Intravenous Heparin Started Within the First 3 Hours After Onset of Symptoms as a Treatment for Acute Nonlacunar Hemispheric Cerebral Infarctions

Massimo Camerlingo, MD; Pietro Salvi, MD; Giorgio Belloni, MD; Tiziano Gamba, MD; Bruno Mario Cesana, MD; Angelo Mamoli, MD

Background and Purpose—Heparin is widely used for acute stroke to prevent thrombus propagation and/or multiple emboli generation, although there is, as yet, no demonstrated efficacy. However, all of the available clinical studies allowed long intervals from stroke to treatment. The purpose of this study was to try an intravenous regimen of unfractionated heparin the acute cerebral infarction starting treatment within the first 3 hours of the onset of symptoms.

Methods—The study was an outcome evaluator-blind design trial. Patients had to display signs of a nonlacunar hemispheric infarction. Selected patients were randomly allocated to receive intravenous heparin sodium or saline. Heparin was infused at a rate to maintain activated partial thromboplastin time ratio 2.0 to 2.5 for 5 days. The primary end point was recovery of a modified Rankin score zero to 2 at 90 days of stroke at phone interview by a single physician blind to treatment. Safety end points were death, symptomatic intracranial hemorrhages, and major extracranial bleedings by 90 days of stroke.

Results—A total of 418 stroke patients were included. In the heparin group, there were more self-independent patients (38.9% versus 28.6%; \( P = 0.025 \)). In addition, in the same group, there were fewer deaths (16.8% versus 21.9%; \( P = 0.189 \)), more symptomatic brain hemorrhages (6.2% versus 1.4%; \( P = 0.008 \)), and more major extracerebral bleedings (2.9% versus 1.4%; \( P = 0.491 \)).

Conclusions—Intravenous heparin sodium could be of help in the earliest treatment of acute nonlacunar hemispheric cerebral infarction, even keeping into account an increased frequency of intracranial symptomatic brain hemorrhages. (Stroke. 2005;36:2415-2420.)

Key Words: anticoagulation ■ cerebral ischemia ■ heparin ■ stroke

No clinical trial has yet proven efficacy of heparin, both unfractionated and low-molecular-weight, in the treatment of the human stroke.\(^1\,2\) Nonetheless, heparin is still frequently prescribed\(^3\) in the hope of preventing either thrombus propagation or early recurrences of stroke. All the studies,\(^3\,11\) however, allowed long intervals from the onset of stroke to the initiation of treatment. On the contrary, both experimental\(^12\,13\) and clinical experiences\(^15\,16\) demonstrated that preservation of ischemic but still viable brain tissue is time-dependent. Thus, no data for the evaluation of heparin in the earliest treatment of stroke are presently available.\(^2\) Previously, we tested safety of anticoagulation with intravenous heparin started within the sixth hour of an acute carotid stroke\(^17\) in a small pilot study. Basing both on that study and on the need to even speed up the start of treatment,\(^15\) we designed a randomized, controlled trial, and here we report the results. The study was made possible because at that time, intravenous thrombolysis was not yet approved in Italy for stroke.

Methods

The study was designed to test whether an anticoagulant regimen of intravenous heparin sodium started within the first 3 hours of an acute nonlacunar hemispheric cerebral infarction could be effective and safe.

The trial was performed at 1 stroke unit, and was controlled and randomized.

Randomization was computer-generated. The study was an outcome evaluator-blind design trial. Informed consent had to be obtained. Start of the study was January 1, 1996.

The primary end point of the study was the rate of patients recovering self-sufficiency by 90 days of stroke. That end point was evaluated by phone by a single physician blind to treatments. Safety end points were the rates of deaths symptomatic cerebral hemorrhages, and major extracranial bleedings by 90 days.
The protocol was found to be in agreement with the ethical rules by our Ethical Committee. Finally, the study was not financially supported by companies or government grants.

