The Time Has Come for New, More Precise Guidelines in the Treatment of High-Risk Acute Coronary Syndromes With Heparin

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Background  The aim of this analysis was to define the risk factors associated with the problematic dose titration of unfractionated heparin (UFH) in high-risk non-ST-segment elevation acute coronary syndrome (NSTE ACS) patients.

Methods and Results  The study group comprised 267 patients with high-risk NSTE ACS managed with an early invasive strategy and treated with the recommended dose of UFH. The subsequent dose was adjusted after measurement of activated partial thromboplastin time (aPTT), using the nomogram. The goal for aPTT was 1.5–2.5-fold of the control value. At 6 h after starting therapy 29% of patients had a therapeutic initial aPTT value; half of them were over-anticoagulated, and 22% were undertreated. By continuing therapy, the proportion of optimally treated patients increased; after 12 h of treatment 40% of patients reached the therapeutic dose, and 58% after 24 h. Undertreatment was a problem in ≤65-year-old men. Women and older patients have a higher risk of overdose. The patients with a therapeutic dose of UFH had the lowest occurrence of major ischemic adverse events.

Conclusions  Expert consensus on more precise dose guidelines for UFH is needed. The dose needs to be not only weight, but also age and sex, adjusted. (Circ J 2008; 72: 1674–1679)

Key Words: Antithrombin therapy; Heparin dose-regimen; Non-ST acute coronary syndrome

Antithrombin therapy with heparin is the evidence-based standard treatment for patients with acute coronary syndrome without ST elevation (NSTE ACS). Low-molecular-weight heparin (LMWH) has several advantages over unfractionated heparin (UFH), including a more predictable anticoagulant effect, better bioavailability, a longer half-life, and simpler application without the need for laboratory monitoring. As the recent data from the registries shows, most patients with NSTE ACS are treated with UFH, and this is also true for most of the high-risk patients undergoing an early (≤48 h) invasive strategy. This could be the consequence of routine, in addition to being related to the capability of stopping antithrombin therapy at the time of percutaneous coronary intervention and also the opportunity to manage this therapy through intervention according to timely measured activated clotting time. Additionally, treatment with (recommended dose of) UFH can be started safely without knowledge of renal function. In contrast to previous investigations, a rapid rebound increase in coagulation activity occurs soon after discontinuation of UFH, as well as with LMWH. Dual antiplatelet therapy (ie, aspirin plus clopidogrel) reduces this reactivation. In our practice, patients are routinely treated with UFH before admission to a cardiocenter (emergency medical service, community hospital). Changing antithrombin therapy during the course of treatment is associated with an increased risk of bleeding.

It is clear that UFH is, and will be, a very important part of the antithrombin therapy for NSTE ACS patients. As the recent Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology recommend, UFH is to be preferred in high-risk NSTE-ACS patients with a planned invasive strategy. The most vulnerable part of its application is correct dosing.

For these reasons, we investigated the quality of UFH treatment in daily clinical practice in a university teaching hospital, to determine what proportion of high-risk NSTE ACS patients with early invasive management treated with continual infusion of UFH reached the target optimal values of activated partial thromboplastin time (aPTT). The aim of this analysis was to define the risk factors associated with problematic dose titration of UFH in high-risk NSTE ACS patients.

Methods

Subjects  We analyzed a group of 267 consecutive patients admitted to the Coronary Care Unit with high-risk NSTE ACS and adequately treated with the recommended dose of UFH. The data from 136 patients were collected retrospectively and from 131 patients prospectively. Patients were managed with an early (≤48 h) invasive strategy. All study participants were on dual antiplatelet therapy consisting of aspirin (100 mg daily) and clopidogrel (initial loading dose 300 mg and maintenance dose 75 mg daily). In this institution, the...
recommended regimen for intravenous UFH is given according to a weight-adjusted nomogram: a bolus of 70 U/kg (maximum of 5,000 U) and an initial infusion of 12–15 U·kg⁻¹·h⁻¹ (maximum of 1,000 U/h initially). The subsequent dose of heparin is adjusted after measurement of the aPTT, using the recommended (ACCP) nomogram. The goal for the aPTT is 1.5–2.5-fold of the control value. Measurements of aPTT were done 6 h after the initialization of therapy and 6 h after any change of dose. When the aPTT value became therapeutic, measurements were made every 12 h.

Data were collected only during the hospitalization in an anonymous fashion without informed consent.

**Definition**

**High-Risk Patients With NSTE ACS** The characteristics of patients with NSTE ACS with high, acute, thrombotic risk of rapid progression to myocardial infarction or death, who should undergo coronary angiography within 48 h are: (a) recurrent resting pain; (b) dynamic ST-segment changes: ST-segment depression ≥0.1 mV or transient (<30 min) ST-segment elevation ≥0.1 mV; (c) elevated troponin-I, troponin-T, or CK-MB levels; (d) hemodynamic instability within the observation period; (e) major arrhythmias (ventricular tachycardia, ventricular fibrillation); (f) early post-infarction unstable angina; (g) diabetes mellitus.

