Efficacy and Tolerability of a Very Low Molecular Weight Heparin Compared with Standard Heparin in Patients with Unstable Angina: A Pilot Study

ANNA VITTORIA MATTIOLI, M.D., EMMA TARABINI CASTELLANI, M.D., LAVINIA GOEDECKE, M.D., LUCA SORMANI, M.D.,
SABINA STERNIERI, M.D., GIORGIO MATTIOLI, M.D.

Department of Cardiology, University of Modena, Modena, Italy

Summary

Background: Unstable angina is an active thrombotic process that involves thrombus formation and platelets. It requires a rapid and intensive treatment with anticoagulants and antiplatelets.

Hypothesis: The aim of the present study was to compare the efficacy of a very low molecular weight heparin, OP 2000, with standard heparin in the treatment of unstable angina. Tolerance and safety were also assessed.

Methods: The study population included 120 consecutive hospitalized patients with unstable angina randomized for treatment with very low molecular weight heparin or with standard heparin. The dosage of the study drug was 200 mg intramuscular (IM) the first day followed by 150 mg IM/day. The control drug was standard heparin starting at a dosage of 5,000 UI/ml intravenously (IV) and followed by continuous infusion at an activated partial thromboplastin time-adjusted dosage. The primary end points were death, acute myocardial infarction, urgent revascularization, and recurrence of angina. Tolerability was assessed using bleeding parameters, thrombocytopenia, and allergic reactions.

Results: Fourteen clinical events were reported in the study group compared with 25 events in the control group ($p < 0.05$). No adverse events were reported in either group.

Conclusion: During the acute phase of unstable angina, treatment with a very low molecular weight heparin plus aspirin was more effective than treatment with standard heparin plus aspirin.

Key words: unstable angina, heparin, very low molecular heparin

Introduction

Unstable angina is a clinical syndrome that presents with chest pain resulting from an active intracoronary process.^{1,2} The treatment of unstable angina includes the administration of both heparin and aspirin, which have the theoretical advantage of increasing the effects of anticoagulants and antiplatelets.³ This combination reduces the recurrence of pain symptoms if heparin administration has to be suspended.⁴ Low molecular weight heparin and fractionated heparin are assuming an increasingly important role in the treatment of unstable angina.^{5,6} A very low molecular weight heparin (OP 2000) has recently been isolated.⁷ It has high antifactor Xa and antithrombin activities similar to those of low molecular weight heparin. It may act on platelets and reduces thrombin-induced platelet aggregability as well as fibrinogen levels in patients with coronary artery disease.^{8,9}

This study was designed to compare the efficacy and tolerability of OP 2000 with standard heparin in patients with unstable angina.

Methods

Study Population

This study analyzed 120 patients aged ≥ 18 years (79 men, 41 women, mean age 67.09 ± 10 years, range 42–92 years) suffering from unstable angina. Patients were randomized into two groups of treatment.

Clinical characteristics of the patients are shown in Table I.

Study Design

The study was an open-label, randomized, parallel group trial.

Patients with confirmed unstable angina were randomized to treatment with a daily fixed dose of very low molecular weight heparin OP 2000 or standard heparin therapy.

Address for reprints:

Anna Vittoria Mattioli, M.D.
Department of Cardiology
University of Modena
Policlinico - Via del Pozzo, 71
41100 Modena, Italy

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TABLE I Baseline characteristics for all randomized patients

Characteristics	OP 2000 (n = 60)	Heparin (n = 60)
Age (years) (range)	67.31 ± 10.66 (49–92)	66.8 ± 12.01 (42–89)
Male (%)	30 (50)	49 (81)
Previous infarct (%)	16 (26)	24 (40)
History of hypertension (%)	31 (51)	21 (35)
Diabetes (%)	3 (5)	7 (11)
Hypercholesterolemia (%)	9 (15)	13 (21)
Systolic blood pressure (mmHg) (range)	145.2 ± 21.82 (100–200)	132.72 ± 21.70 (90–190)
Diastolic blood pressure (mmHg) (range)	80.31 ± 12.78 (54–110)	78.68 ± 12.61 (56–110)
Heart rate (beats/min) (range)	75.75 ± 13.09 (48–110)	77.02 ± 13.94 (55–120)

The study was performed in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the University. All patients gave written informed consent and met inclusion and exclusion criteria.

