Use of Hirulog in the Prevention of Venous Thrombosis After Major Hip or Knee Surgery

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Background The study objective was to determine whether Hirulog, a direct thrombin inhibitor, has potential efficacy and safety in the prevention of deep vein thrombosis (DVT) in orthopedic patients. A phase 2 open-label, dose-escalating design was used to study 222 unselected patients undergoing major hip or knee surgery in tertiary-care, university-affiliated hospitals.

Methods and Results Subcutaneous Hirulog was initiated postoperatively. Patients were evaluated for bleeding and symptomatic pulmonary embolism, and mandatory bilateral venography was performed before discharge. Dose escalations were made on the basis of observed rates of bleeding and venous thrombosis. There were five dosage regimens used: 0.3 mg/kg every 12 hours, 0.6 mg/kg every 12 hours, 1.0 mg/kg every 12 hours for 3 days followed by 0.6 mg/kg every 12 hours for up to 11 days, 1.0 mg/kg every 12 hours, and 1.0 mg/kg every 8 hours. One hundred seventy-seven patients who had technically adequate bilateral venography or objectively documented pulmonary embolism were included in the primary analysis of efficacy. The highest dosage regimen (1.0 mg/kg every 8 hours) provided the lowest rates of total DVT (17%) and proximal DVT (2%), both of which were significantly lower (P=.010 and P=.023, respectively) than the pooled rates of total (43%) and proximal (20%) DVT seen with the first four regimens. Bleeding rates were low (<5%) with all regimens.

Conclusions This study demonstrates that 1.0 mg/kg Hirulog every 8 hours started postoperatively is potentially efficacious and safe for the prevention of DVT after major hip or knee surgery. (Circulation. 1994;90:2385-2389.)

Key Words • anticoagulants • heparin • surgery • thrombosis • veins

Heparin, low-molecular-weight heparins, and warfarin are effective in the prevention of postoperative deep vein thrombosis (DVT) in patients undergoing major orthopedic surgical procedures.1-6 Although these anticoagulants are usually begun preoperatively, low-molecular-weight heparins and warfarin are effective even when begun postoperatively, presumably because they prevent small thrombi, which form intraoperatively, from growing and becoming clinically important. There is evidence that thrombus growth is triggered by thrombin bound to fibrin.7 Thus, during thrombus formation, thrombin binds to fibrin and remains enzymatically active and protected from inactivation by fluid-phase inhibitors.8 Clot-bound thrombin is relatively protected from inactivation by heparin-antithrombin III, which may explain why heparin is limited in its ability to prevent DVT in patients undergoing major orthopedic surgery.8,9 Antithrombin III–independent thrombin inhibitors such as hirudin and Hirulog, a 20-amino acid synthetic peptide that acts as a divalent inhibitor of thrombin, can readily inactivate clot-bound thrombin and may be better than heparin and low-molecular-weight heparins in preventing DVT.7,8

To explore the potential of Hirulog in the prevention of DVT, we performed a phase 2 dose-ranging study in patients undergoing major knee or hip surgery. Subcutaneous Hirulog was started postoperatively, and bilateral venography was performed before discharge to determine the presence or absence of DVT. Our findings establish antithrombotic activity of Hirulog in humans and support further investigations of this novel agent.

Methods

The following centers participated in the study: Chedoke-McMaster Hospitals, Hamilton Civic Hospitals, and St Joseph’s Hospital, Hamilton, Canada; Hotel Dieu de Montreal and Centre Hospitalier Sainte-Jeanne-D’Arc, Montreal, Canada; and Academic Medical Centre, Amsterdam, Netherlands. The study protocol was approved by the institutional review boards of each participating hospital. Informed written consent was obtained from all patients. The study began in January 1991 and ended in March 1992.

Study Population

Eligible patients were 18 years or older and underwent one of the following procedures: elective hip replacement surgery,
surgery for a fractured hip, or elective knee surgery (knee replacement, tibial osteotomy, or patellar shaving). The exclusion characteristics were ongoing need for oral anticoagulant or aspirin therapy, history of gastrointestinal bleeding or ulcer, renal dysfunction (serum creatinine level >177 μmol/L), and/or allergy to contrast medium. The use of aspirin during the study was strongly discouraged.

