Effects of Enoxaparin and Nadroparin on Major Cardiac Events in High-risk Unstable Angina Treated With a Glycoprotein IIb/IIIa Inhibitor

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SUMMARY

Clinical trials have reported the beneficial effects of platelet glycoprotein (GP) IIb/IIIa receptor antagonists and low-molecular-weight heparins (LMWH) on major cardiac events (MACE) in patients presenting with unstable angina or non-ST elevation myocardial infarction. A number of studies have documented the significant superiority of low-molecular-weight heparins, especially enoxaparin, over unfractionated heparin in the treatment of acute coronary syndromes. The purpose of this study was to compare the effects of two different LMWHs, enoxaparin and nadroparin, accompanied by platelet GP IIb/IIIa inhibition on MACE in high-risk unstable angina.

The study was designed as an open-label and observational study. Sixty-eight patients presenting with unstable angina associated with high-risk criteria were randomly assigned to treatment with enoxaparin plus tirofiban (36 patients, mean age 57 ± 11) or nadroparin plus tirofiban (32 patients, mean age: 58 ± 8). In-hospital MACE including acute myocardial infarction (AMI), recurrent refractory angina, death, stroke, and urgent revascularization were compared between the study groups.

Patient characteristics and durations of LMWH and tirofiban treatments were not different between the study groups. Coronary artery risk factors, except family history (which was observed more frequently in the enoxaparin group, $P = 0.02$), were also similar. MACE between the enoxaparin and nadroparin groups including AMI (5.5%, 6%), recurrent refractory angina (19%, 12%), death (0%, 3%), stroke (was not observed in either group), urgent revascularization (14%, 12%) and total MACE (19%, 15%) were not different.

Enoxaparin and nadroparin, accompanied by GP IIb/IIIa inhibitor therapy, have similar effects on the development of major cardiac events in patients presenting with unstable angina and high-risk characteristics. (Jpn Heart J 2003; 44: 899-906)

Key words: Unstable angina, Glycoprotein IIb/IIIa inhibition, Low molecular weight heparin, Major cardiac events

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RESULTS of prospective, randomized, controlled trials evaluating the role of low molecular weight heparin (LMWH) in the management of patients with unstable angina or non-ST elevation myocardial infarction have indicated improved outcomes compared with unfractionated heparin (UFH).[1-4] Management strategies for acute coronary syndromes are making increasing use of both low-molecular-weight heparins and glycoprotein (GP) IIb/IIIa inhibitors. There are theoretical grounds to expect LMWHs to be more effective than UFH in combination with GP IIb/IIIa inhibitors, since UFH, but not LMWH, activates platelets.[5] The antiplatelet effects of GP IIb/IIIa inhibitors are therefore likely to be both more potent and more predictable when combined with LMWH.[6] UFH treatment also has limitations compared to LMWHs like unpredictable anticoagulant effects necessitating frequent monitoring, low bioavailability due to a high rate of protein binding, thrombocytopenia, osteoporosis, and rebound effect after withdrawal of therapy.[7,8] Enoxaparin and nadroparin have each been shown to be superior or equal at reducing cardiac ischemic events compared to UFH in separate trials of patients with unstable angina and non-ST elevation myocardial infarction.[2-4,9] The differences between molecules of enoxaparin and nadroparin may result in different clinical efficacy and outcome particularly when combined with a GPIIb/IIIa inhibitor. To date, however, relatively few studies have compared the clinical outcomes of treatment with these two agents in combination with tirofiban, a GPIIb/IIIa inhibitor. The purpose of this study was to compare the effects of two different LMWHs, enoxaparin and nadroparin, accompanied by GP IIb/IIIa inhibition on MACE in a specific group of patients presenting with unstable angina and high-risk characteristics.

