Original paper

The Incidence of Adverse Events in Patients Treated with Therapeutic Dose Enoxaparin in Relation to Body Mass Index

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Abstract

Background: Low Molecular Weight Heparin (LMWH) has widely replaced its parent and oldest anticoagulant compound "Heparin" due to its numerous advantages. However, LMWH are not devoid of adverse effects which may be serious. Since the therapeutic dose of LMWH "*Enoxaparin*" is determined by a weight-based regimen, the incidence of adverse events may be increased when using higher doses in overweight & obese patients.

Aim: to assess the incidence of adverse events in acutely thrombosed patients treated with therapeutic dose *Enoxaparin* in relation to Body Mass Index (BMI).

Methods: A prospective study conducted through a 6 months period in 2014 including 181 patients (98 males, 83 females) with acute thrombotic disorders admitted to the cardiac care unit in Al-Hussein Medical city in Karbala-Iraq. All patients who had normal renal functions, were received weight-based LMWH in the form of *Enoxaparin*. They were subdivided according to their BMI into 3 groups; normal, overweight and obese. Any evidence of adverse events were followed and recorded.

Results: Bleeding was the most common adverse event occur in 15 out of 181 patients (8.3%), categorized as Major bleeding comprising 2.2% overall, occur in 2% of normal BMI, 1.6% of overweight, & 2.9% of obese patients, and Minor bleeding comprising 6.1% overall, occur in 5.9% of normal BMI, 6.5% of overweight, & 5.8% of obese patients. No death was reported related to bleeding. Other adverse events were thrombocytopenia in 2.6%, and fever in 1.1% overall. There was no statistically significant difference regarding all adverse events among the 3 groups.

Conclusion: The incidence of bleeding and other adverse events was not found to be increased in relation to BMI when using weight-based therapeutic dose *Enoxaparin*, which may indicate the rationale use of this regimen in patients with acute thrombotic disorders.

Key words: Low Molecular Weight Heparin, Enoxaparin, Body mass Index

Introduction

Heparin, the older parenteral anticoagulant which was firstly discovered before a century by McLean in 1916, remained for a long time the standard therapy for most acute thrombotic disorders.(1) In the early 1980s, the development of low molecular weight heparin (LMWH) extended and enhanced the usefulness of this class of drug, and for many indications LMWH has replaced its parent compound.(2,3)

It is well known that unfractionated heparin (UFH) must be administered either intravenously as infusion or subcutaneously as frequent injections, and its effect requires careful monitoring to ensure optimal anticoagulant activity with minimal risk of bleeding. Patients requiring heparin therapy are usually admitted to hospital, in part to make it easier to administer and monitor the drug, together with the seriousness of their acute thrombotic conditions.(4) In spite of its limitations for monitoring UFH, activated partial thromboplastin time (aPTT) remains the most convenient and most frequently used method for monitoring its anticoagulant

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response. However, heparin monitoring is likely to become less problematic as LMWH replaces UFH for most indications.[2,4] LMWH fractions have less effect on the aPTT as they are reduced in molecular size, while still inhibiting activated factor X (factor Xa).[3,5] LMWHs are usually derived from heparin by chemical or enzymatic depolymerization to yield fragments with reduced binding to proteins or cells. Almost all the pharmacokinetic, and phamacodynamic differences between UFH and LMWH can be attributed to the relatively lower binding properties of LMWH.[5,6] LMWH preparations had a better bioavailability and longer plasma half-life at lower doses than UFH, in addition to a more predictable dose response which translates clinically into weight adjusted dosing without laboratory monitoring.[6,7] Despite that anti-factor Xa levels can be used to monitor the effect of LMWH, its benefit for monitoring might be marginal and balanced by inconvenience and added expense, except in patients with renal insufficiency and may be in morbidly obese patients.[4,7,8] These findings provided the rationale for using unmonitored weight-adjusted LMWH over aPTT-monitored UFH.

Heparins, in general, have several side-effects which include bleeding, thrombocytopenia with or without thrombosis, hyperkalaemia, osteoporosis (risk lower with LMWH) & alopecia on prolonged use, injection-site reactions, skin necrosis, and hypersensitivity reactions. [3,9,10]

Primary evidences showed that LMWH produces less microvascular bleeding than UFH in experimental models has not been supported by the subsequent large randomized trials in human, in which LMWH and UFH have shown similar low rates of bleeding.[4,6,9]

Enoxaparin, a commonly used LMWH, is primarily eliminated renally. So, regarding the need for dosage adjustments in patients with renal impairment, the level of creatinine clearance (CrCl) would indicate the adjustments required.[10,11] *Enoxaparin* therapeutic doses are calculated on the bases of actual patient's body weight, however, because the drug is not distributed in fat, there is a possibility of excessive drug exposure in obese patients. Therefore, the manufacturer recommends a maximum dose of no more than (100 mg) for the first two doses only to treat acute coronary syndrome.[10] Hitherto, few studies have been conducted on obese patients and they are inconclusive on the issue of dosage adjustment.[5,7,12]

The aim of this study is to assess the incidence of adverse events in patients with acute thrombotic disorders treated with therapeutic dose *Enoxaparin* in relation to their Body Mass Index (BMI).

