

Head-to-Head Comparison of Two Different Low-Molecular-Weight Heparins in Acute Coronary Syndrome

A Single Center Experience

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SUMMARY

Low-molecular-weight heparins (LMWH) of different types have yielded different results when used in the setting of unstable angina (UA) or non Q-wave myocardial infarction (NQMI). We compared the safety and therapeutic efficacy of two different LMWHs, namely dalteparin (Dalt.) and enoxaparin (Enox.), in the acute phase (first 5 days) of UA or NQMI.

One hundred and forty-two patients with UA/NQMI were randomly assigned to treatment with either Dalt. [120 IU/kg twice daily by subcutaneous (SC) injection] or Enox. [1 mg/kg twice daily by SC injection]. The occurrence of any one of death, myocardial infarction, or angina recurrence within 5 days of the first LMWH injection was the end-point of the study. There were 69 patients in the Enox. group (53 males, 16 females, mean age : 60.3±11.9) and 73 patients in the Dalt. group (54 males, 19 females, mean age : 59.6±10.3). The baseline characteristics of the patients in the two groups were similar. There were no deaths in either group. Myocardial infarction occurred in two patients in the Dalt. group (4%). Angina recurrence was seen in 11 patients in the Enox. group (16%) and in 11 patients in the Dalt. group (15%). Overall, any of the events that made up the endpoint occurred in 11 (16%) and 14 (19%) patients in the Enox. and Dalt. groups, respectively ($P>0.05$). The time to occurrence of the first event, however, was significantly longer in the Enox. group (82.3±33.2 versus 37.6±23.4 hours, $P=0.007$). Thrombocytopenia and allergic reactions were not detected in any patient. Major bleeding was seen in 1 patient in the Enox. group. Minor bleeding occurred in 17 (25%) and 21 (29%) patients in the Enox. and Dalt. groups, respectively ($P>0.05$).

Enoxaparin and dalteparin were found to be equally safe and effective for the early management of UA/NQMI, but enoxaparin appeared to delay the occurrence of MI or angina recurrence as compared to dalteparin in this setting. (Jpn Heart J 2002; 43: 433-442)

Key words: Enoxaparin, Dalteparin, Acute coronary syndrome

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ACETYLSALICYCLIC acid and intravenous (IV) unfractionated heparin (UFH) have long been the standard therapy for unstable angina (UA).¹⁻³⁾ Given some limitations of IV UFH treatment like unpredictable anticoagulant effects necessitating frequent laboratory monitoring, low bioavailability due to a high rate of protein binding, heparin induced thrombocytopenia, osteoporosis, and a rebound effect after withdrawal of therapy,^{4,5)} low-molecular-weight heparins (LMWH) have emerged in the last decade as alternative anticoagulant agents that overcome almost all of these limitations.⁴⁻⁷⁾ Different types of LMWH have shown different clinical effects when used in the setting of UA and non-Q-wave myocardial infarction (NQMI). Some have proven to be superior to IV UFH,⁸⁻¹⁰⁾ some better than placebo,¹¹⁾ and some at least equivalent if not superior to IV UFH^{12,13)} in the management of UA and/or NQMI. In this study, we compared the safety and therapeutic efficacy of two different types of LMWH preparations, dalteparin and enoxaparin, in the acute phase (first 5 days) of UA or NQMI.

MATERIALS AND METHODS

Patients of either sex were eligible for the study if they had rest angina lasting at least 5 minutes within 24 hours of presentation together with at least one of the following three criteria : 1) History of prior myocardial infarction (MI) or a revascularization procedure (either angioplasty or coronary bypass), 2) Invasive or noninvasive laboratory evidence of coronary artery disease, and 3) At least 0.1 mV transient or persistent ST depression or at least 0.1 mV transient or persistent T-wave inversion without accompanying Q-waves in at least 2 ECG leads. Exclusion criteria were as follows : 1) Presentation more than 24 hours after the last anginal episode, 2) ST segment elevation at presentation, 3) Age <18 years, 4) Left bundle branch block at presentation, 5) Development of new Q-waves, 6) Permanent pacemaker, 7) Acute pericarditis, 8) Ongoing treatment with either heparin or oral anticoagulants, 9) Diastolic blood pressure over 120 mmHg or systolic below 90 mmHg, 10) High grade (>39°C) fever, 11) Creatinine clearance rate <30 mL/min, 12) Malignancy, 13) Any surgical procedure within the last month, 14) History of active peptic ulcer disease and/or gastrointestinal bleeding within the preceeding 3 months, 15) Known hypersensitivity to either dalteparin or enoxaparin, and 16) Pregnancy or lactation period.