METHODS

Study population: Patients presenting with unstable angina associated with at least one of the following high-risk criteria: 1) Elevated cardiac markers (troponin T or I), 2) ST depression on ECG, 3) history of myocardial infarction, percutaneous coronary intervention, by-pass surgery, 4) prolonged rest angina (more than 10 minutes and $\geq$ 2 episodes within past 24 hours), were included in the study. Exclusion criteria were acute myocardial infarction with or without ST elevation, pulmonary edema, hypertension (continuously systolic BP $\geq$ 180 mmHg), hemodynamically significant valve disease, congenital heart disease, newly developed left bundle branch block, a history of platelet disorder or thrombocytopenia, high-risk of bleeding, and stroke within the previous year. In accordance with these criteria, 68 patients were included in the study. After informed consent was obtained the patients were randomly assigned to enoxaparin plus tirofiban (36 patients, mean age, 57 $\pm$ 11) or nadroparin plus tirofiban (32 patients, mean

age, 58 ± 8), and followed-up for the development of in-hospital MACE. The TIMI risk scores[10] of the study groups were also calculated in order to provide an objective assessment of the risk factors.

Treatment design: The study was conducted as an open-label and observational study. All patients received aspirin (100-300 mg/day, first dose being ≥ 325 mg), IV nitrate, and beta-blocker or calcium channel blocker in optimal tolerable doses. Tirofiban was infused as a bolus of 0.4 μg/kg/min for 30 minutes, followed by an infusion of 0.1 μg/kg/min for a minimum of 48 hours. Enoxaparin was administered at a dose of 1 mg/kg twice daily by SC injection, and nadroparin 87 IU/kg twice daily by SC injection. LMWH treatment was continued for at least 5 days in all patients. In case of a platelet count below 90,000/mm^3, or major bleeding, tirofiban, LMWH, and aspirin would be stopped, depending on the severity of the bleeding. The study was designed to compare the effects of LMWHs on medical stabilization and prevention of major ischemic events, therefore, early invasive intervention was not performed unless refractory angina developed despite adequate medication.

Major cardiac events: Major cardiac events including refractory angina, acute myocardial infarction, death, stroke, and urgent revascularization were the end points of the study. Recurrent angina was defined as chest pain that lasted more than 10 minutes, resistant to medical therapy, and/or accompanied by ECG and/or enzyme changes. Acute myocardial infarction was defined as elevation of serum CK-MB enzyme levels by two times the upper limit of normal, and/or occurrence of new Q waves. Additionally, major bleeding (decrease in hemoglobin > 2 g/dL or the need for transfusion), and minor bleeding (spontaneous hematomas, ecchymosis or bleeding at the puncture sites) were also recorded during the in-hospital period.

Statistical analysis: Quantitative variables are expressed as the mean and standard deviation (SD) and were compared using the two-tailed Student-*t* test. Qualitative variables are expressed as % and were compared by the chi-square or Fischer exact test, as appropriate. A *P* value less than 0.05 was considered significant.

RESULTS

The study groups were similar with respect to almost all pretreatment characteristics including gender, age, and risk factors for coronary artery disease (Table I). A family history of premature coronary artery disease was more frequent in the enoxaparin group ($P = 0.02$). The frequencies of relatively important risk factors such as diabetes mellitus, previous myocardial infarction, and previous revascularization procedures were greater in the nadroparin group, but were

not statistically significant. The TIMI risk scores were also found to be similar (4.0 ± 0.8 in the enoxaparin group vs 4.4 ± 1.2 in the nadroparin group, P = NS). ST depression and positive cardiac markers (troponin T or I) were present in the majority of patients (Table II). The interval between the beginning of the angina and initiation of treatment, and the duration of the LMWH, and tirofiban treatments were not statistically different (Table II).

