A Pilot, Early Angiographic Patency Study Using a Direct Thrombin Inhibitor as Adjunctive Therapy to Streptokinase in Acute Myocardial Infarction

Rosa-Maria Lidón, MD; Pierre Théroux, MD; Jacques Lespérance, MD; Burt Adelman, MD; Raoul Bonan, MD; Diane Duval, RN; Johanne Lévesque, RN

Background  The success of streptokinase in acute myocardial infarction is hampered by the high failure rate to achieve early reperfusion. This study evaluates the possible benefit of Hirulog (Biogen, Cambridge, Mass), a direct thrombin inhibitor, as adjunct therapy to streptokinase to enhance early patency and prevent rethrombosis. Heparin has been shown to be of very limited benefits in this setting.

Methods and Results  Forty-five patients were randomized to Hirulog or heparin (2:1 ratio). Coronary angiography documented a TIMI 2 or 3 flow after 90 minutes in 77% of the patients treated with Hirulog and streptokinase and in 47% of patients treated with heparin and streptokinase (P<.05) and after 120 minutes in 87% and 47% of patients, respectively (P<.01). TIMI 3 flow was established in 77% of patients with Hirulog compared with 40% with heparin (P<.02). The clinical outcome and the bleeding rate were also favorable to Hirulog; no reocclusion was observed at late angiography performed 4.7 days later.

Conclusions  Hirulog in this pilot study significantly improved the early patency rate of the infarct-related artery with a favorable clinical profile. This new direct thrombin inhibitor exhibits promise as adjunctive therapy to thrombolysis. (Circulation. 1994;89:1567-1572.)

Key Words  • angiography • heparin • streptokinase

Intravenous thrombolytic therapy improves ventricular function and reduces mortality in acute myocardial infarction. However, failure to achieve early patency and reocclusion after successful reperfusion occur in many patients despite the use of various thrombolytic regimens. These unwanted events are associated with poorer left ventricular function and a worse prognosis, limiting the benefits of thrombolysis. Experimental studies, on the other hand, have shown that recombinant hirudin and related specific thrombin inhibitors such as Hirulog (Biogen, Cambridge, Mass) could facilitate thrombolysis and prevent rethrombosis better than heparin and antplatelet therapy when used in combination with tissue plasminogen activator or with streptokinase. This study was designed as a pilot study to determine whether Hirulog, a highly specific and potent bivalent inhibitor of thrombin, could be useful as adjunctive therapy to streptokinase to restore coronary blood flow in the infarct-related artery and to maintain patency.

Methods

Inclusion of Patients

Recruitment for this study was done using a fast-track procedure for early identification and management of patients with acute myocardial infarction. Patients admitted for chest pain were rapidly questioned and examined by the on-site medical staff, and a 12-lead ECG was obtained. The indication for thrombolysis, the absence of contraindications, and the eligibility for the study were immediately established. Inclusion criteria were onset of chest pain within the preceding 6 hours and ST segment elevation ≥1 mm in two contiguous ECG leads. The presence of any exclusion factors was ruled out using a quick checklist: previous administration of streptokinase, the presence of acute pulmonary edema or shock, a history of hemorrhagic stroke, intracranial bleeding or transient cerebral ischemic attacks, uncontrolled hypertension (>180/110 mm Hg), childbearing potential, gastrointestinal bleeding within the previous 2 years, major surgery or trauma within the previous 3 months, arterial puncture in a noncompressible site within the previous month, a known bleeding disorder, or any severe associated disease contraindicating the use of streptokinase. Participation in the study was proposed to eligible patients while the standard monitoring facilities were installed. The study drugs were initiated shortly after obtaining a signed informed consent, and the cardiac catheterization team was notified of patient eligibility. This procedure was operative on a 24-hour-a-day basis including weekends.

