USE OF THE LOW-MOLECULAR-WEIGHT HEPARIN REVIPARIN TO PREVENT DEEP-VEIN THROMBOSIS AFTER LEG INJURY REQUIRING IMMOBILIZATION

MICHAEL R. LAUSEN, M.D., LARS C. BORRIS, M.D., AND ROUMEN L. NAKOV, M.D., PH.D.

ABSTRACT

Background Deep-vein thrombosis is a well-recognized complication after trauma to the legs and subsequent immobilization, but there are no generally accepted approaches to preventing this complication.

Methods We performed a prospective, double-blind, placebo-controlled trial to evaluate the efficacy and safety of subcutaneous reviparin (1750 anti-Xa units given once daily) in 440 patients who required immobilization in a plaster cast or brace for at least five weeks after a leg fracture or rupture of the Achilles tendon. The study drug was given throughout the period of immobilization. Venography of the injured leg was performed within one week after removal of the plaster cast or brace, or earlier if there were symptoms suggesting deep-vein thrombosis.

Results Data on efficacy and end points were available for 371 patients. Deep-vein thrombosis was diagnosed in 17 of the 183 patients randomly assigned to receive reviparin (9 percent) and in 35 of the 188 patients randomly assigned to receive placebo (19 percent) (odds ratio, 0.45; 95 percent confidence interval, 0.24 to 0.82). Most of the thromboses were distal (14 in the reviparin group and 25 in the placebo group). There were two cases of pulmonary embolism, both in patients in the placebo group who also had proximal deep-vein thrombosis. There were no differences between the two groups with respect to bleeding or other adverse events.

Conclusions Deep-vein thrombosis is common in persons with leg injury requiring prolonged immobilization. Reviparin given once daily appears to be effective and safe in reducing the risk of this complication. (N Engl J Med 2002;347:726-30.)

The incidence of leg injury requiring prolonged immobilization is increasing, probably because of the increasing popularity of recreational sports. These injuries include bone fracture and rupture of the Achilles tendon. Options for treatment include surgery followed by immobilization in a plaster cast or brace and immobilization alone. Venous thromboembolism is a common complication in the weeks after high-energy trauma and may be related to long-bone fracture, prolonged immobilization, or both. Previous studies have assessed the use of low-molecular-weight heparin after leg injury, but they have been limited by short immobilization periods, the use of ultrasonography to screen for thrombosis, and relatively small numbers of patients with fractures. Currently, there are no generally accepted recommendations for the prevention of venous thromboembolism in patients requiring immobilization after leg injury.

We designed this study to assess the incidence of deep-vein thrombosis and pulmonary embolism in patients immobilized after an isolated leg injury and to evaluate whether reviparin, a low-molecular-weight heparin, is effective and safe for the prevention of venous thrombosis in these patients.

METHODS

Patients

We conducted the study between April 1997 and September 1999 at six Danish hospitals (participating investigators are listed in the Appendix). Patients were included if they were 18 years of age or older and had a fracture of the leg or rupture of the Achilles tendon requiring at least five weeks of immobilization in a plaster cast or brace within four days after the injury. The criteria for exclusion from the study were as follows: a body weight of less than 35 kg; preexisting venous thromboembolism; systolic blood pressure above 200 mm Hg or diastolic blood pressure above 110 mm Hg; a cerebral vascular aneurysm; a cerebral vascular accident within the preceding three weeks; an active gastroduodenal ulcer; hemorrhagic diathesis; bacterial endocarditis; a platelet count below 100,000 per cubic millimeter; any previous treatment with unfractionated or low-molecular-weight heparin that lasted longer than four days; any previous treatment with fibrinolytic agents or oral anticoagulants; immobilization for more than four days before enrollment; known hypersensitivity to unfractionated or low-molecular-weight heparin or contrast medium; contraindications to venography such as diabetic nephropathy (defined by a creatinine level greater than 130 µmol per liter [1.5 mg per deciliter]), myocardial infarction within the preceding three months, or multiple myeloma; current pregnancy or lactation; current treatment with any investigational drug or such treatment within the preceding four weeks; or a history of drug or alcohol abuse.