Screening Procedure
We considered all alert patients referred to our Stroke Unit within the first 3 hours of the onset of an acute neurologic deficit suspected for cerebral infarction. All those patients were immediately given a neurologic score of severity and submitted to a computed tomography (CT) of the brain in addition to blood routine examination, electrocardiogram (ECG), and duplex scanning of the carotid arteries.

Criteria of inclusion was a clinical syndrome indicating a large-vessel hemispheric stroke that is a total or a partial anterior circulation syndrome (TACS, PACS) to have best chances to visualize the actual ischemic lesion at neuroradiologic controls. Criteria of exclusion were:

1. PACS characterized only by higher cerebral dysfunction alone or by motor deficit confined to the face or to one limb to avoid treatment to patients with an already predictable good spontaneous outcome;
2. a lacunar syndrome (LACS);
3. age <18 and >90 completed years;
4. stupor or coma;
5. any previous handicap making nonapplicable the neurologic scale of evaluation at entry;
6. any uncertainty about the time of onset of stroke;
7. persistent systolic blood pressure >185 mm Hg and/or diastolic blood pressure >110 mm Hg at entry;
8. rapid regression of symptoms before treatment;
9. other diagnoses from CT;
10. any current contraindication to anticoagulants;
11. cancer or any other severe concurrent disease;
12. pregnancy;
13. inability to start treatment within the third hour of stroke; and
14. inability to obtain informed consent from patients or their relatives.

A previous stroke was a matter of exclusion if the patient had persistent motor or higher cerebral dysfunction at the time of the qualifying stroke.

Therapeutic Plan
After recruitment, the patients were assigned to receive for 5 days a pump-assisted infusion of intravenous heparin sodium (24 000 IU per day dissolved in 1000 mL of saline without initial bolus) or of equal quantity of saline. The speed of infusion, either unfractionated heparin or saline, was 42 mL/hr. Prothrombin time international normalized ratio (PTINR), partial thromboplastin time ratio (PTTR), and platelet counts were obtained at 6 hours after the start of infusion and then every day in both groups of patients. Unfractionated heparin was regulated aiming to maintain activated thromboplastin time (PTT) 2.0 to 2.5 times the control ratio. Treatment was immediately withdrawn in case of any hemorrhage. After 5 days of stroke, both groups of patients were given oral aspirin (100 mg/day) or oral anticoagulants (targeted to obtain PTINR between 2.0 and 3.0) in case of cardiac sources of emboli.

Since admission, both groups of patients received supportive general care and control of blood pressure, in addition to rehabilitation maneuvers. Systolic blood pressure was aimed to be maintained 120 to 165 mm Hg and diastolic blood pressure 70 to 95 mm Hg. In the control group, 5000 IU of calcium heparin was administered subcutaneously twice a day for the prevention of deep venous thrombosis (DVT). Furthermore, compression stockings were used in both groups to prevent DVT.

Evaluations After Admission
The etiologic mechanism of stroke was assigned according to the TOAST criteria. CT was repeated between day 4 and day 7 of stroke, in case of stroke recurrence, and whenever there was suspected cerebral bleeding.

In cases of sudden or unexplained inhospital death, a necropsy study was obtained. Cerebral bleedings were differentiated in symptomatic or asymptomatic according to the rules of the NINDS trial.

Extracranial bleedings were defined as major when needing blood transfusions. CT scans were reviewed by a single neuroradiologist (G.B.) who was blind to treatments. The functional status at 90 ± 10 days of stroke was assigned by phone interview by P.S., neurologist and head at a rehabilitation center, settled far from our general hospital. He was blind to the treatments.

To ensure proper blinding, none of the patients had to be sent for rehabilitation to his center. Phone interviews were collected either by the caregivers or the patients. A score of 0 to 2 of the modified Rankin Scale was considered as criterion for recovery of self-independence.

Statistical Analysis
All the data were recorded in a database file and processed for statistical analyses with the Statistical Package for Social Sciences (SPSS Inc.) by B.M.C., who is an experienced statistician. Data were analyzed according to the intention-to-treat principle. All tests were 2-tailed, and probability value <0.05 was considered an indicator of significance. The minimal number of needed patients was provided to be approximately 408 according to a trial attempting to ascertain a difference in favor of heparin of approximately 30% with a power of 90%.