**Statistical Analysis**

Categorical variables are expressed as percentages. Simple linear regression was used to test the association between continuous variables. Potential associations between clinical and biological parameters were tested by the chi-square or Fisher’s exact test for categorical variables. All analyses were performed with the software SPSS 14.0 (SPSS Inc, Chicago, IL, USA).

**Results**

**Accuracy of Dose Regimen**

We analyzed a group of 237 patients with a mean age of 70 years, 40% of whom were women. In the retrospectively analyzed cohort of 136 patients, 29% had a therapeutic initial aPTT value (6 h after starting therapy). Half of them were over-anticoagulated (aPTT >70 s), and 22% of high-risk patients were undertreated (aPTT <45 s). By continuing therapy with UFH, the proportion of optimally treated patients increased: 40% of patients reached the therapeutic dose of UFH after 12 h of treatment, and 58% after 24 h (therapeutic 2nd aPTT 40%, 3rd aPTT 52%, 4th aPTT 58%) (Fig 1). The proportion of over-anticoagulated patients

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**Fig 1.** Effectiveness of weight-adjusted dose of unfractionated heparin (UFH) in high-risk patients with non-ST acute coronary syndrome; aPTT, activated partial thromboplastin time (s), measured parameter of UFH effectiveness; R, retrospectively collected data; P, prospectively collected data.

**Fig 2.** Proportion of patients with therapeutic dose (Top), overdose (Medium) and underdose (Bottom) of unfractionated heparin (UFH) in accordance with age, body mass index (BMI) and gender.
Fig 3. Relationship between body mass index (BMI) (Top) or weight (Bottom) and achieved effectiveness of unfractionated heparin after the first 6h of treatment.

Fig 4. Relationship between body mass index (BMI) and achieved effectiveness of unfractionated heparin in women (Top) and men (Bottom).
diminished stepwise, from 49% to 25% during the 24 h. In contrast, the proportion of undertreated patients changed only minimally (from 22% after the first 6 h treatment to 17% after 24 h of treatment). Surprisingly, data from the prospectively analyzed group of consecutive patients were practically the same (Fig 1).

Risk Factors

Of the patients older than 70 years, the 1st weight-adjusted dose of UFH led to therapeutic levels of aPTT in only one-fifth of patients; 60% of them were over-anticoagulated (Fig 2). Nearly the same distribution appeared in women (22% and 61%) and in patients with a body mass index (BMI) <25 (21% and 62%). Patients 65 years old or younger (30%) had the highest risk for the underanticoagulation. Men were more likely to be undertreated than women (26% vs 17%). A BMI >30 was not associated with an increased risk of undertreatment. In summary, nearly four-fifths of patients older than 70 years, and four-fifths of women, as well as patients with BMI <25, did not reach the optimal therapeutic dose of UFH.

The 1st dose of heparin was weight adjusted, which means the proportion of patients with therapeutic aPTT should be the same in patients who were normal-, under- and overweight. However, the proportion of patients with a therapeutic aPTT differed among various weight and BMI intervals (Fig 3). With respect to BMI, the highest proportion of well-treated patients were overweight (BMI >25–30). Overweight and obese patients constituted three-quarters (47% and 25%) of the whole study population.

The risk for over-anticoagulation was higher in women than in men, whether they were normal, under- or as overweight (Fig 4). In the multivariate analysis, the odds ratio for optimal first dose of UFH in women was 0.598 (95% CI 0.34–1.1), p=0.077.

UFH and Renal Function

We did not find any correlation between the concentration of serum creatinine and aPTT values (Spearman correlation coefficient r=–0.088, p=0.21, coefficient of determination R²=0.0077). Renal function per se did not influence the anticoagulation activity of UFH. Rather, we discovered a correlation between renal function (creatinine clearance) and loss of hemoglobin in patients treated with a full dose of UFH (r=–0.212, p=0.018; R²=–0.45) (Fig 5).

Clinical Complications

The study was not designed to evaluate clinical outcomes. Over-anticoagulated patients had the highest rate of hemorrhage (10%). According to Thrombolysis In Myocardial Infarction criteria,12 no excess major bleeding was noted, nor was intracranial bleeding observed. Most from minor bleeding events were associated with hematoma formation at the vascular access site (72%), followed by gastrointestinal bleeding (18%).

Discussion

UFH is a heterogeneous mixture of chains with molecular weights that range from 5,000 to 30,000 and have varying effects on anticoagulant activity. UFH binds to a number of plasma proteins, blood cells, and endothelial cells. Therefore, it is difficult to find an optimal dose regimen.

