Recombinant Hirudin (Lepirudin) Provides Safe and Effective Anticoagulation in Patients With Heparin-Induced Thrombocytopenia

A Prospective Study

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Background—The immunological type of heparin-induced thrombocytopenia (HIT) is the most frequent drug-induced thrombocytopenia. This study evaluated the efficacy of recombinant hirudin (r-hirudin or lepirudin), a potent thrombin inhibitor, for anticoagulation in patients with confirmed HIT.

Methods and Results—Eighty-two patients in this prospective, multicenter study received 1 of 4 intravenous r-hirudin regimens: A1, HIT patients with thrombosis (n=51), 0.4-mg/kg bolus and then 0.15 mg · kg⁻¹ · h⁻¹; A2, HIT patients with thrombosis receiving thrombolysis (n=5), 0.2-mg/kg bolus and then 0.1 mg · kg⁻¹ · h⁻¹; B, HIT patients without thrombosis (n=18), 0.1 mg · kg⁻¹ · h⁻¹; and C, during cardiopulmonary bypass surgery (n=8), 0.25-mg/kg bolus and then 5-mg boluses as needed. Response criteria were increase in platelet count by ≥30% to >10⁹/L and activated partial thromboplastin time (aPTT) values 1.5 to 3.0 times baseline values achieved with a maximum of 2 dose increases. No placebo control was used for ethical reasons. Outcomes of a subset of r-hirudin–treated patients who met predefined inclusion criteria (n=71) were compared with those of a historical control group (n=120) for combined and individual incidences of death, amputations, new thromboembolic complications, and incidences of bleeding. Platelet counts increased rapidly in 88.7% of r-hirudin–treated patients with acute HIT. In regimens A1 and A2, the 25% and 75% quartiles of the aPTT were within the target range at all but 1 time point. The incidence of the combined end point (death, amputation, new thromboembolic complications) was significantly reduced in r-hirudin patients compared with historical control patients (P=0.014). During first selected treatment, the adjusted hazard ratio for r-hirudin patients versus historical control was 0.279 (95% CI, 0.112 to 0.699; P=0.003). Bleeding rates were similar in both groups.

Conclusions—r-Hirudin treatment is associated with a rapid and sustained recovery of platelet counts, sufficient aPTT prolongations, and true clinical benefits for patients with HIT. (Circulation. 1999;99:73-80.)

Key Words: heparin ■ platelets ■ thrombosis ■ trials ■ anticoagulants ■ immunology

The immunological type of heparin-induced thrombocytopenia (HIT) is a potentially life-threatening, adverse effect of heparin treatment.¹ In a recent prospective study of patients undergoing hip surgery, 7.8% of those treated with subcutaneous unfractionated heparin (UFH) developed HIT antibodies, and 2.7% developed clinically manifest HIT.² HIT-related antibodies most often belong to the IgG class,³ and typically the antigen comprises complexes of sulfated oligosaccharides (eg, heparin)⁴⁻⁵ and platelet factor 4 (PF4).⁶⁻⁹ Multiple antibody binding to these antigens leads to the formation of immune complexes that bind to platelets via the platelet Fc-receptor (CD 32)¹⁰,¹¹ and cause intravascular platelet activation, reduced platelet survival, and thrombocytopenia. HIT antibodies also bind to and activate endothelial cells.⁹,¹² Together, intravascular platelet activation, generation of platelet microparticles¹³ and thrombin, and disturbance of endothelial cells increase the risk of thromboembolic complications (TECs). TECs frequently result in limb amputation or death; therefore, immediate cessation of heparin is mandatory when HIT becomes clinically manifest. However, many HIT patients require further parenteral antico-
agulation because of either their underlying disease or acquired thrombotic complications.

