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Assessment of Enoxaparin anti-Xa activity and Treatment Efficacy's Evaluation

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Research Article

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Abstract

Objective: Assessment of the safety and efficacy of enoxaparin anti-Xa activity in patient with normal renal function, unstable angina and non ST segment elevation myocardial. **Methods**: At its peak, 4 hours post Enoxaparin administration, blood samples were collected and anti-Xa activity was measured. The German Dade-Behring Corporation SysmexCA-7000 automated coagulation analyzer was used to measure the anti-Xa Enoxaparin activity. The clinical data of patient were evaluated to assess bleeding and thrombotic adverse events after treatment with Enoxaparin. **Results**: A total of 70 patients were eligible for our study, with a mean weight of 65.52±9.97kg (BMI: 18.02~29.24kg/m^2). While the minimum anti-Xa activity was 0.3IU/ml, the maximum anti-Xa activity was 1.5IU/ml, and the average anti-Xa activity was 0.62±0.24IU/ml. During the study, 5 (7.2%) patients had minor bleeding events with respective dosage of 0.9~1.2IU/ml, which was below urinary occult blood positive rate in healthy adults (Adults 10.68%; Elderly 17.6%). There was no occurrence of thromboembolic event related to Enoxaparin use. **Conclusion**: The Enoxaparin anti-Xa activity≥ 0.3IU/mL can be achieved when anticoagulant activity is effective with careful patient monitoring. During the treatment, there was no clinically significance of bleeding and thromboembolic events. These findings also show that enoxaparin dosing for the treatment of unstable angina and non ST segment elevation myocardial infarction can be safe and effective at an anti-Xa activity of 0.3 to 0.6 IU/mL.

Keywords: *Enoxaparin; Anti-Xa activity; Treatment, Efficacy, Safety*

Introduction

In treatment of unstable angina and non-Q wave myocardial infarction, low molecular weight heparin (LMWH) is mostly used because of features such as: a predictable anticoagulation; less bleeding side effect; absence of laboratory monitoring and the dosage is based on patient body weight and can gradually be replaced by ordinary heparin[1]. LMWH therapy is monitored by the anti-factor Xa assay. LMHW have a potency of greater than 70 units/mg of anti-factor Xa activity and a ratio of anti-factor Xa to anti-thrombin activity of >1.5[2]. LMWH is excreted from kidneys, however the bleeding rate of patients with severe renal insufficiency (creatinine clearance <30ml/min) will increase if dosage adjustment is still based on body weight [3]; at this point, it needs to monitor the LMWH anti-Xa activity by adjusting the dosage.

The College of American Pathologists has joined the American College of Chest Physicians (ACCP) consensus group in recommending that administration of enoxaparin requires monitoring of anti-Xa activity at 0.6-1.0 IU/ml [4, 5]. The recommended dosage for Enoxaparin therapy of unstable angina and non-Q wave myocardial infarction is 1mg/kg administered subcutaneously every 12 hourly in conjunction with aspirin 100 to 325mg daily. Scientific findings have improved clinicians' understanding of the LMWH anti-Xa activity, clinical significance and evaluation-based treatment.

The purpose of this study is to measure Anti-Xa activity in patient with unstable angina and non-Q wave myocardial infarction and to evaluate the safety and efficacy of Enoxaparin administration method for the local clinical application of Enoxaparin in preventing thromboembolic events.

The Novelty of the work: An anti-Xa activity of 0.3 to 0.6 IU/mL can be achieved when anticoagulant activity is effective with careful patient monitoring, showing at the same time that enoxaparin dosing for the treatment of unstable angina and non-ST segment elevation myocardial infarction can be safe and effective at the same anti-Xa activity range.

Material and Method

Study population: From February to June 2011, a study was undertaken at the Affiliated Drum Tower Hospital, Nanjing, China. Of the 90 eligible patients, 70 completed the study. Patients were eligible in this study if they had received an expected duration of enoxaparin treatment of 48h or more a new prescription of enoxaparin; were 18 years or older. Patients were excluded if they had enoxaparin dosage different from that specified in the protocol; received enoxaparin or another LMWH within 40 hours before the study; participation in another study; pregnancy; antithrombin III deficiency; recent (＜24h) treatment with fibrinolytic therapy; receiving a GP IIb/IIIa receptor antagonist; a baseline ACT＞140s; a prothrombin time international normalized ratio≥2.0; a history of heparin-induced thrombocytopenia; or a contraindication to enoxaparin.