Patient Selection

The study began in November 1995 and ended in April 1996.

Consecutive patients ≥ 18 years of age with unstable angina admitted to the Coronary Care Unit with the last episode of pain within 60 h before the start of treatment were eligible for randomization. Patients were included if they fulfilled at least one of the following criteria: (1) Newly developed angina pectoris during the last 2 months, (2) increased angina pectoris during the last 2 months, (3) ongoing chest pain suggesting myocardial infarction, and at least one of the following electrocardiographic (ECG) criteria without any explanation other than myocardial ischemia: (a) A new ST-segment depression of at least 0.1 mV (> 1 mm) in at least two adjacent leads (irrespective of T-wave changes), and (b) temporary or manifest T-wave inversion of at least 0.1 mV (> 1 mm) below the baseline in at least two adjacent leads.

Exclusion criteria were defined as increased risk for bleeding, cerebral vascular episode during the last 3 months, ulcer or known gastrointestinal bleeding in progress, surgery performed during the previous week, or a known defect of hemostasis: thrombocytopenia (< 100 × 10⁹/l); anemia (male: Hb < 12.5 g/l; female Hb < 11 g/l); renal insufficiency; hepatic insufficiency; indication for thrombolytic therapy; newly developed pathologic Q wave; left bundle-branch block or pacemaker present; suspect endocarditis, myocarditis, or pericarditis; known primary myocardial disease; dilative, hypertrophic, or obstructive cardiomyopathy; aortic valvular disease of hemodynamic significance; planned, elective percutaneous transluminal coronary angioplasty (PTCA), coronary bypass surgery (CABG), or surgery performed within the past 3 weeks; malignant hypertension; hypotension with systolic pressure < 90 mmHg; known hypersensitivity to standard or low molecular weight heparin; shock in progress; malignant tumors; pregnancy or breast-feeding; and presence of IgG antiplatelet antibodies.

Treatment Regimen

In patients randomized to OP 2000, treatment began with a single intramuscular injection of 200 mg on Day 1 followed by a dosage of 150 mg/day.

Antifactor Xa (anti-FXa) activity was assessed in the population treated with OP 2000. Assessment was carried out 0, 3, 12, 24, 27, 48, 51, 72, 96, 120, and 123 h after the initial administration of the drug.

Patients randomized to standard heparin treatment received an intravenous bolus injection of 5000 IU/ml standard heparin followed by continuous intravenous infusion [20,000–40,000 IU/day, at a dosage adjusted to maintain an activated partial thromboplastin time (APTT) between 1.5 and 3 times the upper reference value of the center]. Activated partial thromboplastin time was measured at baseline and 4 to 6 h after initiation of the study and checked twice a day. Plasma samples for measurements of anti-FXa activity were taken from the OP 2000-treated patients on the first 6 consecutive days. The study therapy was administered for a minimum of 48 h to a maximum of 8 days. It was discontinued at the time of discharge from the hospital, or if the patient developed a new myocardial infarction, underwent a revascularization procedure, or did not survive.

Concomitant Treatment

In all patients, aspirin (100 mg/day) was administered on the same day as heparin. All patients also received nitroglycerin infusion during the acute phase (20–40 cc/h). Beta blockers, nitrates, calcium antagonists, and similar drugs could also be used.

Primary End Points

The primary end points were incidence of death, myocardial infarction, recurrence of angina, and urgent revascularization. The cause of death was determined.

Myocardial infarction was confirmed by the development of new Q waves or non-Q-wave diagnostic ECG changes associated with a significantly increased levels of creatine kinase-MB fraction > 50 IU/l (normal reference range 0–25 IU/l).

Urgent revascularization (PTCA or CABG) was deemed necessary if clinical symptoms persisted uncontrolled despite a full medical schedule (anticoagulants and antiplatelets agents, beta blockers, calcium-channel antagonists, and nitroglycerin IV), and/or if ECG changes occurred.

Recurrent angina was defined as chest pain at rest lasting > 10 min associated with a new ST-segment shift (elevation or depression) or T-wave inversions, in two contiguous ECG leads, but under an appropriate anti-ischemic schedule, with a heart rate < 60 beats/min and systolic blood pressure < 130 mmHg.

Patients who achieved one primary end point were included in the primary efficacy evaluation.