When continued anticoagulation is necessary, low-molecular-weight heparin (LMWH), heparinoid danaparoid sodium, anecrod, and several other drugs have been used with various degrees of success. LMWH demonstrates in vitro cross-reactivity with HIT antibodies in >90% of cases. Danaparoid sodium is often used on a compassionate-use basis; however, it also has limitations: in vitro cross-reactivity with HIT antibodies is observed in 10% to 20% of cases. It has a relatively long half-life (1/2 of anti-factor Xa activity of 24 hours), monitoring is required during high-dose treatment to determine anti-factor Xa activity, and no antidote is available. Argatroban, a synthetic thrombin inhibitor, is under investigation for its utility in anticoagulation in HIT patients.

Hirudin, an antithrombotic substance produced by the salivary glands of the medicinal leech (Hirudo medicinalis), is the most potent and specific thrombin inhibitor currently known. It acts independently of cofactors such as antithrombin, and unlike heparin, it is not inactivated by PF4. Moreover, unlike heparin, hirudin can inhibit thrombin bound within the clot. These properties may be especially important in HIT, a clinical condition associated with increased platelet activation, release of large amounts of PF4, thrombin generation, and acute thrombotic events.

The goals of this first major prospective study of HIT patients were to assess the efficacy of recombinant hirudin (r-hirudin) as a new therapeutic approach in HIT and to evaluate its effectiveness relative to other available therapeutic options. Because of the high risk of limb amputations (10% to 20%) and death (20% to 30%) in patients with HIT and complicating thrombosis, placebo treatment is considered unethical. Also, at the time of this study, no approved alternative for treatment of HIT was available to serve as an active comparator. Therefore, we conducted a retrospective analysis to determine how the clinical outcomes of r-hirudin–treated patients compared with those of a historical control group, ie, patients with HIT who had been treated with the best available care before r-hirudin was available.

**Methods**

**Patients**

Patients with a diagnosis of HIT based on clinical criteria (ie, a decrease in platelet count by >30% or <10^9/L and/or new TECs during heparin administration) and HIT antibodies were included in the study. Patients were required to be ≥18 years of age and to have a definite need for parenteral antithrombotic therapy or prophylaxis. Patients were excluded if they required hemodialysis or hemofiltration because of severe renal insufficiency, were anticipated to comply poorly, had a known hypersensitivity to r-hirudin, or were pregnant. Each patient provided informed consent to participate in the trial.

**Study Design and Treatment Schedules**

In this prospective, multicenter study, patients with HIT were treated with 1 of 4 r-hirudin (Lepirudin, Behringwerke AG) regimens: A1, HIT patients with thrombosis, 0.4-mg/kg bolus and then 0.15 mg · kg⁻¹ · h⁻¹; A2, HIT patients with thrombosis receiving thrombolysis, 0.2-mg/kg bolus and then 0.1 mg · kg⁻¹ · h⁻¹; B, HIT patients without thrombosis, 0.1- mg · kg⁻¹ · h⁻¹; and C, during cardiopulmonary bypass surgery, 0.25-mg/kg bolus and then 5-mg boluses when hirudin concentration was <2500 ng/mL as determined by ecarin clotting time. The start of treatment was defined as day 1. Scheduled treatment duration was 2 to 10 days; treatment could be prolonged if clinically indicated. Conversion to oral anticoagulants began with 6 mg/d phenprocoumon until the international normalized ratio was 2. r-Hirudin was then reduced by 50% and stopped when the international normalized ratio reached 2.5. After r-hirudin was stopped, the patient’s clinical course was followed for an additional 2 weeks.

This study was conducted in accordance with the good clinical practice guidelines of the European Community and the Declaration of Helsinki. The study protocol was approved by the ethics committees of the Medical Councils of the States of the Federal Republic of Germany.

**Laboratory Methods**

Hemoglobin, platelet count, serum creatinine, and activated partial thromboplastin time (aPTT) were measured daily. HIT antibodies were determined by use of the heparin-induced platelet activation test; r-hirudin plasma levels were measured with ELISA methodology.