Those patients with either normal 24-hour creatine kinase (CK) and creatine kinase MB (CKMB) levels or a negative 10-hour troponin-T assay were classified as UA, while those with either above normal CKMB or CK more than twice the upper normal limit or a positive 10-hour troponin-T assay were classified as NQMI.

After written informed consent was obtained, all patients were started on acetylsalicylic acid (ASA) 300 mg/day. Those patients who were enrolled after the results of the CURE study were published received clopidogrel 75 mg daily in addition to ASA. Patients were randomly assigned to treatment with either dalteparin [120 IU/kg twice daily by subcutaneous (SC) injection] or enoxaparin [1 mg/kg twice daily by SC injection]. Treatment with either agent was started as early as possible without any IV bolus doses and continued for 5 days or until any event comprising the below mentioned endpoint occurred. The accompanying antianginal treatment and any desired further LMWH treatment beyond 5 days were left to the judgment of the physician who took care of the patient during the whole study period and who was unaware of the assigned treatment. The endpoint was defined as the occurrence of either one or more of the following within 5 days of the first SC injection of either LMWH preparation : 1) Death, 2) MI, and/or 3) Recurrent angina. Coronary angiography was offered to all and performed in those patients who consented at the completion of the study.

Definitions: Cardiac arrest was classified as death even if the patient was successfully resuscitated. Myocardial infarction was diagnosed when either 2 of the following 3 occurred more than 24 hours after the first injection of either study drug : 1) Ischemic chest pain lasting more than 30 minutes, 2) Serial ECG changes typical of MI, and 3) Total CK above twice the upper normal limit and/or CKMB above the upper normal limit. Recurrent angina was defined as either; 1) Angina of sufficient intensity that necessitates the reinstitution of IV nitrate infusion after a completely angina-free 24 hour period, 2) Angina that lasts at least 5 minutes and is accompanied by at least 0.1 mV of either ST segment deviation or T-wave inversion in at least 2 ECG leads at any time during the study period, or 3) Angina of sufficient severity that prompts a decision to perform an emergency revascularization procedure even in the absence of accompanying ECG changes.

Safety parameters that were followed throughout the study were the occurrence of bleeding, allergic reactions, and thrombocytopenia. Bleeding was classified as major when associated with a more than 2 g/dL fall in hemoglobin concentration or a need to perform blood transfusion, or if it was either intracranial or caused death. All other bleeding episodes were regarded as minor.

Statistical analysis: Continuous variables are expressed as mean $\pm$ standard deviation. Continuous variables were compared by the Student's *t*-test and Mann Whitney test where appropriate. Categorical variables were compared by the Pearson chi-square or Fisher's exact test. Statistical significance was defined as a *P* value below 0.05.

RESULTS

One hundred and forty-two patients made up the whole study population. The baseline characteristics, which are shown in Table I, were similar in the two treatment groups. Other clinical variables are detailed in Table II. The 10-hour troponin T value was above the upper limit of normal (>0.1 ng/mL) in 17 (25%) and 21 (29%) patients in the enoxaparin and dalteparin groups, respectively ($P > 0.05$). The accompanying medical treatment, also shown in Table II, did not differ between the two groups. All study patients received 300 mg ASA daily. None received ticlopidine. Forty-four (64%) patients in the enoxaparin group and 48 (66%) in the dalteparin group received clopidogrel. Coronary angiography performed at the completion of the study in 130 patients revealed multivessel disease in 43 (72%) and 49 (70%) of patients in the enoxaparin and dalteparin groups, respectively.