Adverse events considered included major bleeding defined as a hemorrhagic event leading to death, interruption of treatment or blood transfusion, or causing a fall in hemoglobin of > 30 g/l; reduction of platelet count to < 150,000/mm³; and serious allergic reactions.

Tolerability of OP 2000

The end point was to compare the tolerability of nonfractionated heparin and OP 2000. The comparison included hepatotoxicity, assessed as an increase in transaminase (ALT and AST) and bilirubinemia, thrombocytopenia, allergies, major and minor hemorrhages, and thrombocytopenic thrombosis.

Statistical Analysis

Analysis was based on intention to treat. The statistical description of the quantitative data was summarized by mean, standard deviation, the maximum, the minimum, and the median. Qualitative variables were described by a frequency table. The frequency of events was compared using the Mantel-Haenszel test. The incidences were described by calculation of 95% confidence intervals (CI). The time of an event was studied using survival techniques. Quantitative variables were compared by using a two-sided test with a significance level of $p < 0.05$. Qualitative variables were assessed by comparing proportions.

Results

Of the 335 patients with angina who were evaluated for entry into the study between November 1995 and April 1996, 215 did not meet the criteria for eligibility. Of the remaining 120 patients, 60 (Group A) were randomly assigned to receive standard heparin and 60 (Group B) to receive OP 2000. The two groups were comparable in terms of baseline patient characteristics (Table I). However, there was a significantly greater number of women in Group B (30 vs. 11). There was no significant difference in cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia).

Previous myocardial infarction was statistically more frequent in the Group A ($p = 0.02$).

Electrocardiographic features on entry were comparable in the two groups. Laboratory data at enrollment showed no difference between the two groups.

The differences in Hb and erythrocytes can be attributed exclusively to differences between the genders. Platelets, ALT, and AST were measured at enrollment and after 6 days. At enrollment, no differences between the groups were evident.

At baseline, there was no difference in mean APTT value between the groups.

The ability of unfractionated heparin to maintain APTT in the therapeutic range was assessed: within 12 to 24 h, 50% of patients treated with unfractionated heparin had an APTT between 2 and 3 times the upper value and 25% of patients had an APTT between 1.5 and 2. OP 2000 produced a mean anti-FXa activity of 0.8, 0.9, and 0.94 IU on Days 2, 3, and 6, respectively. The time to peak anti-FXa activity was between 3 and 4 h.

Primary End Points

Major events occurred in 41.6% of patients in Group A and in 23.3% of patients in Group B. Events were significantly less frequent in Group B than in Group A (odds ratio 2.3, 95% CI 1–5.25, $p < 0.05$) (Fig. 1). Acute myocardial infarction occurred in two patients in Group A and in none in Group B. Recurrent angina occurred in 20 patients in Group A and in 10 patients in Group B ($p < 0.05$). Urgent revascularization was performed in three patients (5%) in Group A and in four in Group B (6%) ($p = \text{NS}$). There were no deaths in any group.

Electrocardiographic Evaluation

In Group A, ECG remained unchanged in 24% of cases, improved in 36%, and worsened in 40%. In Group B, ECG remained unchanged in 23% of cases, improved in 50%, and worsened in 27%.

Safety Evaluation

At baseline, levels of AST did not differ in the two groups examined (Group A, 28.5 ± 9.7 vs. Group B, 36.7 ± 6.4 , $p = \text{NS}$).

FIG. 1 Event-free curves in the two groups of patients. —○— = Heparin, --▲-- = OP 2000.

FIG. 2 Comparison between platelet count at baseline (■) and after 2 (■) and 6 (■) days in the two groups of patients.

After 6 days of treatment, there was a significant increase in AST with respect to baseline values in the patients treated with standard heparin (Group A, 28.5 ± 9.7 vs. 50.8 ± 4.50 , $p < 0.05$, Group B, 36.7 ± 6.4 vs. 49 ± 5.2 , $p = \text{NS}$).

At enrollment, levels of ALT did not differ in the two groups (Group A, 27 ± 6.5 vs. Group B, 22 ± 5.4 , $p = \text{NS}$). After 6 days of treatment, there was a significant increase in ALT in the group treated with heparin (Group A, 27 ± 4 vs. 42 ± 3.4 , $p < 0.05$; Group B, 22 ± 11.4 vs. 41 ± 9.8 , $p = \text{NS}$).