The protocol and data collection was approved by the Clinical Research Ethics Committee and Review board of The Nanjing Drum Tower Hospital.

***Patient characteristics*:** Patient demographics data are listed in Table 1. The cohort was 67.14% male, an average age of 69.69±8.86 years.

Table 1: Baseline Characteristics

Characteristic	Patients (n)	Characteristic	Patients (n)
Gender		Recent Acute Coronary Syndrome	2
Male	47	Myocardial Infarction	35
Female	23	Unstable Angina	31
Age (years)		Angina Pectoris	3
≥75	24	Ischemic Cardio-myopathy	3
<75	45	Hypertension	48
Weight (Kg)		Diabetes	24
≤50	5	Hyperlipidemia	4
50～60	15	Atrial Fibrillation	7
60～70	33	Current Smoking	24
70～80	14	Current heavy Drinking	5
＞80	3	Previous use of Aspirin	70
CrCl (ml/min)		Previous use of Clopidogrel	70
＜30	0		
30～60	15		
＞60	55		

Statistical Analysis: Measurement data are used mean (X) ± standard deviation (SD); the data are expressed in frequency. SPSS11.5 was used to analyze the single-factor regression of age; weight and creatinine's clearance rate, each of these three factors were analyzed for the anti-Xa Enoxaparin activity.

Instrument and materials: Berichrom® Heparin (Dade-Behring, Germany); standard plasma (Dade-Behring, Germany); SysmexCA-7000 automated coagulation analyzer (Dade-Behring, Germany).

Sample: LMWH considerably accelerates the inactivation of coagulation factor Xa and thrombin by antithrombin III. Factor Xa is inactivated by AT III during the incubation phase of the test. This reaction is catalyzed by heparin. Dextran sulfate (DS) releases heparin which is bound to interfering factors and thus makes it accessible to the assay. After incubation, the quantity of Factor Xa phase is determined at 405 nm.

***Anti-Xa activity*:** Anti-Xa was measured at its peak, 4 h after the administration of enoxaparin [6-8]. It is estimated that seven half-lives (t 1/2) are necessary to reach steady state, actually 35h for renally impaired patients(t 1/2 =5.12 h) [6]. For patients on twice-daily doses, anti-Xa was measured 4h after the third, fourth or fifth enoxaparin dose. Whole blood samples were obtained from the femoral arterial sheath (after first discarding 3 ml of blood) and placed into a 3.2% sodium citrated tube (2.7ml). The citrated blood was immediately centrifuged at 3500 rpm for 7min, and the resulting plasma was aliquoted in cryovials and frozen at -80℃. The anti-Xa concentrations in the archived plasma samples were determined in a central coagulation core laboratory.

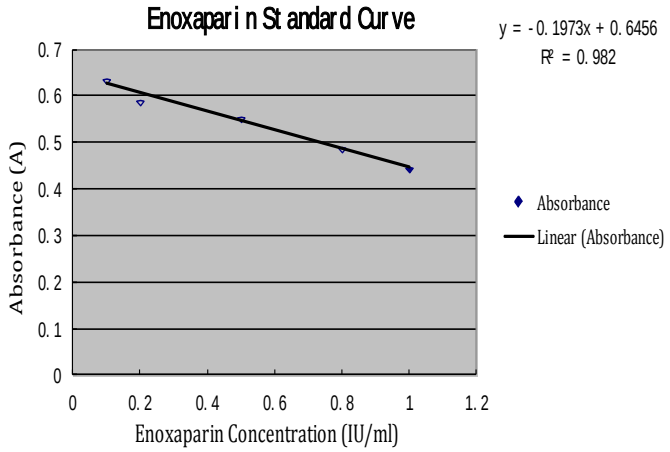
***Determination*:** Plasma stored at -80℃ was to be thawed within 10 minutes at 37 °C before the determination.