At 5 days, there were no deaths or cardiac arrest in any patient in either group. Myocardial infarction occurred in 3 patients in the dalteparin group (4%). Angina recurrence that prompted urgent intervention occurred in 11 patients in

Table I. Baseline Characteristics of the Study Population

Characteristic	Enoxaparin group (<i>n</i> = 69)	Dalteparin group (<i>n</i> = 73)	<i>P</i>
Age [years]	60.3±11.9	59.6±10.3	>0.05
Weight [kg]	81.9±13.4	80.6±16.1	>0.05
Sex [m/f]	53/16	54/19	>0.05
Risk factors [number (%)]			
Hypertension	42 (61)	48 (66)	>0.05
Diabetes Mellitus	19 (27)	12 (26)	>0.05
Smoking	42 (61)	43 (59)	>0.05
Dyslipidemia	36 (52)	21 (45)	>0.05
Family history	28 (41)	21 (29)	>0.05
History [number (%)]			
Prior cardiac cath.	35 (51)	33 (45)	>0.05
Prior MI	28 (41)	26 (36)	>0.05
Prior CABG	20 (29)	16 (22)	>0.05
Prior PTCA	23 (33)	8 (11)	>0.05
ECG at presentation [number (%)]			
Normal	6 (8)	3 (4)	>0.05
ST depression	11 (16)	10 (14)	>0.05
T inversion	41 (60)	44 (60)	>0.05
Both T inv. + ST depr.	11 (16)	16 (22)	>0.05
Initial Diagnosis [number (%)]			
Unstable angina	52 (75)	52 (71)	>0.05
Non-Q MI	17 (25)	21 (29)	>0.05

Table II. Other Clinical Variables

Variable	Enoxaparin group (<i>n</i> = 69)	Dalteparin group (<i>n</i> = 73)	<i>P</i>
10-hour Troponin-T value [number (%)]			
>0.1 ng/mL	17 (25)	21 (29)	>0.05
<0.1 ng/mL	52 (75)	52 (71)	>0.05
Accompanying medications [number (%)]			
Aspirin	69 (100)	73 (100)	>0.05
Clopidogrel	44 (64)	48 (66)	
Beta blocker	39 (56)	49 (67)	>0.05
Nitrate	66 (96)	73 (100)	>0.05
ACE inhibitor	33 (48)	40 (55)	>0.05
Statin	28 (41)	29 (40)	>0.05
Insulin	8 (11)	5 (7)	>0.05
Coronary angiography [number (%)]			
Available	60 (87)	70 (96)	>0.05
Normal	3 (5)	2 (3)	>0.05
Single-vessel disease	14 (23)	19 (27)	>0.05
Multi-vessel disease	43 (72)	49 (70)	>0.05

the enoxaparin group and in 11 patients in the dalteparin group (16% vs 15%, $P>0.05$). Overall, any of the 3 events (death, MI, angina recurrence) occurred in 11 patients in the enoxaparin group and in 14 in the dalteparin group (16% versus 19%, $P>0.05$) during the study period (Table III).

The time to the occurrence of the first event was 82.3 ± 33.2 hours in the enoxaparin group and 37.6 ± 23.4 hours in the dalteparin group and the difference was significant ($P=0.007$).

No patients in either group experienced allergic reactions or thrombocytopenia. Major bleeding in the form of gastrointestinal bleeding that prompted 2 units of blood transfusion occurred in only one patient in the enoxaparin group. Minor bleeding (all injection site ecchymoses, except one patient in the enoxaparin group who developed mild and spontaneously resolving hematuria) was seen in 17 (25%) and 21 (29%) cases in the enoxaparin and dalteparin groups, respectively (Table III).