What do the guidelines say about the correct dose of UFH? The European Society of Cardiology guidelines for the management of NSTEMI1 do not contain any correct dose strategies for UFH. The ACC/AHA guidelines 2002 recommends a weight-adjusted regimen used until now in our daily practice.2 Brand-new published ACC/AHA guidelines 2007 recommend more exactly an initial bolus of 60 U/kg (maximum 4,000 U) and an initial infusion of 12 U·kg⁻¹·h⁻¹ (maximum 1,000 U/h) to maintain aPTT at 1.5–2.0-fold of the control.13 What is the reason for this change in UFH dose strategy? We did not find new evidence-based data from clinical trials with adequate power for this recommendation.

In the well-designed multicenter randomized ESSENCE trial,14 the weight-adjusted first-dose of UFH led to an optimal aPTT in only 30% of patients, and only 46% of patients reached the target aPTT within 12 to 24 h. The findings of the OASIS II study were very similar (35% and 52%).15 Data from our daily clinical practice were nearly the same as those from randomized trials (Fig 1). The first weight-adjusted dose of UFH led to an optimal therapeutic level of aPTT in 29 patients (31%) with NSTEMI. Within 24 h, 58 (59%) patients reached the optimal therapeutic target, which is even more than in the randomized trials. In the ESSENCE trial, when comparing UFH and enoxaparin...
in patients with NSTE ACS, 15% of patients on UFH were undertreated within 48 h. In our practice, the proportion of undertreated patients was 17% within (the very important) 24 h. Montalescot et al. found that, in a large cohort of consecutive patients with NSTE ACS on enoxaparin, 7% of them were undertreated (optimal levels of anti-Xa activity in 76% of patients). How can we improve the quality of treatment with UFH? It will be very difficult (if possible at all) to find a universal weight-adjusted nomogram for UFH dose titration. As our data show, the dose of UFH should be not only weight, but also age and sex adjusted. Undertreatment is a problem in 65-year-old or younger men (Figs 2, 4). In contrast, women and older patients have a higher risk of overdose (Figs 2, 4). From another point of view, we defined a subpopulation of high-risk patients (female sex, older age, underweight) for whom the best option could be the use of LMWH.

Adnand et al. reported on the serious consequence of under- and overtreatment with UFH in their analysis of the OASIS II trial (10,141 NSTE ACS patients). In patients with subtherapeutic aPTT values, the risk of a recurrent cardiovascular event increased. Higher aPTT values were associated with bleeding: for every 10 s increase in the aPTT, the probability of major bleeding was increased by 7%. Optimal dose regimen is a strong predictor of the clinical efficacy of UFH and also of LMWH. The suboptimal anticoagulation with enoxaparin was associated with a significantly higher 30-day mortality rate. Low anti-Xa activity was an independent predictor of 30-day mortality at least as significant as age, left ventricular function, and renal function. UFH is rapidly metabolized in a saturable, zero-order mechanism, mainly by the reticuloendothelial system. This is followed by a slower first-order renal clearance. Less than 10% is excreted in urine unchanged. The mean half-life is dependent on the administered dose, and is unchanged with abnormal renal function. We did not find any correlation between creatinine and aPTT values. Renal function per se did not influence the anticoagulation activity of UFH (Fig 5). The reported higher risk of bleeding in patients with renal dysfunction treated with UFH is a consequence of the complex impairment of coagulation in those patients. In accordance with this, we found a correlation between the level of serum creatinine and loss of hemoglobin (Fig 5).

Some patients require much higher-than-average doses of heparin to prolong aPTT in the therapeutic range. These patients are designated heparin-resistant if their daily heparin requirement is >35,000 U/24 h. The latter finding necessitates further attention and cooperation between hematologists and cardiologists. Heparin resistance has been associated with antithrombin deficiency, increased heparin clearance, elevations in heparin binding proteins, and elevations of factor VIII, fibrinogen, and platelet factor 4. “Heparin-resistant” patients should be managed in cooperation with a hematologist. The dose of UFH should be adjusted to maintain anti-Xa heparin levels of 0.35–0.70 IU/ml. Although measurement of antithrombin levels has also been recommended in the management of heparin resistance, low values are usually secondary to heparin therapy, rather than the cause of heparin resistance.

Conclusion

The recommended weight-adjusted first-dose of UFH led to an optimal antithrombin effect in less then one-third of high-risk patients with NSTE ACS. By using the nomogram, only 50% of patients reached the optimal therapeutic target within 24 h. These significant findings call for an improvement in the quality of UFH treatment of high-risk NSTE ACS patients. An expert consensus on more precise dose guidelines for UFH is needed. The dose of UFH can be not only weight, but also age and sex adjusted. Renal dysfunction does not significantly influence the effectiveness of UFH.

Acknowledgments

This paper was supported by the Charles University Prague Research Project nr. MSM 0021620817 awarded by the Ministry of Education, Youth and Physical Education of the Czech Republic.

Disclosure

The authors do not have financial or personal relationships that could inappropriately influence (or bias) the author's decisions, work, or manuscript.

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