All the patients provided written informed consent. The study was approved by the Danish Medicine Agency, the Danish Data Protection Agency, and local ethics committees (approval no. 1996-2-21G) and was conducted according to Good Clinical Practice guidelines of the International Conference on Harmonization.

Study Design

The study was a prospective, randomized, double-blind, placebo-controlled, parallel-group comparison. Patients were contacted at the time of diagnosis of a fracture of the leg or rupture of the Achilles tendon for which immobilization lasting at least five weeks was planned. Randomization was performed by computer in blocks of four. The patients received identical prefilled syringes contain-
ing either 1750 anti-Xa units of reviparin (Clivarine, Knoll) or pla-
cbo, to be injected subcutaneously once daily. Treatment was start-
ed not more than four days after the injury, in most cases on an
outpatient basis. All the patients were trained by a study nurse to
administer the study medication to themselves.

Displaced fractures were treated surgically by open reduction and
internal fixation before immobilization; other fractures were trea-
ted nonsurgically. Ruptures of the Achilles tendon were sutured or
not, according to the preferred method of the institution. Patients
who underwent surgery before randomization were allowed to have
had heparin treatment lasting up to four days before randomization.
Despite immobilization of the injured leg, all the patients were am-
bulatory, predominantly with crutches.

The participating patients were contacted by telephone weekly
and interviewed with the use of a standardized questionnaire to
identify symptoms suggesting the development of deep-vein throm-
boembolism, pulmonary embolism, or adverse events. They were also asked
to report such events immediately to the study investigators. Man-
datory study visits were scheduled to take place 10 to 14 days after
randomization and at the time of removal of the plaster cast or
brace. Patients were contacted for the last time on day 90 after ran-
domization, in most cases by telephone. Compliance with the study
medication was assessed by counting the number of syringes at the
end of the treatment period and by measuring activated factor X
(factor Xa) inhibition in plasma samples drawn on the day of ran-
domization (base line), on day 14, and at the time of removal of the
cast or brace. The analyses of factor Xa inhibition were performed
at the end of the study, and to preserve the double-blind design of
the study, the results were not revealed before the data base was
locked.

Assessments of Efficacy

All the patients underwent ascending venography of the injured
leg within one week after removal of the plaster cast or brace. Ve-
nography was performed earlier if there was a clinical suspicion of
thrombosis. All venographic procedures were performed by the
method described by Rabinov and Paulin,4 with the use of iohexol
contrast medium (Omnipaque 240, Nyegaard). A central adjudica-
tion committee of three experienced radiologists who were blind-
ed to the treatment assignments evaluated all the venograms. Dis-
crepancies were resolved by consensus. The criterion for a diagnosis
of deep-vein thrombosis was an intraluminal filling defect seen in
at least two projections; thrombi confined to the superficial or com-
municating veins were not counted. In cases of a suspected pulmo-
nary embolism, ventilation–perfusion lung scanning or pulmonary
angiography was performed and the images were evaluated by the
central adjudication committee with use of the classification sys-
tem of the Prospective Investigation of Pulmonary Embolism Di-
agnosis.10

Assessments of Safety

Bleeding complications and other adverse events were document-
ated by interview or were reported by the patients during the study.
Major bleeding was defined as any clinically apparent bleeding as-
associated with a decrease of at least 2.0 g per deciliter in the hemo-
globin level, requirement for transfusion of at least 2 units of packed
red cells, or retroperitoneal or intracranial bleeding or other bleed-
ing that the investigators decided required permanent discontinu-
tion of treatment. Bleeding that did not meet this definition was
considered minor. An adverse event was considered serious if it was
fatal or life threatening, caused permanent permanent disability, or required
hospitalization or prolonged hospitalization. The hematocrit and the
levels of hemoglobin, alkaline phosphate, lactate dehydrogen-
ase, aspartate aminotransferase, alanine aminotransferase, and serum
creatinine were measured before randomization, between days 10
and 14, and on the day of removal of the plaster cast or brace. The
platelet counts were determined every third day four times after ran-
domization and thereafter at the discretion of the investigators.

was repeated if deep-vein thrombosis or pulmonary embolism oc-
curred.