Treatment Regimens

The study objective was to identify a Hirulog regimen associated with an overall DVT rate of ≤15%, a proximal DVT rate of ≤5%, and a bleeding rate of <5%. These values represent the approximate rates seen with low-molecular-weight heparins, which at present are reported to provide the greatest effectiveness in this patient population.10,11 The decision in selecting an active and tolerable regimen was based on the observed rates of bleeding and thrombosis and the estimated 95% confidence interval. It was planned to monitor the rates of bleeding and thrombosis in every 10 patients; the following guidelines were used: for a given regimen, if the lower 95% confidence limit for bleeding was greater than 5% and/or the lower 95% confidence limit for thrombosis was greater than 15%, the regimen would be changed appropriately. A priori, it was decided that a starting dose of 0.3 mg/kg every 12 hours subcutaneously would be used because, in phase 1 studies, this produced a 50% prolongation of the activated partial thromboplastin time (aPTT).12 The five dosage regimens used were 0.3 mg/kg every 12 hours, 0.6 mg/kg every 12 hours, 1.0 mg/kg every 12 hours for 3 days followed by 0.6 mg/kg every 12 hours for up to 11 days, 1.0 mg/kg every 12 hours, and 1.0 mg/kg every 8 hours.

Intervention

Subcutaneous Hirulog was initiated 12 to 24 hours postoperatively and was discontinued after contrast venography. Patients were evaluated daily for bleeding, symptomatic DVT, and pulmonary embolism, and the aPTT was measured 2 hours after each morning injection of Hirulog.

Assessment of Deep Vein Thrombosis

Bilateral ascending contrast venography was attempted in all patients on day 14 or just before hospital discharge if earlier. To optimize safety and to identify clinically important DVT that occurred early, noninvasive screening with impedance plethysmography was performed on days 5, 7, 9, 11, and 13, and B-mode duplex ultrasonography was performed on days 5 and 9. If either test was abnormal, confirmatory contrast venography was performed. DVT was diagnosed when venography revealed a constant intraluminal filling defect in a deep vein in two or more views13; it was classified as proximal if it involved the popliteal or more proximal veins and distal if it involved only the calf veins. Patients with clinically suspected pulmonary embolism underwent ventilation perfusion lung scanning, and pulmonary embolism was diagnosed if the scan was classified as high probability. All patients with confirmed DVT or pulmonary embolism were treated with conventional anticoagulant therapy. Patients were contacted 6 weeks after discontinuation of Hirulog to determine whether subsequent symptoms of DVT or pulmonary embolism had occurred.

Assessment of Bleeding

Each patient was assessed daily for bleeding. Bleeding was classified as major if it was clinically overt and associated with a fall in hemoglobin of ≥20 g/L or transfusion of ≥2 U of blood or if it was retroperitoneal or intracranial. All other clinically overt bleeding was classified as minor.

Avoidance of Bias

Because this was an open-label study, considerable efforts were made to minimize bias. The venograms were initially interpreted by on-site radiologists. All venograms and bleeding events were subsequently adjudicated on a weekly basis by a panel of at least two experts (central review). All analyses are based on the results of adjudicated venograms. To address the possibility of bias caused by selective underreporting or over-reporting of venography results by the central adjudication panel, the agreement or disagreement between the on-site radiologist and the central review was determined at the end of the study.

Analysis

The primary analysis of efficacy was based on the proportion of patients with confirmed DVT or pulmonary embolism during Hirulog administration or within 72 hours of discontinuation of Hirulog. Patients were excluded from the primary analysis if they did not have pulmonary embolism as well as no venography, normal unilateral venography, or technically inadequate bilateral venography. The relation between the different regimens and the development of DVT was evaluated using a multiple logistic regression analysis. This allowed adjustment for possible differences in mean age, sex, and type of surgery among the treatment groups. The primary analysis of bleeding was based on the major bleeding rate in all patients entered into the study.