Results
Study Population
Of 2589 consecutively screened stroke patients by December 31, 2001, 418 patients (16.1%) met the selection criteria. They were 247 women and 171 men, with a mean age of 70.9 years (range, 22 to 90 years). The vascular risk factors of the study population were: hypertension in 278 patients (66.5%), diabetes in 73 (17.5%), smoking in 136 (32.5%), hyperlipidemia in 62 (15.1%), and known cardiac diseases in 218 (52.1%).

Atrial fibrillation was found at entry ECG in 173 patients (41.3%), whereas an appropriate internal carotid artery disease (stenosis >50% or occlusion) was seen at duplex scanning in 127 patients (30.4%).

Stroke was a TACS in 204 patients (48.8%) and a PACS in 214 (51.2%).

According to subtype classification, stroke was considered to be cardioembolic in 178 (42.6%), atherothrombotic in 101 (24.2%), and of unknown/undetermined origin in 139 (33.2%).

Figure reports the flow diagram of the study. Two hundred eight patients were given intravenous heparin sodium. The 2 groups were well balanced as baseline characteristics by randomization (Table 1).

None of the patients in either group received any treatment before randomization. The interval stroke to needle was quite similar in both groups. It was 147 minutes (range, 59 to 178 minutes) in the heparin group and 152 minutes (range, 54 to 180 minutes) in the control group (P = 0.455, Student t test).

Blood pressure also was similar between groups at time of starting treatments. It was (systolic/diastolic mm Hg mean values ± standard deviation) 137.6/78.2 ± 20.3/10.9 in the heparin group and 139.1/79.5 ± 22.7/10.1 in the other group (P = 0.477 for systolic and P = 0.207 for diastolic blood pressure, Student t test).
All the patients assigned to heparin sodium received planned treatment.

None of the patients in the control group was shifted to unfractionated heparin.

All of the patients had a second CT, except a woman on intravenous heparin, who was found at necropsy to have a large hemorrhagic transformation of the cerebral infarction.

**Primary End Point**

At 90 days of stroke, the patients recovering self-sufficiency were 81 of 208 (38.9%) in the heparin sodium group and 60 of 210 (28.6%) in the other group. That difference was statistically significant ($P=0.025$).

Table 2 shows the rates of the patients per single score on the modified Rankin Scale.

**Safety End Points**

Eighty-one patients (19.4%) died within 90 days of stroke. Thirty-five deaths were recorded in the group treated with heparin sodium (16.8%) and 46 in the other group (21.9%). That difference did not achieve statistical significance ($P=0.189$). The causes of deaths are reported in Table 3. Symptomatic cerebral hemorrhage was seen in 16 patients. Of those, 13 patients were in the treatment group (6.2%) and 3 patients in the control group (1.4%) ($P=0.008$).

Asymptomatic hemorrhagic transformations of the brain ischemia were seen at control CT in 44 patients (23 versus 21, $P=0.725$).

Table 4 shows the hemorrhagic complications of the brain we have seen. Major extracranial bleedings were seen in 9
patients. Of them, 6 patients received intravenous heparin (2.9%) and 3 were in the control group (1.4%) (P/H11005 0.491).

Those extracranial bleedings occurred in the abdominal muscle wall (4 patients), in the gastrointestinal tract (4 patients), and in a shoulder (1 patient). No death was the result of an extracranial major bleeding.

Finally, none of the patients had platelets decreased below 100 000/cm3.

Discussion
Our study suggests that an anticoagulant regimen of intravenous heparin sodium, administered within the first 3 hours of the onset of symptoms, could be of benefit for the patients with an acute nonlacunar hemispheric cerebral infarction.