**Response Criteria**

r-Hirudin therapy was monitored by aPTT with a target range of 1.5- to 3.0-fold prolongation (based on the use of Actin FS or Neothrombin reagents; with other reagents, aPTT target range is 1.5- to 2.5-fold prolongation) of baseline values (the median normal aPTT value of the laboratory was taken if the patient’s aPTT was prolonged by heparin treatment), with a maximum of 2 dose adjustments for low aPTT values. Additionally, response in patients with thrombocytopenia was an increase in platelet counts ≥30% of the nadir value to >10^9/L on day 10, and in patients without thrombocytopenia, response was a platelet count >10^9/L on both days 3 and 10. During cardiopulmonary bypass (regimen C), r-hirudin was monitored by use of ecarin clotting time.

**Comparison With Historical Control Group**

Clinical outcomes were compared with those of a historical control group for combined and individual incidences of death, limb amputations, new TECs, and incidences of bleeding. Patients in the historical control had confirmed HIT (heparin-induced platelet activation test) between 1989 and 1993 and had been treated with the best available care. To ensure comparability between groups, exclusion criteria were prospectively defined and applied to both the historical control and r-hirudin–treated patients. These criteria were age <18 years, missing date of HIT confirmation, time between onset of clinical symptoms and laboratory confirmation of HIT ≥21 days, and cardiopulmonary bypass. Outcomes were measured for each group across 2 time intervals: (1) from the day of laboratory confirmation of HIT until the end of the observation period and (2) during the time of the first selected active treatment administered within 2 days of laboratory confirmation of HIT in historical control patients.

**Statistical Analysis**

aPTT prolongation and platelet count recovery were measured in patients who received r-hirudin for ≥2 days. Incidences of death, limb amputations, and new TECs were monitored for all patients. Comparisons were conducted by use of a Kaplan-Meier time-to-event analysis, beginning with events occurring on the day of laboratory confirmation of HIT for the r-hirudin–treated group, and 1 day after laboratory confirmation for the historical control group (conservative assessment). Results were compared using the log-rank test. To adjust for potential prognostic factors (sex, age, underlying disease, time between onset of clinical symptoms and laboratory confirmation of HIT, TECs during heparin/heparinoid treatment), r-hirudin and historical control patients were compared by use of a likelihood ratio test based on a Cox regression model with 95% CIs for the hazard ratio.
Results

Prospective r-Hirudin Treatment

Eighty-two patients were treated with r-hirudin; 74 (90.2%) completed the study according to protocol. Eight patients prematurely discontinued treatment because of nonfatal adverse event (n=4; none was a major bleeding), fatal adverse event (n=3; 2 septicemia, 1 heart failure with pulmonary embolism detected at autopsy), or planned colonoscopy/biopsy (n=1). Patient characteristics at baseline and treatment durations are shown in Table 1. Before the start of treatment, patients had been anticoagulated with UFH (n=41, 50.0%); UFH and LMWH (n=9, 11.0%); UFH and danaparoid sodium (n=19, 23.2%); UFH, LMWH, and danaparoid sodium (n=5, 6.1%); danaparoid sodium (n=2, 2.4%); and not specified (n=6, 7.3%).

Sixty-six patients (75.6%) were classified as acute HIT patients, with a decrease in platelet counts >30% or <100 G/L during recent heparin therapy. Sixteen patients with a history of confirmed HIT were classified as “latent” HIT patients. In 55 of 62 (88.7%) patients with acute HIT and evaluable platelet counts, platelet counts increased to >10^10/L within 10 days (Figure 1). Median platelet count remained nearly constant in patients with normal platelet counts at baseline (data not shown).

In regimens A1, A2, and B, aPTT increased rapidly to between 1.5 and 3.0 times baseline values. The 25% and 75% quartiles of the aPTT were within this target range at all time points in treatment regimen A1 and at all but 1 time point in regimen A2. Median aPTT prolongations in regimen B were slightly lower than those in the other 2 groups.