Study Drug Administration

The solutions were prepared daily by the hospital pharmacist and kept in a sealed bag at the emergency room. Randomization was double-blind, and the sequence included a ratio of two patients receiving Hirulog for one patient receiving heparin. The rationale for this design was to increase the statistical power for the analysis of the experimental group (Hirulog) compared with the control group (heparin), considering the many available reports in the literature showing very consistent data for the angiographic patency rates observed with heparin. Once the seal was broken, the study drug, Hirulog or heparin, was administered single blind. It was started immediately before or simultaneously with streptokinase, with no initial bolus. Aspirin 325 mg had been previously administered orally to all patients. The initial infusion rate of Hirulog was...
0.5 mg/kg per hour and of heparin, 1000 U/h. After 12 hours, the infusion rate of Hirulog was reduced to 0.1 mg/kg per hour, whereas the rate of heparin infusion was titrated to maintain an activated partial thromboplastin time (aPTT) 2.0 to 2.5 times control. The infusions were discontinued approximately an hour before the second angiogram, which was performed a mean of 4.7 days later; the heparin infusion was reinstalled if a decision for angioplasty was made during this procedure. The dose of streptokinase administered was 1.5 million U over 45 to 60 minutes (mean, 48.8±13 minutes).

**Cardiac Catheterization**

A percutaneous transfemoral approach was used for coronary angiography. The coronary artery not suspected to be involved was initially injected to determine the presence or absence of contralateral collaterals. The culprit coronary artery lesion was subsequently rapidly identified and the Thrombolysis In Myocardial Infarction (TIMI) grade flow determined.14 Dye injections of the culprit coronary lesion were performed every 10 minutes until 120 minutes after the start of streptokinase. The TIMI flow was recorded at each injection of the infarct-related artery. The opposite coronary artery was fully opacified between these injections, and a left ventriculogram was obtained in the 30° right oblique position. If grade 2 or 3 flow was achieved at 120 minutes, the procedure was stopped, the patient was transported to his or her room in the coronary care unit, and the infusion of Hirulog or heparin was maintained. Mechanical recanalization was attempted using conventional balloon angioplasty if the flow grade at 120 minutes was 0 or 1. The infusion of Hirulog was discontinued in this instance, and all patients received a bolus of heparin followed by a heparin infusion. The femoral sheath was removed in all patients the following day. A second coronary angiography was performed 3 to 7 days after initial therapy at a mean of 4.7 days. Coronary angioplasty of the culprit coronary artery lesions, based on clinical and angiographic indications, was performed during this second procedure in 18 patients.

**Study End Points**

The study had two predefined major end points. The first was restoration of TIMI 2 or 3 flow 90 and 120 minutes after the start of the streptokinase injection; the second was the absence of reocclusion at the late angiogram obtained 3 to 7 days later.

Secondary predefined end points were (1) TIMI grade 3 flow at 90 and at 120 minutes and (2) reinfarction, hemodynamic deterioration, and hemorrhagic complications during the study period. All TIMI flow grades used for data analysis were provided separately by an experienced radiologist and an interventional cardiologist completely blinded to treatment, with a consensus obtained when disagreement was present.

**Statistical Analysis**

χ² and Student's t tests were used to compare the baseline characteristics of the two study populations. Endpoint events were analyzed by the Fisher's exact probability test and confidence limits by the Taylor series. Data are presented as mean±SD; a value of P<.05 was considered significant.

**Results**

**Patient Characteristics**

Ninety-one of the 129 consecutive patients admitted for an acute myocardial infarction at the Montreal Heart Institute between March and September 1992 fulfilled study entry criteria of chest pain presentation with ST segment elevation. Forty-six of these patients were not enrolled. In most instances, patients were excluded by predefined exclusion criteria except for refusal by two patients and nonavailability of the catheterization laboratory for two others (Table 1).

A total of 45 patients, 10 women and 35 men with a mean age of 56±10 years (range, 26 to 77), were included in the study. The clinical characteristics of these patients are listed in Table 2. Age, sex, blood pressure at admission, and site of the myocardial infarction were the same in the two study groups. Mean time elapsed from onset of pain to start of streptokinase was 149±59 minutes and from onset of streptokinase to coronary angiography, 65±19 minutes, similar in the two study groups. The Hirulog patients were less frequently smokers and more often had experienced a previous infarction.

**Early and Late Patency**

Fig 1 shows the early patency rates achieved 90 and 120 minutes after streptokinase administration as defined by the presence of TIMI 2 or 3 flow and by the presence of TIMI 3 flow and the relative risks of success and 95% confidence limits. TIMI grade 2 and 3 flows were significantly more frequent at all times with Hirulog compared with heparin. At 120 minutes, TIMI grade 3 flow was present in 23 (77%) of the patients compared with six of the 15 (40%) heparin patients (P<.02). Grade 2 or 3 flow was achieved in 87% and 47% of patients receiving Hirulog and heparin, respectively (P<.01). No patients showed deterioration of TIMI grade flow between 90 and 120 minutes. Guide wire perforation of the clot and balloon angioplasty were performed successfully in all patients with TIMI 0 or 1 flow at 120 minutes.