Statistical Analysis

We calculated that 190 subjects would be required in each group
for the study to detect a reduction in the cumulative incidence of
venous thromboembolic events from 28 percent in the placebo
group to 14 percent in the reviparin group, assuming a power of
90 percent and a significance level of 0.05 with a two-sided Fisher's
exact test.11 Assuming that approximately 15 percent of the pa-
tients would have venograms that could not be adequately evaluat-
ed, the planned sample size was 440 subjects.

The primary end point was a diagnosis of deep-vein thrombosis
indicated by venography within one week after removal of the plas-
ter cast or brace. We used a Mantel–Haenszel test to calculate odds
ratios and P values in the analysis of the treatment effect (after ad-
justment for previous treatment with other heparins), taking into
account all available observations of venous thromboembolic com-
plications in both groups. Differences in outcomes between patients
who had received other heparins before randomization and those
who had not were assessed with use of the Breslow–Day test for
heterogeneity. Multiple logistic regression was used to analyze the
treatment effect after adjustment for sex, age, previous heparin
treatment (any vs. none), smoking status (current vs. former or nev-
er), the presence or absence of a history of thromboembolism, and
the presence or absence of hypercholesterolemia and diabetes mel-
itus. Analysis of the treatment effect of reviparin in the prevention
of deep-vein thrombosis in proximal and isolated distal segments
was performed with use of a two-sided Fisher’s exact test. All the
patients who received at least one dose of study medication were
included in the analysis of safety and tolerability, which included
bleeding, other adverse events, and laboratory test results. The analy-
ses were performed with SAS software (version 6.12).

The authors designed the study, interpreted the data, and wrote
the article. All the data were collected by a Danish contract research
organization and transferred to the statistical department of the
sponsor, Knoll. The authors had full access to the data and reviewed
the statistical plan and analyses. The final statistical analysis was
performed by the sponsor. The central adjudication committee was in-
dependent of the sponsor.

RESULTS

Of the 440 patients enrolled, 217 were randomly assigned to receive reviparin and 223 to receive pla-
cebo. A total of 69 patients were excluded from the analysis of efficacy: 2 (in the placebo group) received
no injections, 2 (in the reviparin group) withdrew their consent, 4 (1 in the reviparin group and 3 in the
placebo group) withdrew because of adverse events, and 61 (31 in the reviparin group and 30 in the pla-
cebo group) did not have venograms that could be evaluated (23 and 19 patients, respectively, in whom
venography was technically impossible; 2 and 8, re-
respectively, in whom the venograms were judged to be
inadequate for the evaluation of all venous segments;
and 6 and 3, respectively, in whom the venograms
were adequate only for the evaluation of the proximal
venous segments). Thus, 371 patients (183 in the re-
viparin group and 188 in the placebo group) were in-
cluded in the intention-to-treat analysis of thrombosis
in any venous segment. An additional six patients in
the reviparin group and three in the placebo group
were included in the analysis of proximal thrombosis.


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Base-line characteristics and risk factors related to vascular disease did not differ significantly between the two groups, except that there were fewer current smokers in the reviparin group than in the placebo group (Table 1). Malleolar fractures were significantly less common and ruptures of the Achilles tendon more common in the reviparin group than in the placebo group; otherwise, the groups were similar with respect to types of injury and types of treatment (other than the study treatment). About 55 percent of the patients in each group were treated surgically and were hospitalized at the time of randomization, and approximately one third in each group received other heparins before randomization. The mean duration of immobilization was 43 days in the reviparin group and 44 days in the placebo group. Compliance with the study treatment was close to 100 percent in both groups.

Deep-vein thrombosis was diagnosed in 17 of the patients randomly assigned to receive reviparin (9 percent) and 35 of those randomly assigned to receive placebo (19 percent) (Table 2). This difference is consistent with a significant reduction in the risk of deep-vein thrombosis with the use of reviparin therapy (odds ratio as compared with placebo, 0.45; 95 percent confidence interval, 0.24 to 0.82). The effect of reviparin was similar in the patients who had received previous treatment with other heparins and those who had not (P=0.94 by the Breslow–Day test). One patient in the placebo group who had a distal thrombus underwent venography 11 days after removal of the cast (i.e., 4 days after the allowed 1-week interval); however, the overall results of analysis remained the same after this patient’s data were excluded. Approximately 75 percent of the thrombi were visualized only in the distal veins; the remainder appeared in the proximal veins or in both the proximal and distal veins. Three patients in the reviparin group and 10 in the placebo group had thrombosis in a proximal deep vein (P=0.09 by a two-sided Fisher’s exact test).