Incidences of death, limb amputations, new TECs, and major bleedings are summarized in Table 2. Six patients died (3 in group A1 and 3 in group B); causes of death were heart failure (n=3), sepsis (n=2), and multiorgan failure (n=1). All fatal events were judged to be due to the severity of the underlying disease and not to the use of study drug. New TECs observed during the study were arterial-peripheral

![Figure 1. Time course of platelet counts in patients with acute HIT treated with regimens A1, A2, and B shows rapid increase in platelet counts after cessation of heparin to >10^10/L. Median and 25% and 75% quartiles of platelet counts are given.](image-url)
Bypass (n=58), time between onset of clinical symptoms and the prospectively defined exclusion criteria: cardiopulmonary comparisons with the historical control group for not meeting Eleven of the 82 r-hirudin patients were excluded from Comparison With the Historical Control Group.

During the study, 27 patients (32.9%) experienced at least 1 bleeding event (regimen A1, 33.3%; A2, 20.0%; B, 33.3%; and C, 37.5%). Eleven patients (13.4%) experienced 15 major bleeding events (8 bleedings at invasive sites, 7 spontaneous bleedings: urogenital (n=2), into a liver cyst with concomitant thrombolysis, soft tissue, gastrointestinal, into phenprocoumon-induced necroses, and diffuse bleeding). Incidence of major bleeding in the highest-dose group, A1 (7 of 51 patients, 13.7%), was comparable to that of the remaining treatment regimens (4 of 31 patients, 12.9%). Some patients experienced minor bleeding (n=27), isolated drop in hemoglobin (n=7), hematuria (n=5), hematoma at a puncture site (n=4), or hematoma (n=4).

Except for patients undergoing cardiopulmonary bypass, there were no significant differences in hemoglobin values between baseline and the last measurement during r-hirudin treatment. No clinically relevant changes in serum creatinine were observed. Median hirudin plasma levels ranged between 1149 and 1698 ng/mL in regimen A1 and between 874 and 1136 ng/mL in regimen B, comparable to other studies.

**Comparison With the Historical Control Group**

Eleven of the 82 r-hirudin patients were excluded from comparisons with the historical control group for not meeting the prospectively defined exclusion criteria: cardiopulmonary bypass (n=8), time between onset of clinical symptoms and laboratory confirmation of HIT >21 days (n=2), and date of HIT confirmation missing (n=1). Thus, 71 r-hirudin patients were compared with 120 eligible patients in the historical control group for combined and individual incidences of death, limb amputations, new TECs, and incidences of bleeding. Patient characteristics of each group at baseline are summarized in Table 3. Patients in the r-hirudin group were, on average, 7 years younger than historical control patients, but more patients in the r-hirudin group had multiple TECs before the start of treatment. Cumulative incidences of the combined and individual events of interest (deaths, limb amputations, new TECs) are shown in Figure 2, and individual end points at days 7 and 35 are listed in Table 4. The log-rank test indicated a significant difference in favor of the r-hirudin–treated patient group (P=0.014). The unadjusted hazard ratio (r-hirudin to historical control) was 0.525 (95% CI, 0.310 to 0.889); after adjustment for prespecified prognostic factors (Table 3), the hazard ratio was 0.508 (95% CI, 0.290 to 0.892; P=0.014).

In addition, the combined cumulative incidences of only limb amputations and deaths in the 2 patient groups were consistently lower in the r-hirudin group than in the historical control group (P=0.043, log-rank test; Table 4). There was a slightly higher bleeding rate in the r-hirudin group (Table 5).

For comparison of outcomes with only the first selected treatment of the historical control patients, incomplete data precluded treatment assignment to 17 of the 120 patients.