Late angiograms were obtained 4.7±0.7 days after admission in 38 of the 45 patients, 26 treated with Hirulog and 12 with heparin. The reasons for not performing the late catheterization were death in two patients, stroke in one, medical contraindications in two, and patient refusal in two. Only one patient had reocclusion; this patient was in the heparin group. No reocclusion occurred among the Hirulog patients.

**Table 1. Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion and Exclusion Criteria</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients admitted for MI</td>
<td>129</td>
</tr>
<tr>
<td>Absence of an inclusion criterion</td>
<td></td>
</tr>
<tr>
<td>Chest pain for more than 6 hours</td>
<td>15</td>
</tr>
<tr>
<td>No ST elevation</td>
<td>23</td>
</tr>
<tr>
<td>No. eligible</td>
<td>91</td>
</tr>
<tr>
<td>Exclusion</td>
<td></td>
</tr>
<tr>
<td>Age &gt;78 years</td>
<td>7</td>
</tr>
<tr>
<td>Cardiogenic shock/pulmonary edema</td>
<td>9</td>
</tr>
<tr>
<td>Previous SK administration</td>
<td>7</td>
</tr>
<tr>
<td>Ongoing heparin treatment</td>
<td>7</td>
</tr>
<tr>
<td>Excessive bleeding risk</td>
<td>12</td>
</tr>
<tr>
<td>Catheterization laboratory not available</td>
<td>2</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>2</td>
</tr>
<tr>
<td>No. enrolled</td>
<td>45</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; SK, streptokinase.
TABLE 2. Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Hirulog (n=30)</th>
<th>Heparin (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>56.3±10.6</td>
<td>55.5±9.4</td>
</tr>
<tr>
<td><strong>Sex (male/female)</strong></td>
<td>24/6</td>
<td>11/4</td>
</tr>
<tr>
<td><strong>Smokers</strong></td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td><strong>High blood pressure</strong></td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Previous PTCA</strong></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Systolic pressure at admission, mm Hg</strong></td>
<td>129±22</td>
<td>132±25</td>
</tr>
<tr>
<td><strong>Time from onset of pain to SK administration, min</strong></td>
<td>147±55</td>
<td>153±69</td>
</tr>
<tr>
<td><strong>Time from onset of SK to coronary angiography, min</strong></td>
<td>62±19</td>
<td>70±18</td>
</tr>
<tr>
<td><strong>Site of MI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior MI</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Inferior MI</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td><strong>Culprit coronary artery lesion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td><strong>Concomitant treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Intravenous nitroglycerin</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Intravenous β-blocker</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Oral β-blocker</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>

PTCA indicates percutaneous transluminal coronary angioplasty; SK, streptokinase; and MI, myocardial infarction.

Clinical Evolution

The clinical evolution and the bleeding complications are shown in Table 3. Chest pain lasted a total of 179±62 minutes with Hirulog and 236±85 minutes with heparin (P<.02), with similar doses of morphine used in the two groups (5.8±5 and 7.4±3 mg per patient, respectively, NS). Time until relief of chest pain after initiation of adjunctive therapy was also shorter with Hirulog, 36±35 minutes compared with 81±40 minutes with heparin (P<.001). The ejection fraction, calculated during the initial catheterization, was similar in the two study groups, 43±7% and 47±10%, respectively. Mean peak creatine kinase was 1927±1367 U/L in the Hirulog group and 1995±1015 U/L in the heparin group (NS). Peak MB-CK elevations also were not different: 212±137 U/L and 212±108 U/L, respectively. Myocardial infarct extension occurred in no patients treated with Hirulog and in one patient treated with heparin.