Methodology

This prospective, open-label study was conducted in Iraq-Karbala at Al-Hussein Medical City - Cardiology Department, along a period of 6 months from January till July 2014. One hundred eighty one patients (98 males, 83 females) with acute thrombotic diseases (i.e. acute venous thromboembolism, acute cardiac thromboembolism and acute coronary syndrome excluding those received thrombolytic) were included and followed up during their stay in the cardiac care unit (CCU) in hospital for period of 5-7 days.

A full medical and medication history was taken and the objective data was recorded. Body mass index (BMI) of each patient was calculated from the weight and height. Complete Blood Count (CBC) including platelets counts in addition to renal and liver function tests were measured. All patients who had normal renal functions in term of normal blood urea and serum creatinine, were received weight-based LMWH in the form of *Enoxaparin*. The dose of *Enoxaparin* given was calculated based on the actual body weight as 1mg/kg/dose twice daily, and the maximum 12-h dose was capped to 120 mg.[10,13] The patients were subdivided according to their

BMI into 3 groups; normal (BMI <25), overweight (BMI 25-<30) and obese (BMI ≥30). Any evidence of adverse events of anticoagulation especially bleeding were followed and recorded. The fates of patients were followed to see the effects of treatment and the mortality rate.

The variables are shown as numbers and percentages. Statistical analysis was done using Fisher's exact test. *P*-value < 0.05 was considered as statistically significant.

Results

Figure 1 shows the distribution of patients into 3 groups according to the BMI into Normal weight, Overweight, and Obese. Patients' characteristics are shown in Table 1, including age, sex, smoking history and indications of anticoagulation, which were almost statistically matched among the 3 groups of patients. Table 2 demonstrates the incidence of adverse events in the 3 groups of patients.

Bleeding was the most common adverse event occur in 15 out of 181 patients (8.3%), categorized by GUSTO bleeding classification[14,15] as "Major bleeding" (including severe and moderate bleedings e.g. gastro-intestinal, central nervous system or intra-ocular hemorrhage, & any bleeding that requires blood transfusion or interventions) comprising 2.2% overall, occur in 2% of normal BMI, 1.6% of overweight, & 2.9% of obese patients, and "Minor bleeding" (e.g. bruising, brief epistaxis, transient haematuria and any bleeding that does not require blood transfusion or intervention) comprising 6.1% overall, occur in 5.9% of normal BMI, 6.5% of overweight, & 5.8% of obese patients. No death was reported related to bleeding. Other adverse events were thrombocytopenia in 2.6%, and fever in 1.1% overall. There was no statistically significant difference regarding all adverse events among the three groups.

UA= Unstable Angina, NSTEMI= Non-ST segment Elevation Myocardial Infarction, DVT= Deep Venous Thrombosis, PE= Pulmonary Embolism, AF= Atrial Fibrillation, CT= Cardiac Thrombosis.

Discussion

The distribution of patients according to body mass index (BMI) was; 28.2% within normal weight (BMI <25), 33.7% overweight (BMI 25-30), and 38.1% obese (BMI ≥30) patients. Hence, obesity might increase the risk of cardiovascular thrombosis.

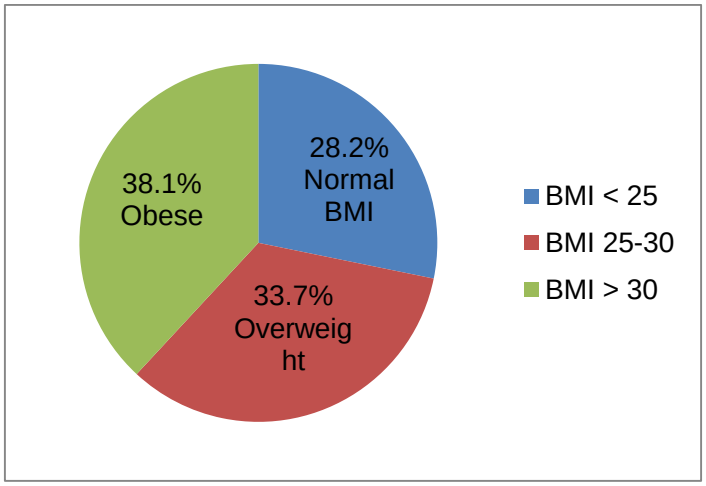

Figure 1. Distribution of Patients according to BMI

Table 1. Patients Characteristics according to Body Mass Index (BMI)