***Bleeding*:** Five days after the treatment, bleeding episodes were documented for all the patients. A modified version of the Warfarin Optimized Outpatient Follow-up Study Classification was used to classify bleeding severity [9]. According to this classification; 'minor' bleeding has no or little clinical significance, is associated with no cost and does not require medical evaluation. In contrast, 'significant' bleeding requires medical evaluation or is associated with at least a 3% reduction in hematocrit, or more than 12 g/L (1.2g/dL) reduction in the hemoglobin level. 'Major' bleeding requires hospitalization and transfusions. 'Life threatening' bleeding is associated with cardiopulmonary arrest, surgical or

angiographic intervention or irreversible sequelae and 'fatal' bleeding is directly related to death.

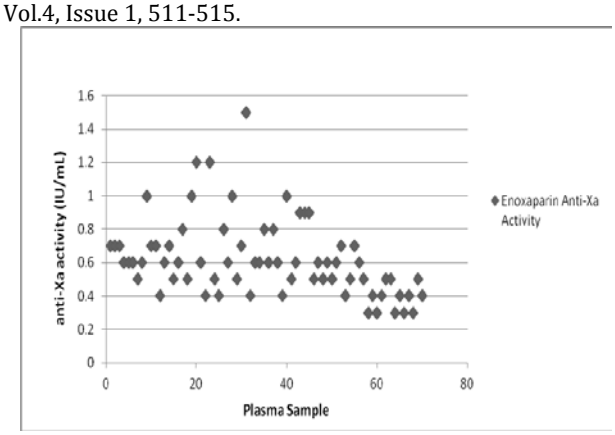
Results

Standard curve: The standard curve was listed in Figure1. y=-0.1973x+0.6456 ,R^2=0.982



Results Analysis: Seventy eligible patients were enrolled; all the blood coagulation factors, renal function and platelet count were within the range. The minimum anti-Xa activity is 0.3IU/ml; the maximum is 1.5IU/ml, and an average is 0.62 ± 0.23IU/ml. After a person has once used the enoxaparin, there was a significant conjunctival hemorrhage; anti-Xa activity is 0.6IU/ml. The condition has considerably improved with no treatment. It is considered that it's unrelated to the treatment with the application of enoxaparin; the urine occult blood were positive in 9 patients after the treatment with enoxaparin, which may be related to the drug, and also the disease state is a performance under the stress. The anti-Xa activity was 0.9~1.2IU/ml (trace of urine occult blood); in which the anti-Xa activity of 0.6 IU/ml in patient with skull head MRI presented a fresh lacuna. It brings us to consider that the embolic cerebral infarctions of these cerebral vascular obstructions were caused by failing. The patient who had anti-Xa activity 0.3IU/ml died the next day after taking his blood samples, the cause of death was a sudden cardiac death. During the treatment, five patients had no clinical symptoms of bleeding, one patient had experienced a weakness at his left hand one day after the PCI procedure, the condition improved after treatment, and we consider that the original small emboli during surgery caused by cerebral vascular obstruction led to loss, anti-Xa activity 0.6IU/ml.

Figure 2: Enoxparin anti-Xa activity (n=70)



This explains that enoxaparin anti Xa-activity ≥ 0.3 IU/mL can be achieved when effective anticoagulant activity, among this there is 60 (85.7%) patients with anti-Xa activity within the 0.3-0.8 IU/mL, while there is no bleeding occurred.

When the anti-Xa activity is superior or equal to 0.0 IU/mL, 5 patients (7.1%) among 10 experienced minor bleeding.

Factors Analysis: Patients enrolled had an average age of 69.69 ± 8.86 years (p> 0.05); average weight of 65.52±9.97kg (p>0.05); average creatinine clearance rate of 117.46±30.09mL/min (p>0.05); explaining that during this study the weight and the creatinine clearance rate don't affect the enoxaparin anti-Xa activity. Selected range of patients with creatinine clearance 63.7~212.5mL/min, patients with normal renal function under this dosage regimen is safe and effective. Results are shown in table 2

Table 2: Results of Univariate Analysis of influencing factors

Factors	Average	p-Value
Age (years)	69.69±8.86	0.532
Weight (kg)	65.52±9.97	0.362
Creatinine Clearance rate (mL/min)	117.46±30.09	0.237