Results

Clinical Findings

There were 222 patients (131 women and 91 men) entered into the study: 134 (60.5%) underwent elective hip replacement surgery; 25 (11.3%), elective knee replacement surgery; 48 (21.6%), surgery for fractured hip; and 15 (6.8%), other hip or knee surgery (Table 1). There was a higher proportion of patients who underwent elective hip replacement surgery and a lower proportion of patients who underwent surgery for a fractured hip in the last three dosage regimens. Of the 222 patients entered into the study, 177 (79.7%) had technically adequate bilateral venography (176 patients) or pulmonary embolism without venography (1 patient) and were included in the primary analysis of efficacy. The rates of venous thromboembolism with each regimen are listed in Table 2. The overall DVT rates were similar for the first four regimens and then fell substantially with the last regimen. On the basis of the multiple logistic regression analysis, the observed difference in overall DVT rates between the first four regimens (43%) and the last regimen (17%) is statistically significant (P=.010). As with the overall DVT rates, the observed difference in proximal DVT rates between the first four regimens (20%) and the last regimen (2%) of Hirulog is statistically significant (P=.023).

To demonstrate the consistency of the observed reduction in the DVT rate seen with the last regimen of Hirulog in the different categories of patients, we performed two analyses. First, we performed a subgroup analysis of the study patients who underwent elective hip surgery and compared the rates of total and proximal DVT seen with the first four regimens with the corresponding rates seen with the last regimen. The total and proximal DVT rates were 41% (31/75) and 20% (15/75), respectively, with the first four regimens and 21% (7/33) and 3% (1/33), respectively, with the last regimen. The difference in proximal DVT rates is statistically significant (P=.02), and the difference in total DVT rates shows a strong trend (P=.07). Second, we performed an analysis of the subgroup of patients
TABLE 1. Demographic Data of Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hirulog Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3 mg/kg every 12 h (n=18)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>74.2</td>
</tr>
<tr>
<td>Sex, women</td>
<td>12 (66.7%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Elective hip</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Elective knee</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td>Fractured hip</td>
<td>8 (44.4%)</td>
</tr>
<tr>
<td>Other orthopedic surgery</td>
<td>1 (5.6%)</td>
</tr>
</tbody>
</table>

*1.0 mg/kg every 12 hours for 3 days followed by 0.6 mg/kg for up to 11 days.

who underwent elective knee surgery or surgery for a fractured hip. In this subgroup, the incidence of total DVT was 45% (25/56) and the incidence of proximal DVT was 16% (9/56) with the first four regimens, whereas the incidence of total DVT was 8% (1/13) and the incidence of proximal DVT was 0% (0/13). The difference in total DVT rates is statistically significant (P=.012). These analyses support the efficacy of the last regimen for the prevention of DVT in all three groups of patients evaluated.

There were 2 patients who suffered nonfatal pulmonary embolism during the study, both of whom were receiving Hirulog 0.6 mg/kg every 12 hours. One patient who received Hirulog 1.0 mg/kg every 12 hours and had normal venography before discharge had an autopsy-proven fatal pulmonary embolism 11 days after discharge from the hospital. For the analysis, this patient was considered negative for DVT because the pulmonary embolism occurred more than 72 hours after discontinuation of Hirulog. No other confirmed episodes of DVT or pulmonary embolism occurred within the 6-week follow-up period.

The agreement in categorizing venographic outcomes (positive for DVT, negative for DVT, or inadequate) between the local radiologist and the central review was high for (1) all five regimens of Hirulog (86%), (2) the first four regimens only (84%), and (3) the last regimen only (92%). In addition, there was no evidence of the central review over-calling the first four regimens or under-calling the last regimen.

Overall, 3 patients (1.4%) suffered major bleeding events: 1 patient who had received 0.6 mg/kg Hirulog every 12 hours, 1 who had received 1.0 mg/kg every 12 hours for 3 days followed by 0.6 mg/kg every 12 hours, and 1 who had received 1.0 mg/kg every 8 hours. In addition, 3 patients suffered minor bleeding events: 2 patients who had received 0.6 mg/kg Hirulog every 12 hours and 1 who had received 1.0 mg/kg every 12 hours.

No other adverse experiences were observed during the study.