Those patients were more likely to be self-independent and alive by 90 days of stroke. The absolute risk reduction for the recovery of self-independence was approximately 10%, which would appear to be interesting because of the clinical severity of the patients included in the study. Possibly, intravenous heparin could have been effective because of utilization closest to the onset of stroke. To date, information on heparin was from studies allowing intervals because stroke to initiation of treatment was up to 12 hours,10 24 hours,7,8 or 48 hours.3–6.9.11 Because all of those studies dealing with systemic thrombolysis beyond 3 hours of the onset of stroke failed,15,16,24–28 the time intervals of the previous studies on heparin appear to be really very long.

Another explanation of our results could have been the anticoagulant regimen of heparin administration. Complete anticoagulation was shown to be superior than fixed doses because it prevents not only of embolisms to the brain,29 but also of severity of the strokes occurring during treatment of patients with atrial fibrillation.30 Thus, the high rate of patients with cardioembolic subtype of stroke we included could have optimized the effect of heparin. Furthermore, a recent experimental study has demonstrated that steady plasma concentration of unfractionated heparin can reduce the infarct volume after transient focal cerebral ischemia in the rat.31

In our opinion, timing and dosage of unfractionated heparin and patients’ selection could have concurred together resulting in the success of the study.

A possible criticism of our study might be the choice to accept scores 0 to 2 of the modified Rankin Scale23 as criterion for the recovery of self-independence. That choice could have apparently enlarged the benefit from intravenous heparin.

To consider recovery of self-independence, a score ≤1 (complete recovery of the neurologic deficit) or ≤2 (no or slight neurologic disability) on the modified Rankin Scale23 is not without meaning because it was the cause of failure of a large clinical trial.28 NINDS trial accepted grade 0 and 1, but it included also patients with modest deficit.15 On the contrary, PROACT II trial, which probably selected patients as severe as ours, considered as self-independent the patients recovering grade 0 to 2.32

Finally, the authors of the original article23 considered scores 0 to 2 as recovery of self-independence. Thus, both the clinical severity of the patients we selected and the indications from the original paper would be in agreement with our criterion.

TABLE 1. Patients’ Characteristics by Group of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Control, n (%)</th>
<th>Heparin, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>210</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>71 (23–90)</td>
<td>70 (22–90)</td>
<td>0.752</td>
</tr>
<tr>
<td>Men</td>
<td>85 (40.5)</td>
<td>86 (41.3)</td>
<td>0.856</td>
</tr>
<tr>
<td>Women</td>
<td>125 (59.5)</td>
<td>122 (58.6)</td>
<td></td>
</tr>
<tr>
<td>Rankin score one before stroke</td>
<td>12 (5.7)</td>
<td>14 (6.7)</td>
<td>0.820</td>
</tr>
<tr>
<td>Median NIHSS at entry (full range)</td>
<td>17 (6–27)</td>
<td>17 (6–28)</td>
<td>0.654</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (64.8)</td>
<td>142 (68.3)</td>
<td>0.447</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34 (16.2)</td>
<td>39 (18.7)</td>
<td>0.491</td>
</tr>
<tr>
<td>Smoking</td>
<td>68 (32.3)</td>
<td>68 (32.7)</td>
<td>0.946</td>
</tr>
<tr>
<td>Any heart disease</td>
<td>103 (49.0)</td>
<td>115 (55.3)</td>
<td>0.201</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>80 (38.1)</td>
<td>93 (44.7)</td>
<td>0.170</td>
</tr>
<tr>
<td>Carotid artery disease</td>
<td>60 (28.6)</td>
<td>67 (32.2)</td>
<td>0.418</td>
</tr>
<tr>
<td>TACS</td>
<td>102 (48.6)</td>
<td>102 (49.9)</td>
<td>0.924</td>
</tr>
<tr>
<td>PACS</td>
<td>108 (51.4)</td>
<td>106 (50.1)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic subtype</td>
<td>85 (40.5)</td>
<td>93 (44.7)</td>
<td>0.330</td>
</tr>
<tr>
<td>Atherothrombotic subtype</td>
<td>46 (22.8)</td>
<td>53 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown/undetermined subtype</td>
<td>77 (36.7)</td>
<td>62 (29.8)</td>
<td></td>
</tr>
</tbody>
</table>

