Once-daily nadroparin versus twice-daily nadroparin in the treatment of patients with acute coronary syndromes

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Aim: We performed a randomised, open-labelled, pilot study to determine whether once-daily nadroparin at double concentration could be as safe and effective as twice-daily nadroparin at standard concentration for the treatment of non-ST elevation acute coronary syndromes (the SAFRAX study).

Patients and methods: A total of 710 patients subcutaneously received, either once-daily nadroparin (19,000 anti-Xa IU/mL), or twice-daily nadroparin (9,500 anti-Xa IU/mL) according to body weight for three days. Major haemorrhages occurred in six (1.6%) patients in the once-daily group and three (0.9%) patients in the twice-daily group (p = 0.51). The respective incidences of the composite efficacy endpoint in the once-daily and twice-daily groups were 16.9% (62/366) and 17.4% (60/344) (p = 0.86).

Results and conclusion: Thus, once-daily nadroparin is as safe and effective as twice-daily nadroparin in the treatment of patients with acute coronary syndromes.
Key words: Acute coronary syndrome – Low-molecular-weight heparin

HRICÁK V, LEIZOROVICZ A **Jedna denná dávka nadroparínu versus dvojitá denná dávka nadroparínu pri liečbe pacientov s akútnymi koronárnymi syndrómami.** Cardiol 2007;16(4):158–160

Cieľ: Uskutočnili sme otvorenú pilotnú štúdiu, ktorá porovnávala bezpečnosť a účinnosť liečby akútnych koronárnych syndrómov bez elevácie segmentu ST v EKG obraze, heparínom s nízko molekulárnou hmotnosťou – nadroparínom podkožne v jednej dennej dávke v dvojitej koncentrácii oproti nadroparínu v dvoch denných dávkach v štandardnej koncentrácii (štúdia SAFRAX).

Pacienti a metódy: Celkovo bolo liečených 710 pacientov tri dni buď jedinou dávkou nadroparínu (19 000 anti-Xa IU/mL), alebo v dvoch denných dávkach (9 500 anti-Xa IU/mL) podľa hmotnosti. Veľké krvácavé komplikácie vznikli u šiestich pacientov (1,6 %) v skupine jedinej dávky nadroparínu oproti trom pacientom (0,9 %) liečeným nadroparínom v dvoch denných dávkach (p = 0,51). Kombinovaný kardiovaskulárny ukazovateľ ("endpoint") účinnosti liečby bol v skupine pacientov liečených jedinou dávkou 16,9 % (62/366) oproti 17,4 % (60/344) pacientom liečených v dvoch denných dávkach (p = 0,86).

Výsledky a záver: V našej pilotnej štúdii bola jedna celodenná dávka nadroparínu rovnako bezpečná a účinná ako doterajšie štandardné dávkovanie nadroparínu v dvoch denných dávkach pri liečbe pacientov s akútnym koronárnym syndrómom bez elevácie segmentu ST.
Kľúčové slová: akútny koronárny syndróm – heparín s nízkou molekulárnou hmotnosťou

Introduction

Low-molecular-weight heparins have proved their efficacy and safety in the management of patients with acute coronary syndromes without ST elevation (1, 2). However, where as all studies performed to date have employed a twice-daily (bid) injection regimen, a once-daily (od) injection should further simplify the management of patients with an acute coronary syndrome.

The FRAX.I.S. trial showed that bid nadroparin was at least as effective and safe as unfractionated heparin in the treatment of unstable angina and non-Q-wave myocardial infarction (3). A more concentrated form of nadroparin has been developed in order to allow an od regimen (4). Once-daily subcutaneous nadroparin at double concentration was as effective and safe as bid subcutaneous nadroparin at standard concentration for the treatment of deep-vein thrombosis (5). We performed a prospective, international, multicentre, randomised, open-labelled, pilot trial to test whether od nadroparin at double concentration is as safe and effective as bid nadroparin at standard concentration for the treatment of non-ST elevation acute coronary syndromes.

Material and Methods

Patients

Patients aged over 19 years with rest or severe effort angina in the previous 48 hours associated with electrocardiographic signs compatible with the clinical diagnosis of unstable angina or non-ST elevation myocardial infarction, or with positive qualitative cardiac troponin I or quantitative troponin T test, or with known coronary

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disease in case of pre-existing and documented left bundle branch block, were considered for inclusion. Patients were excluded if in particular they presented ST segment elevation of more than 0.1 mV in two consecutive leads.