Table III. Clinical Events during 5 Day Follow-up

Event [number (%)]	Enoxaparin group (<i>n</i> = 69)	Dalteparin group (<i>n</i> = 73)	<i>P</i>
Death	0	0	>0.05
MI	0	3 (4)	>0.05
Recurrent angina	11 (16)	11 (15)	>0.05
Any one of above 3	11 (16)	14 (19)	>0.05
Allergic reaction	0	0	>0.05
Thrombocytopenia	0	0	>0.05
Bleeding			
Major	1 (1)	0	>0.05
Minor	17 (25)	21 (29)	>0.05

DISCUSSION

Unfractionated heparin consists of a heterogeneous mixture of saccharides and has a mean molecular weight of approximately 15,000 Da.¹⁴⁾ Binding of heparin to antithrombin III (AT III) results in the inactivation of thrombin (factor IIa), factor Xa, and factor IXa, resulting in its anticoagulant activity.¹⁵⁾ The ability of UFH to inhibit thrombin (anti factor IIa activity) is dependent on saccharide chain length and heparin molecules with less than 18 saccharide units [below critical length molecules (BCLM)] with a molecular weight below 5400 Da, are unable to catalyze factor IIa inactivation although they retain their ability to catalyze the inactivation of factor Xa.¹⁶⁾ Overall, standard UFH inhibits factor Xa and factor IIa in a 1:1 ratio.¹⁴⁾

Low-molecular-weight heparins are produced by either enzymatic or chemical depolymerization of UFH resulting in chains with a molecular weight between 4000-6500 Da with an average molecular weight of 5000 Da.^{5,14,17)} Similar to UFH, LMWHs exert their anticoagulant activity by activating AT III, but owing to their high content of BCLM, they have less ability to catalyze the inactivation of factor IIa when compared to that of factor Xa, yielding an antifactor Xa : antifactor IIa ratio above 1 and varying from 2:1 to 4:1 among different types of LMWHs.¹⁵⁾

Unfractionated heparin binds nonspecifically to plasma proteins, endothelial cells, and platelets and is sensitive to inactivation by platelet factor 4. In contrast, LMWHs are less frequently bound to plasma proteins, endothelial cells, and platelets and are resistant to inactivation by platelet factor 4. These properties improve their bioavailability and confer a more predictable anticoagulant activity which precludes laboratory monitoring that is necessary with UFH usage.¹⁶⁾

Evidence suggests that, in addition to the anti Xa and anti IIa activities, heparin and LMWHs may exert their antithrombotic effects by stimulating the

release of an endogenous tissue factor pathway inhibitor (TFPI).^{5,18-20} One may speculate that LMWHs may also release TFPI more efficiently than UFH owing to their higher bioavailability. Another potential mechanism by which LMWHs may exert their antithrombotic effect is through inhibition of the interaction of von Willebrand factor (vWF) with platelets resulting in reduced vWF dependent platelet adhesion and aggregation.^{21,22}

Three different LMWHs have been studied in acute coronary syndromes. The pharmacological properties of these compounds are shown in Table IV. Nadroparin was found to be superior to UFH in decreasing major and minor events in patients with UA within 5 to 7 days of treatment in a small randomized study.⁸ But a larger subsequent trial found nadroparin to be equal but not superior to UFH in the initial treatment of UA/NQMI.¹³ Another LMWH, dalteparin, was shown to be superior to placebo¹¹ but only equivalent to UFH¹² in the acute management of UA/NQMI. Two major trials with enoxaparin showed this agent to be better than UFH in preventing the occurrence of death/MI/recurrent angina in the acute phase of UA/NQMI.^{9,10} The differing results obtained from these studies could be explained by differences in pharmacological properties of the LMWH preparation used or may be related to differences in trial population and design, or to both. Of the 3 different LMWHs, enoxaparin has the highest percentage of BCLM which yields a high anti Xa : anti IIa ratio of 3.9. One might easily think that the clinical superiority of enoxaparin stems from this high ratio. However, the FRAX.I.S study¹³ demonstrated no superiority of nadroparin (a LMWH with an anti Xa : anti IIa ratio of 3.6, which is very close to that of enoxaparin) over UFH in UA/NQMI. Other properties like TFPI activity or vWF neutralizing activity,²³ or the potential to inhibit thrombin generation may also be important factors to influence clinical outcomes achieved with different LMWHs. Differences in pharmacokinetic properties may also be important. In a direct comparison of three LMWHs, enoxaparin was found to provide the fastest peak of anti Xa activity, the highest bioavailability, and the longest duration of anti Xa activity after SC injection compared with dalteparin and nadroparin.²⁴ But still the question remains as to whether these pharmacological differences translate into differ-