NIHSS indicates National Institute of Health Stroke Scale.15

TABLE 2. Rates of Scores on the Modified Rankin Scale

<table>
<thead>
<tr>
<th></th>
<th>Heparin, n (%)</th>
<th>Control, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18 (8.6)</td>
<td>12 (5.7)</td>
</tr>
<tr>
<td>1</td>
<td>34 (16.3)</td>
<td>23 (10.9)</td>
</tr>
<tr>
<td>2</td>
<td>29 (13.9)</td>
<td>25 (11.9)</td>
</tr>
<tr>
<td>3</td>
<td>20 (9.6)</td>
<td>24 (11.4)</td>
</tr>
<tr>
<td>4</td>
<td>39 (18.7)</td>
<td>37 (17.6)</td>
</tr>
<tr>
<td>5</td>
<td>33 (15.9)</td>
<td>43 (20.5)</td>
</tr>
<tr>
<td>Deaths</td>
<td>35 (16.8)</td>
<td>46 (21.9)</td>
</tr>
</tbody>
</table>

TABLE 3. Causes of Deaths

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke itself</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Brain hematoma</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia/sepsis</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary embolism*</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

*There were 2 more nonfatal pulmonary embolisms in the heparin group, but no nonfatal pulmonary embolism in the control group.

TABLE 4. Hemorrhagic Complications of the Brain

<table>
<thead>
<tr>
<th></th>
<th>Control, n (%)</th>
<th>Heparin, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>3 (1.4)</td>
<td>13 (6.2)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1 (0.5)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>2 (0.9)</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>21 (10.0)</td>
<td>23 (11.0)</td>
</tr>
</tbody>
</table>
However, even when considering in our study only the patients achieving a score of 0 or 1 at 3 months of stroke as recovery of self-independence, the difference would remain statistically significant (52 versus 35; \( P = 0.0479, \chi^2 \) test).

Thereby, independently from the criteria to tribute recovery of self-independence, intravenous heparin would seem to be an effective treatment of the acute hemispheric cerebral infarction. Another matter of criticism might be the open design of the study, which left to a phone interview the assessment of the final functional status. However, the assessment was made by a single physician, skilled of disability measures, who stayed far from our unit and was completely blind to the medical records. We used that method because it was already validated in Italy.33

In addition, a similar procedure was already used in the up-to-date largest clinical trial on stroke treatment, and in a large clinical trial on thrombolysis too.24

As for thrombolysis, also intravenous heparin was associated with an increased risk of symptomatic intracranial hemorrhage. However, our rate did not look high and it was similar to the one found in the NINDS trial.15 Other trials of thrombolysis reported greater rates, but they included patients whose signs started up to 6 hours since stroke.16,24–28 No information is available for the clinical trials on intravenous heparin.3,4

In our study, we observed almost 28.5% patients recovering self-independence in the control group. This should be a consequence that all the patients were managed in a stroke unit.24 In conclusion, we think that the main suggestion from our study was that it might be another brick to the concept limit of the 3 hours from onset of stroke to start treatment. That limit could be valid whichever the treatment really interfering with the cascade of coagulation, because the favorable results observed also by another trial, which used a different agent within the same time interval of stroke.35

However, other data have to be obtained to confirm this impression.

Addendum

By this time this manuscript was submitted, another trial dealing with unfractionated heparin and stroke was published (Chamorro A, Busse O, Obach V, Toni D, Sandercop P, Reverer JC, Cervera A, Torres F, Davalos A; for the RAPID Investigators. The RAPID Medicine Service of The Ospedali Riuniti di Bergamo. 2005;19:402–404). That trial, which included patients up to 12 hours from the onset of stroke, was prematurely interrupted after 67 patients were enrolled. The main result was a trend toward a lower recurrence rate in the patients treated with unfractionated heparin. There was no difference in the rate of “hemorrhagic worsening.”

Acknowledgments

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References


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