In patients with fractures, the effects of reviparin and placebo were similar (rate of venous thromboembolism, 14 of 134 patients vs. 29 of 159, respectively; odds ratio, 0.52; 95 percent confidence interval, 0.27 to 1.03); the same was true of patients with rupture of the Achilles tendon (rate of venous thromboembolism, 3 of 48 patients vs. 6 of 28, respectively; odds ratio, 0.24; 95 percent confidence interval, 0.06 to 0.98). In a multivariate analysis, with adjustment for sex, age, previous heparin treatment (any vs. none), smoking status (current vs. former or never), the presence or absence of a history of thromboembolism, and the presence or absence of hypercholesterolemia and of diabetes mellitus, the reduction in the risk of deep-vein thrombosis with reviparin remained similar in the study population as a whole (odds ratio, 0.46; 95 percent confidence interval, 0.24 to 0.86) and in the subgroups of patients with fracture (odds ratio, 0.54; 95 percent confidence interval, 0.27 to 1.08) or rupture of the Achilles tendon (odds ratio, 0.15; 95 percent confidence interval, 0.02 to 0.99).

During immobilization, symptoms suggesting deep-vein thrombosis developed in seven patients in the reviparin group and eight in the placebo group. Venography revealed deep-vein thrombosis in four of these patients, all of them in the placebo group. In one patient in the reviparin group and in four in the placebo group, clinical signs of pulmonary embolism developed, and ventilation–perfusion scanning confirmed the diagnosis in two, both of whom were in the placebo group; both of these patients also had a proximal deep-vein thrombosis (Table 2).
The evaluation of drug safety included 438 patients. Fourteen patients in the reviparin group and 12 in the placebo group had a bleeding event. Major bleeding occurred in two patients in the reviparin group (retroperitoneal bleeding in one and permanent discontinuation of the study medication due to minor bleeding in another) and in one patient in the placebo group (permanent discontinuation of the study medication due to minor bleeding). All three patients with major bleeding recovered without sequelae. There were no deaths, and there were no differences between the groups in the rate of serious adverse events or other adverse events. Heparin-associated thrombocytopenia did not occur, despite treatment periods of up to 80 days. Apart from the results of the analyses of factor Xa inhibition, no difference was observed between the groups concerning the other laboratory tests done. On day 14, the median factor Xa inhibition was 0.18 μmol per liter in the patients assigned to reviparin, as compared with 0.01 μmol per liter in the patients assigned to placebo.

**DISCUSSION**

We found a 19 percent incidence of deep-vein thrombosis with the use of venography in patients who had a leg fracture or rupture of the Achilles tendon that had been immobilized in a plaster cast or a brace for at least five weeks and who received placebo. The incidence was significantly lower (9 percent) in patients who received daily subcutaneous injections of reviparin during the entire period of immobilization. Other studies have documented a high risk of deep-vein thrombosis after injury to the legs. In a cohort study that included patients with trauma who had a score of 9 or higher on an injury-severity scale (on which higher scores indicate more severe injury) and who were not receiving any prophylactic treatment, deep-vein thrombosis was verified by venography in 69 of 104 patients (66 percent) who had an isolated fracture of the leg. Our patients had less severe trauma than the patients in the cohort study and had injuries that are considered less serious. Nevertheless, symptomatic pulmonary embolism developed in two patients in the placebo group and was verified by ventilation–perfusion scanning.

Our finding of a significant reduction in the risk of venous thrombosis with the use of reviparin during the period of immobilization is similar to the results of previous studies of patients receiving long-term prophylaxis after hip- or knee-replacement surgery. A recent meta-analysis documented similar reductions in symptomatic and asymptomatic venous thromboembolic events in patients who have undergone such surgery. In a clinical trial of another low-molecular-weight heparin in which compression ultrasonography was used to identify deep-vein thrombosis in immobilized patients, the incidence of asymptomatic deep-vein thrombosis was reduced from 4.3 to 0 percent. However, the sensitivity of compression ultrasonography for the detection of asymptomatic thrombi is low.