Laboratory Findings

The anticoagulant activity of Hirulog was measured 2 hours after drug administration. The lowest dosage regimen (0.3 mg/kg) produced a mean aPTT response of 41.5±14.2 seconds (control, 32 seconds). In the last three dosage groups, aPTT assays were performed after administration of a 1.0-mg/kg injection, showing aPTT responses ranging from 49.1±12.1 seconds to 54.6±10.6 seconds.

To estimate the duration of anticoagulant effect associated with Hirulog administration, aPTT measurements were performed on plasma samples drawn approximately 7 hours after drug administration in 25 patients who received 1 mg/kg Hirulog every 8 hours. Twenty-three of 25 (92%) patients showed an anticoagulant effect 7 hours after drug administration (±3-second prolongation of aPTT). We also performed aPTT measurements on plasma samples drawn 11 hours after drug administration in 4 patients who received Hirulog injections every 12 hours (3 patients received

TABLE 2. Rates of Venous Thromboembolism Observed With Each Hirulog Regimen

<table>
<thead>
<tr>
<th>DVT Rate</th>
<th>0.3 mg/kg every 12 h (n=17)</th>
<th>0.6 mg/kg every 12 h* (n=54)</th>
<th>1.0 and 0.6 mg/kg every 12 h (n=40)</th>
<th>1.0 mg/kg every 12 h (n=20)</th>
<th>1.0 mg/kg every 8 h (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10 (59%)</td>
<td>23 (43%)</td>
<td>16 (40%)</td>
<td>7 (35%)</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Proximal</td>
<td>7 (41%)</td>
<td>9 (17%)</td>
<td>6 (15%)</td>
<td>4 (20%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis.

*Includes 2 patients who had pulmonary embolism, 1 who had proximal DVT by venography, and 1 who did not undergo venography. The latter is considered positive for both overall and proximal DVT.

11.0 mg/kg every 12 hours for 3 days, followed by 0.6 mg/kg for up to 11 days.
0.3 mg/kg every 8 hours and 1 received 0.6 mg/kg every 12 hours). All four samples were normal and not prolonged from baseline results. These data provide evidence that injections of Hirulog every 8 hours produce an anticoagulant effect throughout the day in most patients, whereas injections every 12 hours do not.

**Discussion**

Heparin and low-molecular-weight heparins exert their anticoagulant effect by inhibiting the generation and the activity of thrombin through an antithrombin III–dependent mechanism. Although these anticoagulants are effective antithrombotic agents, there is evidence that their ability to prevent thrombus growth is limited because they are unable to inhibit clot-bound thrombin.7,8 Direct thrombin inhibitors such as hirudin and Hirulog14 are potent inhibitors of both soluble and clot-bound thrombin and so have the potential for improved antithrombotic activity.

As part of the development of all new drugs, phase 2 dosage-ranging studies are necessary to establish potentially efficacious and safe regimens. In this study, our aim was to identify a regimen that would be associated with an overall DVT rate of ≤15%, a proximal DVT rate of ≤5%, and a bleeding rate of <5%, since these were our original estimates of the expected rates associated with the use of low-molecular-weight heparins.

To meet our objectives, we chose to perform a dosage-escalating cohort study. We were able to achieve two of our three objectives, since the rates of proximal DVT (2%) and bleeding (<5%) were low; the rate of overall DVT (17%) was slightly greater than our targeted objective. The results of a recent meta-analysis of randomized trials comparing several methods of DVT prophylaxis in patients undergoing elective hip surgery support the efficacy and safety of the last Hirulog regimen. First, the pooled rates of overall and proximal DVT were 50% and 24%, respectively, in placebo-treated patients. Second, low-molecular-weight heparins provided the greatest efficacy for the prevention of DVT, with pooled rates of overall DVT of 12% to 20% and of proximal DVT of 4% to 6%. The rates of overall (17%) and proximal (2%) DVT with the last Hirulog regimen are comparable to the corresponding pooled rates reported with low-molecular-weight heparins. The low rate of proximal DVT seen with the last Hirulog regimen is particularly promising because proximal DVT is more important clinically than DVT in the calf.