### Table 2. Incidences of Death, Limb Amputations, New TECs, and Major Bleeding in the r-Hirudin Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients With Event*</th>
<th>Time of First Occurrence</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During r-Hirudin</td>
<td>After r-Hirudin</td>
<td>Not Assessable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>7.3</td>
<td>1</td>
<td>1.2</td>
<td>5</td>
<td>6.1</td>
</tr>
<tr>
<td>New TEC</td>
<td>8</td>
<td>9.8</td>
<td>2</td>
<td>2.4</td>
<td>5</td>
<td>6.1</td>
</tr>
<tr>
<td>Limb amputation</td>
<td>3</td>
<td>3.7</td>
<td>3</td>
<td>3.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Combined</td>
<td>15</td>
<td>18.3</td>
<td>6</td>
<td>7.3</td>
<td>8</td>
<td>9.8</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>11</td>
<td>13.4</td>
<td>11</td>
<td>13.4</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Patients may have suffered >1 event.
†Patient developed deep vein thrombosis and pulmonary embolism.

| n=82. |

<table>
<thead>
<tr>
<th><strong>TABLE 3. Historical Control Comparison: Baseline Characteristics</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>r-Hirudin (n=71)</strong></td>
</tr>
<tr>
<td>Sex, n (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age, (mean±SD), y</td>
</tr>
<tr>
<td>Underlying disease, n (%)</td>
</tr>
<tr>
<td>Surgery and traumaology</td>
</tr>
<tr>
<td>Internal medicine and others</td>
</tr>
<tr>
<td>Onset of clinical symptoms before laboratory confirmation (mean±SD), d</td>
</tr>
<tr>
<td>TECs during heparin/heparinoid treatment, n (%)</td>
</tr>
<tr>
<td>Patients with TEC/evaluable patients</td>
</tr>
<tr>
<td>Type of TEC, n (%)</td>
</tr>
</tbody>
</table>

| Venous-distal | 35 (74.5) | 53 (66.3) |
| Pulmonary embolism | 23 (48.9) | 35 (43.8) |
| Venous-proximal | 22 (46.8) | 23 (28.8) |
| Arterial-peripheral | 16 (34.0) | 17 (21.3) |

*A patient could have suffered multiple TECs of different types.*
Mean duration of treatment for the remaining 103 historical control patients was 14.9 ± 15.8 days (mean ± SD), comparable to that of the 71 r-hirudin patients (14.0 ± 9.9 days). For historical control patients, the mean treatment durations were as follows: danaparoid sodium, 23.0 ± 22.0 days (n = 32); ongoing phenprocoumon, 14.3 ± 12.3 days (n = 22); no anticoagulation, 10.4 ± 9.7 days (n = 23); and miscellaneous, 9.5 ± 8.5 days (n = 26). Miscellaneous first selected treatments were ongoing LMWH (n = 6), phenprocoumon (n = 5), ongoing danaparoid sodium (n = 4), ongoing aspirin (n = 3), LMWH (n = 2), aspirin (n = 2), thrombolytics (n = 2), and ongoing thrombolytics (n = 2).

Two patients in the historical control group and 1 patient in the r-hirudin group were excluded from the combined end-point analysis and analysis of new TECs because the time to event was not evaluable. Two additional patients in the historical control group were excluded because treatment duration was only 1 day. Thus, the analysis was based on 99 historical control patients and 70 r-hirudin–treated patients. Cumulative incidences of the combined end point (death, limb amputations, new TECs) in the first selected treatment comparison are shown in Figure 3. Incidence was consistently higher in the historical control group across all time points (9.1% versus 32.8% by day 14; \( P < 0.001 \), log-rank test), even after adjustment for the prespecified prognostic factors in a Cox regression analysis (\( P = 0.003 \)). The estimated adjusted hazard ratio (r-hirudin to historical control) was 0.279 (95% CI, 0.112 to 0.699). Cumulative incidences of death (\( P = 0.02 \)) and new TECs (\( P = 0.006 \)) during treatment were significantly lower in the r-hirudin group than in the historical control group.

### Discussion

Although much has been learned about the incidence, clinical presentation, laboratory diagnosis, and pathogenesis of HIT, an optimal treatment strategy for affected patients has not yet been determined. This study indicates that r-hirudin not only provides effective anticoagulation in patients with HIT but also allows rapid platelet recovery.