Most of the thrombi in this study were located in distal veins. The clinical significance of such thrombi has been debated. However, we observed that reviparin therapy was associated with similar reductions in the risks of proximal and distal thrombi. Nevertheless, a thrombus is a symptom of the underlying disease process, hypercoagulopathy, which we believe should be treated.

We also found that treatment with reviparin was safe. There was no significant difference between the

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**TABLE 2. RISK OF THROMBOEMBOLIC EVENTS WITHIN ONE WEEK AFTER REMOVAL OF A PLASTER CAST OR BRACE AMONG PATIENTS RANDOMLY ASSIGNED TO TREATMENT WITH REVIPARIN OR PLACEBO.**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>REVIPARIN</th>
<th>PLACEBO</th>
<th>ODDS RATIO (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In any venous segment</td>
<td>17/183 (9)</td>
<td>35/188 (19)</td>
<td>0.45 (0.24–0.82)</td>
<td>0.01†</td>
</tr>
<tr>
<td>In a proximal segment</td>
<td>3/189 (2)</td>
<td>10/191 (5)</td>
<td>0.30 (0.09–1.02)</td>
<td>0.09‡</td>
</tr>
<tr>
<td>In a distal segment</td>
<td>14/183 (8)</td>
<td>25/188 (13)</td>
<td>0.54 (0.27–1.07)</td>
<td>0.09‡</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0/217</td>
<td>2/221 (1)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*The denominators are the numbers of patients with end points that could be evaluated. CI denotes confidence interval.
†The P value was calculated with the use of the Mantel–Haenszel test, after adjustment for previous treatment with other heparins.
‡The P value was calculated with the use of a two-sided Fisher’s exact test.
§Both of these patients also had proximal thrombosis.
groups in the incidence of major bleeding. No cases of heparin-associated thrombocytopenia were observed, although it should be recognized that our study did not have sufficient power to evaluate the incidence of this complication. Previous studies have suggested that heparin-induced thrombocytopenia occurs more often in patients treated with unfractionated heparin than in those treated with low-molecular-weight heparin,22 which is more resistant to platelet factor 4.23

Compliance was excellent in our study. This suggests that long-term prophylaxis with reviparin is feasible, despite the need for subcutaneous administration. However, it must be recognized that compliance is usually higher in study populations than in actual patient populations seen in clinical practice.

Our study suggests that the routine use of reviparin for prophylaxis against thrombosis during the period of leg immobilization after fracture of the leg or rupture of the Achilles tendon is beneficial. However, further evaluation is warranted before such treatment can be recommended for routine use. It will be important to determine whether this therapy can reduce the risk of long-term sequelae of deep-vein thrombosis, such as venous insufficiency, and to assess its cost effectiveness.

Supported by a grant from Knoll. Knoll provided the reviparin that was tested in the study.

Drs. Lassen and Borris have served as consultants to Knoll and other companies that develop antithrombotic compounds. Dr. Nakov is an employee of Knoll.

We are indebted to Silke Wurzinger of Knoll for contributions to the statistical analysis.

APPENDIX

The following investigators participated in the study (all in Denmark unless otherwise indicated): Executive Committee — M.R. Lassen, Hillerød; L.C. Borris, Århus; and R.L. Nakov, Ludwigshafen, Germany; Writing Committee — M.R. Lassen, Hillerød; L.C. Borris, Århus; F. Misselwitz, R.L. Nakov, S. Schäffer, Ludwigshafen, Germany; Adjudication Committee — A.M. Nehen, Århus; R.H. Jensen, Sandby; and L. Kjær, Herlev; participating investigators and radiologists — M.R. Lassen, Hillerød; L.C. Borris, Århus; P.S. Jørgensen, Gentofte; B.L. Madsen, Glostrup; L.J. Jensen, Odder; P. Hviid, Viborg; B.P. Tørholm, Gentofte; C. Jensen, Hillerød; D.J.B. Hovgaard, Glostrup; E.N. Rasmussen, Odder; T.M. Christiansen, Århus; N. Kerbouche, Gentofte; H.E. Christensen, Glostrup; and A.B. Nielsen, Viborg.

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