Table IV. Pharmacological Properties of Nadroparin, Enoxaparin, and Dalteparin

	Mean molecular weight (Da)	Anti Xa activity (IU/mg)	Anti IIa activity (IU/mg)	Anti Xa : IIa ratio
Nadroparin	4500	98	28	3.6
Dalteparin	6000	130	58	2.2
Enoxaparin	4200	98	25	3.9

ences in clinical efficacy. Another important factor that may influence the different clinical outcomes obtained with different types of LMWHs in UA/NQMI is the trial design and population used in these trials. Therefore, it is not possible to compare the effects of different LMWH molecules in the setting of UA/NQMI by looking at the results of all these trials that compare different LMWH preparations to either placebo or UFH under differing trial designs.

To our knowledge, our study is the first to head-to-head compare two different LMWH molecules in the setting of UA/NQMI. We chose to compare two LMWHs with considerably different anti Xa : anti IIa ratios, enoxaparin at one end and dalteparin at the other. Although the sample size is quite small to draw any firm conclusions, we found no difference between weight adjusted dalteparin and enoxaparin with regard to the occurrence of a triple endpoint of death, MI, and recurrent angina during the first 5 days of an acute coronary syndrome. The 16% rate of occurrence of the triple endpoint in the enoxaparin group in our study is similar to the 16.6% of the same endpoint at 14 days in the enoxaparin arm of the ESSENCE trial.⁹⁾ On the other hand, the FRIC trial,¹²⁾ which used the same triple endpoint as in our study, reported a 9.3% rate of any of the three events at 6 days in the dalteparin group, a rate that is considerably lower than the 19% rate of the same endpoint at 5 days in the dalteparin arm of our study. The UFH arm in the FRIC trial did even better (event rate 7.6%), though not statistically significant, than dalteparin. The majority of the events comprising the triple endpoint were recurrent angina in both of these trials and ours. Recurrent angina is not an objective and hard endpoint and moreover the definition may change from center to center and therefore these differing event rates may be ascribed to this factor. Slightly different endpoints were utilised in the FRISC and TIMI 11B trials. The rate of the combined endpoint of death/MI/urgent revascularization and IV heparin usage at 6 days was 5.4% and 10.3% in the dalteparin and placebo arms, respectively, of the FRISC trial.¹¹⁾ The combined endpoint of death/MI/urgent revascularization occurred in 12.4% of patients in the enoxaparin arm of the TIMI 11B trial.¹⁰⁾ These numbers, even those achieved by placebo in the FRISC trial, are considerably better than in our series and this can probably be ascribed to the absence of angina recurrence in the combined endpoint definition used in these two studies and also to the different patient inclusion criteria utilised. The inclusion criteria we used in our study were very similar to those used in the ESSENCE trial,⁹⁾ the results of which are quite similar to ours with respect to event rates in the enoxaparin arms.

Dalteparin and enoxaparin appeared to be equally safe with regard to bleeding complications, allergic reactions, and thrombocytopenia. The interesting finding in our study is that, although the triple endpoint occurred at similar frequencies in both groups, events comprising the endpoint were seen at a signifi-

cantly earlier time point in the dalteparin group. This may be a reflection of the superior pharmacokinetic profile of enoxaparin providing a faster peak of anti Xa activity and thus an earlier effective anticoagulant activity compared to dalteparin. We believe this point and the question of which LMWH should be the preferred one in the setting of UA/NQMI can only be clarified in a large-scale, prospective, multicenter randomized trial comparing different LMWHs.

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