TABLE 3. Clinical Evolution and Hemorrhagic Complications

<table>
<thead>
<tr>
<th></th>
<th>Hirulog (n=30)</th>
<th>Heparin (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical evolution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class 3-4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>MI extension</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>2 (7%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>No. of patients with complications</td>
<td>2 (7%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td><strong>Bleeding complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All bleeding</td>
<td>20 (67%)</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>4 (13%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Catheter site</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Systemic</td>
<td>1*</td>
<td>3</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.
* Bleeding and death in this patient occurred while on heparin therapy.
therapeutic range; the values were higher during the first 12 hours of treatment and above three times control with both Hirulog and heparin. aPTT prolongation at the time of the first angiogram was significantly greater with Hirulog than with heparin \((P=0.01)\). The plasma levels of Hirulog determined by an enzyme immunoas-
say were \(532\pm 479\, \text{ng/mL}\) after 90 minutes of infusion and \(534\pm 762\, \text{ng/mL}\) after 3 days.

Bleeding complications were recorded in 30 patients. They were minor in 22 patients, at the femoral puncture site in 15, and at other sites in 7. Bleeding complications were as frequent with Hirulog as with heparin. Serious bleeding events were observed in eight patients, four in each study group, for a 13% incidence with Hirulog and 27% with heparin (NS). The severe bleedings were

in guinal, at the puncture sites in three Hirulog patients and one heparin patient. They were systemic in three heparin patients (retroperitoneal, intracranial, and of unknown site) and in one Hirulog patient (aortic rupture). This last patient died 16 hours after thrombolytic therapy; he received Hirulog for 2 hours and heparin for 14 hours because of unsuccessful reperfusion; the post-
mortem examination revealed an aortic perforation close to the right coronary ostium that was probably related to the catheterization procedure. The second

death in this study was the patient with intracranial bleeding, and the third was the patient with retroperi-
toneal bleeding who also had poor left ventricular function. Thus, bleeding led or contributed to death in three patients while receiving heparin therapy.

**Discussion**

This study suggests that Hirulog, one of the new direct thrombin inhibitors, can potentiate the thrombo-
lytic efficacy of streptokinase, resulting in an enhanced rate of early patency of the infarct-related artery. Consecutive patients were randomized to enter the study within 6 hours of the onset of pain. The relative risk for restoring blood flow with Hirulog compared with heparin was 1.86 (95% confidence limits, 1.06 to 3.25) and for restoring TIMI grade 3 flow, 1.92 (95% confidence limits, 1.00 to 3.67). Recoelection occurred in no Hirulog-treated patients.

Hirulog is a 20-amino-acid, synthetic peptide modeled on hirudin. It binds both to the anion-binding

exo site and to the catalytic site of the thrombin mole-


ule.\textsuperscript{15} The inhibition is equimolar, direct, and specific. Like hirudin, its use in experimental models of coronary artery thrombosis resulted in accelerated thrombolysis and prevention of rethrombosis.\textsuperscript{13} Explanations provided for a better efficacy of the direct thrombin inhibi-


tors have been the absence of endogeneous inhibitors\textsuperscript{16} and their ability to inhibit clot-bound thrombin,\textsuperscript{17} over-


coming two limitations of heparin.

This study was designed as a pilot study, and the small sample size limits the power of all conclusions that can be derived. However, consecutive patients were ran-

domized in a double-blind fashion to Hirulog or hepa-


rin. The study end points were objective and quantified in a blinded manner. The baseline characteristics were in general well balanced, with the exception of fewer smokers and more previous myocardial infarctions in the Hirulog group; these two factors are associated with a less favorable clinical outcome after myocardial infarction\textsuperscript{18,19}; nonsmokers also experienced early recurrent infarction more often.\textsuperscript{18} The study was designed to detect a risk reduction of 66%, with a value of \(P=.05\) and a power of 0.75. The randomization to Hirulog and heparin was uneven. Only one third of the population received heparin because numerous previous trials have consistently documented that standard therapy with streptokinase resulted in early patency of the culprit coronary artery lesion in approximately half the patients, with no further gain with high intravenous doses of heparin.\textsuperscript{7,20-23} The 90-minute patency rate observed in this study with heparin was 47%. This rate was 77% with Hirulog. After 120 minutes, the patency rate, unchanged with heparin, improved further to 87% with Hirulog. Defining success by the presence of TIMI 3 flow, which is clearly associated with better clinical evolution and left ventricular function,\textsuperscript{24,25} showed a success rate of 40% with heparin; yet, the success rate with Hirulog was 77%, nearly twice as frequent.