Similarly, we observed a statistically significant reduction in platelet count in Group A [heparin 185 ± 56 vs. 171 ± 33 (Day 2) vs. 168 ± 23 (Day 6), $p < 0.05$; OP 2000 216 ± 56 vs. 205 ± 47 (Day 2) vs. 229 ± 66 (Day 6), $p = \text{NS}$]. Platelet count never fell below the threshold of $150,000 \text{ mm}^3$ (Fig. 2).

Assessment of Tolerance

No adverse events were reported by patients or observed by the medical staff. In no case was it necessary to suspend treatment as a result of negative side effects. Treatment was suspended in four patients in Group B and in two patients in Group A because consent was withdrawn.

Discussion

The objective of this study was to assess the efficacy and safety of OP 2000, given once a day in comparison with a continuous dose-adjusted infusion of standard heparin in patients with unstable angina. The two treatment groups were similar in their baseline characteristics, except for the prevalence of women. Other factors, such as previous myocardial infarction, were significantly higher in Group A.

Patients with unstable angina developed cardiovascular events in the first 5–7 days following appearance of symptoms.^{1,2}

The study provided evidence that fixed-dose, intramuscular OP 2000, given once a day, is equivalent or potentially better than unfractionated heparin therapy in terms of cardiovascular events occurring during the acute phase of unstable angina.

Patients in Group B presented events during hospitalization in 23.3% of cases, while Group A patients presented events in approximately 41.6% of cases.

The usefulness of unfractionated heparin in unstable angina is well documented.^{3,10} The heparin treatment presents many difficulties because the dose–response ratio is not constant.¹¹ Recent reports suggested that heparin frequently falls to a sub-therapeutic range¹² as reflected by APTT times. Heparin is also influenced by different substances.

Recent reports suggest that low molecular weight heparin reduces cardiovascular events during hospitalization in patients with unstable angina.^{13–15} The effectiveness is similar to the combination of heparin and acetylsalicylic acid (ASA, aspirin) and greater than heparin or ASA alone.¹⁶ The advantage of low molecular weight heparin is the lower incidence of side effects, particularly in comparison with standard heparin.

Low molecular weight heparins are, in fact, extremely easy to use and have the advantage that they can be administered in single or double doses, as the dose–response ratio is constant.

We tested a very low molecular weight heparin, OP 2000, which has a specific anti-FXa effect. OP 2000 has no particular effect on APTT, but its effectiveness can be monitored by assessing the FXa response. Pharmacokinetic studies on small groups of patients compared with a normal population using 100 mg, 150 mg, and 200 mg regimens have shown that maximum therapeutic effectiveness is obtained with a dose of 150 mg, with a reduction in the incidence of side effects. This dose was effective in a randomized study compared with unfractionated heparin in patients with unstable angina.^{6,7} Toxicity studies have shown that the drug causes no significant changes in hepatic enzymes and thrombocytopenia.¹⁷

An increase in transaminase levels occurs in almost all patients treated with bovine or pig heparin.^{18,19} The increase occurs more frequently in men. The mechanism underlying the increase is unknown. This effect was not observed in patients treated with OP 2000.

The presumed heparin-induced liver damage is dose dependent and is not accompanied by allergotoxic phenomena, which tends to exclude an allergic mechanism. Another possible interpretation is that heparin exercises its toxic action by a metabolic conversion in the endoplasmic reticulum, causing alkylates and arylates to bind with molecules within the hepatocyte, resulting in cell death.^{18,19}

Limitation of the Study

The present study demonstrated the safety of a very low molecular weight heparin in patients with unstable angina. Because of the chemical characteristics of the drugs, we do not blind physicians for logistic reasons.

An original project included a higher number of patients to obtain a significant reduction of events. An interim analysis was performed and revealed an unexpected reduction of ischemic events in Group B. The termination of this pilot study on the basis of the analysis could be considered an important limitation. A multicenter study is now in progress.

Conclusion

Our findings show that patients with unstable angina can be treated effectively and safely with a fixed, once-daily dose of OP 2000. Since the need for intravenous infusion and repeated laboratory monitoring is negated with this therapeutic regimen, this strategy has important implications in terms of reducing the cost of treatment.

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