Discussion

Low Molecular Weight Heparin is a heparin as the raw material through chemical modification, enzymatic methods such as chromatography or made, with a selective factor Xa anticoagulant activity, which affects less the thrombin and other coagulation factors. Lower is the molecular weight stronger is the anti-coagulation factor Xa activity [10]. This will permit to separate the role of antithrombotic effect and the bleeding, to maintain the risk of bleeding of the antithrombotic effect of heparin. Enoxaparin is a low molecular weight heparin, with an average molecular weight of

3500~5500kD, the ratio between antithrombin III and antithrombin II is 8 [11]. Compared to unfractionated heparin, LMWH is one of the most important advantages of the anticoagulant effect which can be predicted when administered in the basis weight, and without the need for laboratory monitoring. However, LMWH excretion is through renal fluids [12], for patients with severe renal insufficiency (Creatinine Clearance <30ml/min), if you or simply adjust the dose according to body weight, the patient will increase the incidence of bleeding [13, 14]. In a meta-analysis, Wendy Lim et al [3] showed that if you do not monitor LMWH in patients with severe renal insufficiency, the rate of bleeding increases, so monitoring of LMWH anti-Xa activity is necessary in such patients.

Considering the accumulation of body fluid and the bleeding risk of the LMWH in patients with renal dysfunction, The American College of Chest Physicians and The American Association of Pathologists recommended creatinine clearance 30ml/min or less when LMWH was used in patients with unfractionated heparin, administration of LMWH requires monitoring of anti-Xa activity (0.6-1.0 IU/ml) [4, 5]. The ethnic differences are still a question whether the scope of this safe and effective for our patients. One of the purposes of this study is to identify the safety administered range of enoxaparin in Chinese patients by detecting anti-Xa activity.

There was only 5(7.2%) patients had minor bleeding events and; no thromboembolic event was found. Studies found that the percent the young and the elderly people whose urinary occult blood were positive are respectively 10.68% [11], 17.6% [12]. Therefore, this study considered positive urinary occult blood events has nothing to do with the drug enoxaparin. Enoxaparin anti-Xa activity≥0.3IU/ml can be achieved when effective anticoagulant activity. In 67 (95.7%) patients the anti-Xa activity is within the 0.3-1.0 IU/ml, 60 (85.7%) patients have their anti-Xa activity within 0.3-0.8 IU/ml. When anti-Xa activity is superior or equal to 0.9IU/mL, 5 (7.1%) of 10 patients experienced urinary occult blood, but there was no clinical significant events. Analysis of patients' age, weight, creatinine clearance ratio on anti-Xa enoxaparin activity analysis shows that, these factors on the anti-Xa enoxaparin activity were not statistically significant; telling us the application of this dosage regimen on this kind of patients is safe and does not require a routine laboratory monitoring. Under the conditions taken during this study, we found that enoxaparin anti-Xa activity is safe and effective between 0.3-0.8IU/mL, and by comparison with the American College of Chest Physicians safe and effective recommended range (0.6-1.0IU/mL) is not completely consistent. For a step forward to precise the scope of this safety and effectiveness, we recommend further studies with a large scale clinical trials.

Conclusion

Thus, we reach the following conclusions: In this study on the enoxaparin dosing body mass index in the range of 18.02 ~ 29.24kg/m^2 patients with normal renal function, unstable angina and non ST segment elevation myocardial infarction, it is safe and effective at an anti-Xa activity of 0.3 to 0.6 IU/mL, does not require laboratory monitoring.

This study has some few insufficient points, first of all the small sample size, representativeness is not very strong, slightly bleeding events occurred in patients with anti-Xa activity 0.9~1.2IU/mL, higher is the value of anti-Xa activity in patients who did not have bleeding events, we think that it's due to these differences in individual patients, or maybe the disease affects the generated stress, further studies need to be conducted to confirm this funding. Secondly, patients were selected with normal renal function, excluding the case of patients with renal dysfunction; guiding significance for these patients is very small. Therefore in future studies we hope to have a larger sample size, including the clinical trials of patients with renal dysfunction.

Ethical Considerations

Approval of data collection was granted from the Clinical Research Ethics Committee of The Nanjing Drum Tower Hospital.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

Not commissioned; externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.