Study design

The trial was a randomised, open-labelled study conducted in 47 centres in 11 countries. Patients were randomised to receive subcutaneous nadroparin according to two dosing regimens, either od injections of nadroparin at 19,000 anti-Xa IU/mL (Fraxiparine® Forte/Fraxodi®, GlaxoSmithKline) or bid injections of nadroparin at 9,500 anti-Xa IU/mL (Fraxiparine®, GlaxoSmithKline). For both groups, the injection volume was 0.6 mL in patients below 70 kg; 0.8 mL in patients between 70 and 90 kg; and 1.0 mL in patients above 90 kg. Treatment was scheduled to last three days; if necessary, it could be prolonged for up to five days. All patients received aspirin (up to 325 mg per day). Antiplatelet agents other than aspirin could be used. Patients were followed up for 30 days. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by independent ethics committees and written informed consent was obtained from all patients before randomisation.

Study endpoints

The primary study endpoint was a composite of major and minor haemorrhages and severe thrombocytopenia at 30 days. All events reported by the investigator were blindly categorised and validated by the study monitor.

The efficacy endpoint was the combined incidence of recurrent/refractory angina, myocardial infarction, or atheromatous or cardiovascular death at 30 days.

Statistical analysis

Safety and efficacy analyses were by intention-to-treat. Data were processed and analysed by the SAS-Windows™ software (version 8.2). A p value of less than 0.05 (two-tailed) was considered to indicate statistical significance.

Results

Study population

A total of 710 patients were recruited, randomised and treated between November 2001 and March 2003. The median age was 63.6 years; 58% of patients were men. Regarding the diagnostic features, 66.9% of patients had ST segment depression, 5.7% had ST segment elevation in two or more leads, and 27.0% had a positive troponin test.

Medications

The median duration of treatment for both dosing regimens was 4.0 days. Aspirin was given to 86.3% (n = 613) of patients, clopidogrel or ticlopidine to 34.2% (n = 243), and platelet glycoprotein IIb/IIIa inhibitors to 1.4% (n = 10). The two study groups were equivalent in terms of the number of patients receiving these treatments or other major cardiovascular treatments.

Safety

No patients in either study groups experienced major haemorrhage, minor haemorrhage and severe thrombocytopenia all together (**Table 1**). There were no statis-

Table 1 Safety and efficacy results at 30 days

	Once-daily nadroparin N = 366	Twice-daily nadroparin N = 344	p value
Primary endpoint: Combined safety events, n (%)	0 (0)	0 (0)	–
Major haemorrhage only	6 (1.6)	3 (0.9)	0.51
Major haemorrhage during study treatment (plus one calendar day)	2 (0.6)	2 (0.6)	1.0
Minor haemorrhage only	24 (6.6)	21 (6.1)	0.80
Minor haemorrhage during study treatment (plus one calendar day)	13 (3.6)	13 (3.8)	0.87
Severe thrombocytopenia	0 (0)	0 (0)	–
Combined cardiovascular events, n (%)	62 (16.9)	60 (17.4)	0.86
Refractory/recurrent angina	42 (11.5)	28 (8.1)	0.14
Myocardial infarction	16 (4.4)	27 (7.9)	0.052
Atheromatous or cardiovascular death	11 (3.0)	16 (4.7)	0.25

tical differences in the rates of major haemorrhage or minor haemorrhage in the two groups. Overall, one major haemorrhage (in the od group) was fatal; other major haemorrhagic events were bleedings requiring transfusion, or symptomatic bleedings associated with a decrease in haemoglobin of more than 2 g/dL.

Efficacy

The incidences of combined refractory/recurrent angina, myocardial infarction, or atheromatous or cardiovascular death in the od and bid nadroparin groups were comparable. At 30 days, 3.8% (14/366) of patients in the od group and 5.8% (20/344) of patients in the bid group had died.

Conclusion

This is the first randomised trial in which an od low-molecular-weight heparin dosing regimen was tested in the treatment of acute coronary syndromes. No differences in safety and efficacy between od and bid nadroparin dosing regimens were detected. Compared with the bid dosing regimen, the od dosing regimen may be advantageous in terms of convenience for both the patients and the healthcare team. The safety of this dosing regimen should be further confirmed in patients being managed according to an early invasive strategy.

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