The sequelae of acute HIT can be severe. Six patients with HIT in this study died (no death was associated with bleeding complications from the use of r-hirudin). Three patients (3.7%) underwent limb amputation, 2 of whom were treated with r-hirudin for perioperative (limb amputation) anticoagulation. Only 2 of 9 new TECs occurred during r-hirudin treatment; indeed, most new TECs occurred after cessation of r-hirudin treatment, despite the cessation of heparin and the normalization of platelet counts. Even oral anticoagulation could not completely prevent new TECs. This suggests that HIT antibodies may be cross-reacting with endogenous heparin-PF4 complexes, as we have been able to absorb and elute HIT antibodies from endothelial cells in vitro.

Because neither a placebo-controlled nor a randomized study could be performed for ethical and formal reasons, we compared the outcome of r-hirudin–treated patients with a historical control group treated with the best care available before r-hirudin. Despite moderate differences in clinical status at baseline between the 2 groups, we could not identify
any bias in the selection of historical control patients from the registry. When the cumulative incidences of death, limb amputations, and new TECs after HIT confirmation were compared, patients in the r-hirudin–treated group had significantly better outcomes (25.4% versus 52.1% in the historical control 5 weeks after HIT confirmation; \( P = 0.014 \)). Even after exclusion of TECs, which are subject to potential misclassification errors, the incidence of the combined end point of limb amputations and deaths was consistently lower in the r-hirudin group than in the historical control group.

Patients with HIT are often severely ill, and the underlying diseases might contribute to complications in the follow-up period. We therefore compared event rates in patients during r-hirudin treatment with event rates in historical control patients during the first selected treatment after HIT confirmation. Patients’ risk of experiencing potential HIT-related adverse events was reduced by 72% (\( P < 0.001 \)) during r-hirudin treatment.

Hemorrhage has been associated with r-hirudin treatment in other clinical studies.\(^{29,34,35}\) In the present study, no intracerebral or fatal hemorrhages were observed. In most cases, major bleeding occurred as a perioperative or postoperative complication. Bleeding complications were not correlated with r-hirudin plasma levels. Furthermore, the incidence of bleeding in the r-hirudin group was not statistically different from that in the historical control group. To prevent bleeding complications, renal function should be monitored carefully during r-hirudin treatment, because renal elimination is \( > 90\% \). Severe hemorrhages have been observed in patients with acute HIT and renal failure who had a concomitant uremic platelet function defect.\(^{36}\)

In conclusion, this first prospective study with r-hirudin in patients with confirmed HIT has shown r-hirudin to be an effective and safe anticoagulant, yielding significant aPTT prolongations. r-Hirudin did not cross-react with heparin-induced antibodies, as evidenced by rapid and sustained platelet recovery. Furthermore, this study provides clear evidence that treatment with r-hirudin results in true clinical benefits for patients suffering from HIT. Comparison of health outcomes of r-hirudin–treated patients with those of historical control patients with confirmed HIT revealed a marked reduction in the combined incidence of death, limb amputations, and new TECs. Finally, r-hirudin enables parenteral anticoagulation despite the presence of HIT antibodies, providing life-saving treatment for severely ill patients.

Appendix

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**TABLE 5. Cumulative Incidences of Bleeding Events After HIT Confirmation**

<table>
<thead>
<tr>
<th></th>
<th>r-Hirudin (n=71)</th>
<th>Historical Control (n=120)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleedings or transfusions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>49</td>
<td>76</td>
<td>26.0</td>
</tr>
<tr>
<td>Day 14</td>
<td>45</td>
<td>60</td>
<td>30.2</td>
</tr>
<tr>
<td>Day 28</td>
<td>16</td>
<td>27</td>
<td>35.3</td>
</tr>
<tr>
<td><strong>Bleedings requiring transfusions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>65</td>
<td>99</td>
<td>7.0</td>
</tr>
<tr>
<td>Day 14</td>
<td>61</td>
<td>79</td>
<td>9.1</td>
</tr>
<tr>
<td>Day 28</td>
<td>24</td>
<td>40</td>
<td>9.1</td>
</tr>
</tbody>
</table>

*Log-rank test.
Investigators

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References


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