The aPTT prolongations achieved with Hirulog and with heparin were above the accepted therapeutic range throughout the study. The higher values observed at 60 and 120 minutes with Hirulog may be explained by the different half-life and distribution volume of Hirulog and heparin with bolus injections given. The values observed with Hirulog in this study were almost twice the values observed at similar doses in a previous study of patients with unstable angina; the plasma levels of the drug were, however, the same.\textsuperscript{26} The aPTT values with heparin also were higher than expected and above the usual target therapeutic range. These exaggerated prolongations of the aPTT with both drugs are probably related to the effects of fibrinolytic therapy, producing a systemic hypocoagulable state. The early difference in aPTT observed between the two drugs probably does not explain the differences in the patency rates. In the angiographic substudy of GUSTO,\textsuperscript{7} the use of a 5000-U bolus of heparin followed by an infusion of 1000 U per hour resulted in no better patency rate at 90 and 180 minutes than when heparin was started subcutaneously after 4 hours; indeed, TIMI 2 flow at 90 minutes was observed in 28% of patients with the bolus injection and in 25% with the subcutaneous administration and TIMI 3 flow in 32% and 29% of patients, respectively. At 180 minutes, these figures were 33% and 38% for TIMI 2 and 41% and 35% for TIMI 3 flow. These results of GUSTO validate our study design with no intravenous bolus of heparin given. The GUSTO trial showed that the best therapeutic strategy was accelerated recomb-


inant tissue plasminogen activator (rtPA) plus intrave-
uous heparin, resulting in TIMI 3 flow in 54% of patients at 90 minutes and in 43% at the 180-minute angiogram. In this study, the combination of Hirulog and of streptokinase resulted in further improvement with TIMI 3 flow in 67% of patients at 90 minutes and in 77% of patients at 120 minutes.

Whether the findings of this study with enhanced thrombolysis with Hirulog added to streptokinase will be reproduced in a larger and more definitive trial and whether they will also apply to the use of other fibrinolytic agents remain to be investigated. The dose of Hirulog selected was based on a previous dose-ranging study in patients with unstable angina observing the anticoagulant and antithrombotic properties of Hirulog: the optimal dose to use as adjunctive therapy to thrombolysis remains to be investigated. A patency rate of approximately 80% could represent as much as can be gotten; it is possible, however, that a better strategy can still improve results. Two abstracts have reported the use of recombinant hirudin as adjunctive therapy to rTPA. In the TIMI-5 study, infarct vessel patency at 90 minutes was 79% with hirudin and 83% with heparin (NS)27; reocclusion or recurrent ischemic pain occurred significantly less frequently with hirudin, however: 8% of patients compared with 18% with heparin. The other report described satisfactory angiographic results with the combination of recombinant hirudin and rTPA in 40 patients and an absence of major bleeding.28 The benefits of a new adjunctive therapy may be more easily documented when streptokinase is used as a fibrinolytic agent, since this drug is associated with delayed reperfusion compared with rTPA.29 This study lacks sufficient power to evaluate clinical events; these were more frequent than expected in the heparin group because of the small number of patients. However, much evidence now relates a favorable clinical evolution to more complete and earlier restoration of blood flow.22,23 The large trials have shown that earlier treatment resulted in lower mortality, suggesting that early reperfusion is important.3,4 Many studies have also suggested that early patency was associated with smaller infarcts, better left ventricular function, and reduced morbidity and mortality.24 The GUSTO trial confirmed this relation by showing that reperfusion achieved 90 minutes after thrombolysis, either with rTPA or with streptokinase, was associated with smaller end-systolic volume, better ejection fraction, and reduced mortality. In our study, a composite end point of clinical events showed a favorable profile for Hirulog: the only two events that occurred were congestive heart failure in one patient and death by aortic rupture in another patient who received heparin after failed reperfusion with streptokinase and Hirulog. Bleeding complications were frequent, but most were minor and related to the catheterization procedure. Severe bleeding complications occurred less frequently with Hirulog, and severe systemic bleeding was observed only during heparin therapy. The TIMI-5 study also has shown less bleeding with hirudin combined with rTPA compared with heparin combined with rTPA.27 Heparin has a narrow risk-benefit ratio; both efficacy and risk increase with higher doses.29 Such may not be the case with the new antithrombin drugs. The results of this study suggest enhanced thrombolysis with adjunctive therapy to streptokinase and a favorable clinical profile. These findings, if confirmed in larger trials, could lead to more optimal use of thrombolytic agents, defining a new adjunctive therapy specifically targeted at thrombin inhibition.

**Acknowledgments**

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**References**


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