Characteristics	BMI<25 N=51	BMI25-<30 N=61	BMI ≥30 N=69	*P -value*
Patients No.(%)	51 (28.2%)	61 (33.7%)	69 (38.1%)	
Age, mean ± SD	57.6 ±17.2	56.1 ±14.3	58.2 ±15.4	0.74
Male, No.(%)	28 (54.9%)	35 (57.3%)	36 (52.1%)	0.84
Smokers, No.(%)	18 (35.3%)	23 (37.7%)	24 (34.7%)	0.93
Indications of Anticoagulation:				
UA & NSTEMI No.(%)	34 (66.7%)	37 (60.7%)	43 (62.3%)	0.80
DVT& PE No.(%)	7 (13.7%)	13 (21.3%)	14 (20.2%)	0.54
AF&CT No.(%)	10 (19.6%)	11 (18.0%)	12 (17.3%)	0.95
Dose of LMWH used:				
Enoxaparin dose in mg/day, mean ± SD	110.4 ±19.9	151.3 ±22.7	190.8 ±30.8	<0.00001

Table 2. Incidence of Adverse Events in Relation to Body Mass Index (BMI)

Adverse Events	BMI<25 N=51	BMI25-<30 N=61	BMI ≥30 N=69	*P -value*
Major Bleedings	1 (2.0%)	1(1.6%)	2 (2.9%)	0.97
Minor Bleedings	3 (5.9%)	4(6.5%)	4 (5.8%)	0.96
Thrombocytopenia	1 (2.0%)	2 (3.2%)	2 (2.9%)	0.92
Fever	1 (2.0%)	0 (0%)	1 (1.4%)	0.63
Death related to Bleeding	0 (0%)	0 (0%)	0 (0%)	1.0
Death related to Thrombosis	2 (3.9%)	2 (3.3%)	2 (2.9%)	0.95

Anticoagulant therapy is used in the treatment of several different thrombotic diseases such as acute coronary syndrome (unstable angina & myocardial infarction), venous thromboembolism (deep venous thrombosis &pulmonary embolism, and cardiac thrombosis (severe heart failure, mural thrombosis & atrial fibrillation).[4] In this study, patients with acute coronary syndrome were comprising about (63%), patients with venous thromboembolism were about (18.8%), while patients with cardiac thrombosis and AF were about (18.2%).

Bleeding was the most common adverse event in patients treated with therapeutic dose *Enoxaparin*, comprising about (8.2%) overall. The percentage of bleeding in patients with normal BMI was about (7.8%), while in overweight patients was about (8.2%), and in obese patients was about (8.7%). As the body weight increases, the dose of LMWH used should be increased and thereby the risk of bleeding may be increased, yet there was no statistically significant difference between the three groups of patients. These finding were in accordance with a study done in Canada by Bazinet *et al*, who found that (10.7%) of patients presented with a bleeding episode during the first 5 days of treatment, and there was no difference in mean anti-Xa between patients who had a bleeding and those who did not.[13] On the other hand, another study on the effect of BMI on bleeding in patients receiving UFH found that there's no increase in the risk of bleeding in obese patients treated with UFH without a capped initial dose.[16]

Other adverse effects that were recorded in this study include: thrombocytopenia occur in (2.6%) and fever occur in (1.1%) overall. A critical assessment of Heparin-induced thrombocytopenia (HIT) suggests a

frequency of 0.2 to 5.0 percent in patients exposed to heparin both UFH & LMWH with an overall incidence of 2.6 percent noted in a meta-analysis.[17]

Although aPTT is commonly used to monitor UFH effect, it has no use in LMWH monitoring due to pharmacodynamic difference. Nevertheless, anti-factor Xa test measures the anti-activated factor X (anti-Xa) in blood can be used to monitor LMWH effect in some selected cases,[6,7] however, there is no strong consensus regarding the need to monitor anti-Xa activity with LMWH, only in patients with particular situations such as those with renal impairment or extreme weight.[8,13] Accordingly, in addition to the high variability of anti-Xa activity, and unavailability in our hospitals, it was not used in this study.

In this cohort of patients, the mortality rate was collectively (3.3%), which was mostly related to the diseases themselves and no one was found to be related to the bleeding or other adverse effects of anticoagulation. Thus, our data demonstrate the safe and effective use of unmonitored weight-based therapeutic dose LMWH in different weights.

Conclusions

Enoxaparin was safe and useful in treatment of patients with acute cardiovascular thrombosis. Bleeding was the most common adverse effect of therapy occurs in (8.3%) of patients in this study, yet these bleedings did not increase the death rate.

The incidence of bleeding and other adverse events was not found to be increased in relation to BMI when using weight-based therapeutic dose *Enoxaparin*, which may indicate the rationale and effective use of this regimen in patients with acute thrombotic disorders.

Acknowledgement

The Author wishes to thank all the medical staff in the CCU of Al-Hussein Medical City in Karbala.

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