We expected that the lowest dosage selected would be effective, because, in phase 1 studies, it safely produced a substantial anticoagulant effect, prolonging the aPTT by approximately 50%. If this dosage regimen had been effective, it was our intention to compare the DVT rates observed with historical control data from other orthopedic studies. This seems reasonable because the DVT rates in placebo-treated patients have been quite constant.2,13 However, since the first dose was ineffective, escalating dosage regimens were used until an effective regimen was found. The DVT rates in the last dosing group were then compared with the DVT rates in the first four groups.

Because this was an open study, extra care was taken to minimize bias. Venograms and lung scans were adjudicated by a panel of experts that was unaware of which dosage regimen of Hirulog each patient had received. The high level of agreement in venographic interpretation between the local radiologists and the central review, as well as the fact that there was no evidence of over-calling the first four regimens or under-calling the last regimen, virtually eliminates the possibility of bias on the part of the central review. The exclusion from the primary analysis of efficacy of patients who did not have adequate bilateral venography is appropriate because noninvasive tests fail to detect the majority of calf DVT and many proximal vein thrombi.16,17

We carefully considered the ethical implications of performing a phase 2 study in a high-risk group of patients for whom effective and safe prophylaxis is available. Patient safety was optimized in four ways. First, early and frequent impedance plethysmography and B-mode duplex ultrasonography were performed postoperatively to quickly identify and treat patients with large proximal DVT. Although the sensitivity of duplex sonography for proximal DVT is only about 60% and that of impedance plethysmography is even less,17 there is evidence that it is safe to leave symptomatic patients untreated if either of these noninvasive tests remains normal on serial testing.18,19 Second, venography was performed before discharge to identify (and treat) patients with thrombi undetected by noninvasive testing. Third, the starting dose of Hirulog was one that we (wrongly) predicted would be effective, since it produced a prolongation of the aPTT by 50% in volunteers.12 Fourth, the rates of DVT and bleeding associated with each regimen were carefully monitored, and dose alterations were made when the DVT rates were too high; this minimized the number of patients exposed to ineffective doses of Hirulog.

Two points are noteworthy in this study. First, for the drug to be effective, it appears that a sufficient concentration of Hirulog to produce a prolongation of aPTT at all times must be present. Thus, with injections every 8 hours, the aPTT was prolonged (in most patients) 7 hours after an injection, and Hirulog markedly reduced the DVT rate. In contrast, when regimens of twice-daily injections were used, the aPTT normalized 11 hours after an injection, and there were high DVT rates. It remains to be determined whether twice-daily injections of higher doses are effective and whether injections three times daily of greater than 1.0 mg/kg can safely reduce the DVT rate still further. The basis for a requirement for sustained drug levels is unknown but suggests that either the dosages of Hirulog used were unable to completely inhibit clot-bound thrombin or that continuous production of fluid-phase thrombin, associated with tissue injury, contributes to the pathogenesis of DVT, and continuous inhibition is necessary to optimize DVT prophylaxis.

The second novel observation pertains to the aPTT results. Effective doses of Hirulog produced substantial and consistent prolongation of the aPTT. By comparison, when administered to patients who are at high risk for bleeding (such as postoperative orthopedic patients), heparin in doses that prolong the aPTT to the same extent would produce considerably more bleeding.20 On the other hand, doses of heparin (but not Hirulog) that produce minimal prolongation of the aPTT are effective at preventing DVT in orthopedic patients. These findings suggest that neither the efficacy
nor the safety of Hirulog (and possibly other direct thrombin inhibitors) can be predicted from the considerable experience with the use of aPTT to monitor heparin therapy. The low incidence of bleeding associated with Hirulog administration is encouraging and suggests that potential improvements in clinical efficacy may not come at the expense of increased risk of bleeding.

This study provides data indicating that 1.0 mg/kg Hirulog every 8 hours initiated postoperatively has the potential to be effective and safe for the prevention of DVT in orthopedic patients. However, for definitive evidence of its role as a prophylactic agent in patients having major orthopedic surgery, large randomized trials of Hirulog and other effective agents such as low-molecular-weight heparin, adjusted-dose heparin, or warfarin are required.

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