The frequency of MACE including AMI, recurrent refractory angina, death, stroke (not observed in either group), urgent revascularization, and total MACE were not significantly different between the study groups (Table III). One patient died in the enoxaparin group due to cardiogenic shock following an anterior myocardial infarction. Major hemorrhage occurred only in one patient in the enoxaparin group (2.1%), which was a gastrointestinal hemorrhage that required 2 units of blood transfusion. Major hemorrhage did not occur in the nadroparin group. The frequency of minor hemorrhage was also similar between the study groups (6 patients (16%) in the enoxaparin group vs 8 patients (25%) in the nadroparin group) and a majority of the cases was due to ecchymoses at the subcutaneous injection site.

Table I. Patient Characteristics

	Enoxaparin *n*= 36 (%)	Nadroparin *n*= 32 (%)
Mean age (SD)	57 (11)	58 (8)
Male	30 (83)	28 (87)
Hypertension	18 (50)	20 (62)
Diabetes mellitus	8 (22)	6 (18)
Hyperlipidemia	19 (52)	15 (46)
Smoking	18 (50)	14 (43)
Family history of CAD	17 (47)*	8 (25)
ST depression	28 (77)	22 (68)
Positive troponin	32 (88)	28 (87)
Previous myocardial infarction	4 (11)	7 (22)
Previous revascularization	2 (5.5)	6 (18)
Previous aspirin therapy within prior 7 days	17 (47)	19 (59)

SD=standard deviation; CAD=coronary artery disease.
* P = 0.02

Table II. Mean Times Between the Beginning of Angina and Initiation of Treatment, and the Durations of Treatments

	Enoxaparin *n*= 36	Nadroparin *n*= 32
Mean time to treatment (h) (SD)	4.9 (3.8)	5.6 (4.0)
Mean duration of tirofiban therapy (h) (SD)	60 (20)	63 (25)
Mean duration of LMWH therapy (d) (SD)	5.9 (2.1)	6.4 (2.4)

LMWH = low molecular weight heparin; h = hour; d = day; SD = standard deviation.

Table III. Frequency of Major Cardiac Events

	Enoxaparin *n* = 36 (%)	Nadroparin *n* = 32 (%)
Acute myocardial infarction	2 (5.5)	2 (6)
Recurrent refractory angina	7 (19)	4 (12)
Death	0 (0)	1 (3)
Stroke	0 (0)	0 (0)
Urgent revascularization	5 (14)	4 (12)
Total MACE	7 (19)	5 (15)

MACE = major cardiac events.

DISCUSSION

Randomized studies have shown that administration of GP IIb/IIIa receptor antagonists provides a significant reduction in morbidity and mortality in patients with UA and non-ST elevation MI with or without early invasive intervention.[11-14] A number of studies have been performed in order to assess the efficacy and safety of different anticoagulant agents in acute coronary syndromes. A majority of these studies have been designed to compare standard heparin versus one of the low molecular weight heparins, and in almost all these studies LMWHs, especially enoxaparin, have been found to be superior to standard heparin. Two recent large studies with enoxaparin have shown that this agent significantly reduces the risk of major ischemic events compared with UFH.[3,4] In the TIMI 11B study, enoxaparin was associated with a significant reduction in the risk of death, myocardial infarction, or urgent revascularization compared with unfractionated heparin.[3] In the ESSENCE study, treatment with enoxaparin for 2 to 8 days reduced the risk of death, myocardial infarction, or recurrent angina by 20% at 14 days compared with treatment with UFH.[4] A meta-analysis of these two studies showed that the risk of death or MI was consistently approximately 20% lower in enoxaparin-treated patients than heparin-treated patients.[15]

In contrast, studies with other LMWHs have not shown consistent superiority over unfractionated heparin. This may reflect the pharmacological heterogeneity of LMWH and/or differences in trial design. The other study drug, nadroparin, has been compared with UFH in two large studies: Gurfinkel, *et al*[2] showed that nadroparin was more effective than heparin in reducing adverse clinical outcomes, including myocardial infarction, but the results of the FRAX.I.S. study[9] which has been conducted in a larger patient population, indicated that there were no differences with regards to the primary combined end point of car-

diovascular death, MI, and recurrent/refractory angina at 14 days between the nadroparin and UFH groups.

