). The main finding of our study was that use of the first nomogram was associated with a markedly shorter time to exceed the therapeutic aPTT threshold. Time to pass the therapeutic threshold was on average 7.63±3.95 hours for group 1, similar to results reported by Folstad *et al.* (13) and shorter than several other studies (9,14,15). Therefore, the initial dose in group 1 was closer to patient heparin requirements, as manifested by a shorter time to reach aPTT levels within the therapeutic range.

Six hours after initiating heparin infusion, 38.57% and 24.29% of patients in group 1 and 2 were in the therapeutic range, respectively. These numbers are in the range of results of other studies (11,16-18). However, they are considerably lower than the 52% reported by Smith and Wheeler (19), probably due to different settings or heparin monitoring.

A significantly higher proportion of patients treated on the basis of nomogram 1 reached therapeutic anticoagulant levels within 24 hours of treatment (60.00%), as compared to patients treated according to nomogram 2 (48.57%). Likewise, in a study close to the first nomogram, Raschke and colleagues reported that 57% of their patients were in the therapeutic phase at 24 hours (9). However, unlike the results of Hochman *et al.,* a much lower percentage of patients in group 2 had reached therapeutic aPTT levels (10). Our results in group 1 were considerably higher than the report of Davydov and colleagues, and may question their claim that a low percentage of patients fall in the therapeutic range with weight-based nomograms (20). Also, in group 1, the proportion of patients in the therapeutic range increased after 24 hours, but this number did not change considerably for group 2. This could be attributed to a higher rate of heparin infusion in group 1, especially the initial rate which, as stated earlier, is of great importance in maintaining therapeutic aPTT over the first 24 hours (14). It should be pointed out that unlike some other studies (9), successful anticoagulation did not wane over time in either group and, in fact, the percentage of subtherapeutic patients in group 2 markedly dropped.

Furthermore, patients in group 1 stayed a longer period of time in the therapeutic range in comparison to group 2. However, the results for both groups are lower

than in some similar studies (10,15). This discrepancy could be due to differences in the main complaint of enrolled patients, and probably varied racial backgrounds, even though Lee *et al.* pointed out that Western weight-based heparin regimens are equally relevant to Asian patients; therefore, racial difference may not be very important (21).

A parameter that indicates the simplicity and effectiveness of a dosing regimen is the number of dosing adjustments required to attain therapeutic levels. There were markedly fewer changes in the rate of infusion over 24 and 48 hour periods in group 1 as compared to other group. The result for group 2 was different from Hochman *et al.'s* study (10), which reported 1.05±1.0 changes over a 24 hour period in a group with a similar dosing nomogram as group 2.

The average rate of infusion in the first 24 hours for group 1 was higher and it seems closer to the needs of patients, as a higher proportion of them were in the therapeutic range. The mean of heparin rate in the last 12 hours before termination of infusion in group 1 was higher and was closer to the initial infusion rate. This is another indication that the first nomogram is nearer to individual needs. However, these rates for both groups were higher than the median rate of 13.8 U/Kg/h at the time of discontinuing heparin in the GUSTO-IIb study (7). Also, the low bleeding events among our patients reveals a tight control of anticoagulation. Nevertheless, episodes of minor bleeding may not have been documented by physicians or nursing staff.

It has been demonstrated that about 30% of the variations in heparin requirements are explained by body weight (9,22), while other factors, such as age, sex and diabetes mellitus, influence patient requirements. However, these factors are not taken into account in these nomograms. Besides, differences in platelet activation and the potential confounding effect of aspirin may result in the variable responses of patients (10). These possible factors explain some of the problems encountered in improving the rates of UFH and also in the obtaining of different results from some previous studies.

In summary, the current study indicates the substantial superiority of the first nomogram (the modified Raschke nomogram) over the second nomogram in the anticoagulation of patients with ACS. The use of the first nomogram facilitated a more rapid achievement of therapeutic APTT, while reducing the number of changes in heparin infusion rates. Importantly, higher proportions of patients were in the therapeutic range in the first 24 and 48 hours. For institutions that use UFH for patients with ACS, the first nomogram could be helpful in reaching individual heparin needs.

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