On the other hand, it is still not clear "which LMWH is better". Regarding treatment issues, there is no differentiation between the available LMWHs in the final graded recommendations of the sixth American College of Chest Physicians' Consensus.[16] The European perspective on this issue states that enoxaparin and dalteparin can be considered as first-choice agents for unstable angina.[17]

To the best of our knowledge, the current study is the first study comparing enoxaparin and nadroparin combined with tirofiban therapy in high-risk unstable angina. The preference of tirofiban as a study drug instead of the other available GP IIb/IIIa inhibitors was mainly based on the results of major clinical trials, especially the TARGET and GUSTO IV-ACS trials.[18,19] Although earlier results from the TARGET trial showed that abciximab was significantly better than tirofiban at preventing death, myocardial infarction, and repeat surgery within 30 days after coronary-artery angioplasty,[18] at 6th months, tirofiban provided a similar level of overall protection to abciximab against the composite of death, myocardial infarction, and target-vessel revascularisation.[20] Additionally, the GUSTO IV-ACS trial indicated that abciximab was not beneficial as a first-line medical treatment in patients admitted with acute coronary syndromes who were not undergoing early revascularisation.[19] Possible causes of discrepancies between the results of the GUSTO IV and other studies include differences in trial design, patient populations, dosing regimens, and possibly the biological profile among all three GP IIb/IIIa inhibitors. Recently, a new meta-analysis that pooled the results of all large randomized trials designed to study the clinical efficacy and safety of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularisation has showed a modest but significant reduction in death and MI.[21] Accordingly, tirofiban was one of the appropriate drugs for use in our study designed to treat patients without early intervention. In this study, enoxaparin and nadroparin showed similar impacts on the development of major cardiac events. The frequency of the most important end points, MI and death, were similar. Only one death occurred in the enoxaparin group due to cardiogenic shock following anterior myocardial infarction. Stroke was not observed in either group. The most frequent ischemic event was the recurrent refractory angina in both groups and almost all of those patients underwent urgent revascularization following coronary angiography.

Although there are important limitations (eg, limited number of patients, open-label drugs), the study consisted of a rather specific group of patients with high-risk characteristics. Patients with non-ST elevation myocardial infarction were excluded, which was the major difference from other studies performed in

ACS. There is similarity in both acute coronary events with regard to the underlying pathophysiologic mechanism, but when comparing to unstable angina, the non-ST elevation myocardial infarction constitutes higher risk for the development of MACE. The demographic characteristics of the patients were quite similar, except the family history of coronary artery disease, and we thought that it was not a "hard" risk factor with regard to an effect on the incidence of MACE. The frequency of important risk factors such as diabetes mellitus, previous MI, and previous revascularization procedures were relatively more frequent in the nadroparin group, but were not statistically significant. The TIMI risk scores, which is a more objective method than comparison of each risk factor separately, were also similar. These homogeneous characteristics of the patients may increase the power of the study.

Major hemorrhage occurred only in one patient in the enoxaparin group and the frequency of minor hemorrhage was similar between the study groups. A majority of the minor hemorrhage cases was due to ecchymosis at the subcutaneous injection site. We may conclude that both enoxaparin and nadroparin combined with GP IIb/IIIa receptor antagonists can be used safely in combination.

In conclusion, the results of the study suggest that enoxaparin and nadroparin, accompanied by GP IIb/IIIa inhibitor therapy, have similar effects on the development of major cardiac events in patients presenting with unstable angina and high-risk characteristics, and both LMWHs can be used in combination with a platelet GP IIb/IIIa inhibitor for the treatment of patients with acute coronary syndromes. Prospective, randomized studies evaluating the effects of different LMWHs in a larger patient population are needed to determine the one that is most superior.

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