ORIGINAL CONTRIBUTION

Immediate Anticoagulation With Heparin for First-Ever Ischemic Stroke in the Carotid Artery Territories Observed Within 5 Hours of Onset

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Objective: To evaluate the safety and possible efficacy of heparin sodium anticoagulation within 5 hours of the onset of first-ever nonlacunar ischemic strokes in the internal carotid artery territories.

Design: Pilot study, prospective and open.

Setting: Inpatient stroke unit.

Patients: Of 360 stroke patients observed during 13 months, 45 (12.5%) were included in the study.

Interventions: Heparin sodium was administered intravenously, starting with a bolus of 10 000 U, followed by continuous infusion over 4 days at a rate adjusted to maintain an activated partial thromboplastin time ratio between 2 and 2.5. The mean interval from stroke to treatment was 197 minutes.

Results: Two patients had cerebral hemorrhage, one of which was fatal. None had extracranial major bleeding, while six had minor bleeding. The conditions of 23 patients improved, 16 patients were stable, and six patients worsened by day 1, while 29 patients improved, eight patients were stable, and eight patients worsened by day 7. Six patients died by the first month and five more by the sixth month. Twenty-one patients were self-sufficient, both at 1 and 6 months. Hemorrhagic complications were unrelated to any investigated factor. Multivariate analysis indicated that short-term outcome was predicted only by infarct size ($P<.0001$) and long-term outcome by infarct size ($P=.002$) and large vessel status ($P=.0235$).

Conclusions: Our study suggests that immediate heparin treatment for ischemic carotid stroke is feasible and generally safe and that patients whose conditions improve are those with smaller infarct size and no evidence of large vessel obstruction.

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HEPARIN SODIUM is widely used in the treatment of brain ischemia[1] despite inconclusive available data,[2,3] which are derived from several uncontrolled studies[4-8] and few randomized studies.[9,10] Those studies delayed initiation of treatment from the onset of stroke, using heparin as a preventive drug against early stroke recurrence or enlargement of thrombi. By contrast, experimental data[11,12] support the earliest treatment possible to save ischemic but still viable brain tissue.

Because cardiac embolism is a frequent cause of the arterial occlusions seen during the first few hours after stroke,[13] patients with early observed stroke might benefit from anticoagulation therapy.[14] Thus, we have prospectively evaluated the safety and possible effectiveness of heparin, which was administered within 6 hours of the onset of a first-ever nonhemorrhagic stroke in the internal carotid artery territories.

RESULTS

Of 360 consecutively screened patients, 48 were treated within 6 hours of stroke, and 45 (12.5%) were included in

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PATIENTS AND METHODS

From February 1, 1991, to March 31, 1992, all patients referred to our stroke unit because of a first-ever, acute neurological deficit of presumed vascular origin, suggesting involvement of carotid artery territories referred within 5 hours of onset. These patients were considered for immediate heparin anticoagulation therapy. Those patients underwent a computed tomographic (CT) scan immediately after hospital admission.

Table 1 summarizes our exclusion criteria. We excluded lacunar syndromes, defined according to Bamford et al,[15] because of their peculiar, usually benign prognosis. We also retrospectively excluded treated patients without demonstration of a recent consistent infarction in the anterior circulation on the second CT scan because of ambiguous location of the brain ischemia. Suitable patients underwent a scored neurological examination using the Canadian Neurological Scale[16] and ultrasounds (both extracranial and transcranial). Patients with poor signal quality at transcranial Doppler ultrasounds also were submitted to cerebral angiography before treatment.

After receiving informed consent from the patients, they were treated intravenously with a 10 000-U bolus of heparin sodium, followed by continuous pump-assisted administration at a rate adjusted to achieve an activated partial thromboplastin time (aPTT) ratio between 2 and 2.5 times the control ratio. The aPTT, together with the prothrombin time international normalized ratio and platelet count, were obtained at 4 hours after administration of the bolus and then every day, up to day 7.[5] Heparin therapy was discontinued on the fifth day after stroke, and treatment with oral aspirin (325 mg/d) was begun. Patients with atrial fibrillation who were self-sufficient after the first month of stroke were then shifted to oral anticoagulation therapy. The CNS test was repeated on days 1 and 7, and a second CT scan was performed by day 4. If hemorrhagic transformation of the brain ischemia was suspected, another CT scan was performed. An increase or decrease of at least 1 point on the CNS test between day 1 and hospital admission and day 7 and hospital admission was considered to show clinical improvement or worsening. Modifications of ± 0.5 points were considered to show no change. Functional outcome was rated at 1 and 6 months using the Rankin[17] score. Good outcome was self-sufficiency (Rankin score, <3), a poor outcome was disability (Rankin score, ≥ 3) or death. All adverse experiences possibly related to heparin therapy and death were recorded.

Variables related to outcome at months 1 and 6 (χ^2 test), death, and hemorrhagic complications (Fisher's Exact Test) were sought. The investigated variables included age (<70 vs ≥ 70 years), sex, history of hypertension, side of the brain ischemia, timing of start of heparin bolus (<180 or ≥ 180 minutes after stroke), CNS score at study entry and at day 1 (<6.5 vs ≥ 6.5), electrocardiogram (normal, atrial fibrillation, or left ventricular hypertrophy), arterial obstruction detected by ultrasound, size of brain infarction at CT scan (<3 vs ≥ 3 cm in diameter), prothrombin time international normalized ratio after bolus (<1.25 vs ≥ 1.25), aPTT ratio after bolus (<4 vs ≥ 4), and lowest platelet count ($<150\times10^9$/L vs $\geq 150\times10^9$/L). The relative risk for significant variables was assigned by an odds ratio test. Finally, the selected variables were entered into a multiple logistic regression analysis.

Table 1. Exclusion Criteria

Age <40 and >80 y
Stupor or coma
Brain hemorrhage
Canadian Neurological Scale score >8
Lacunar syndromes
Regression of signs before treatment
Contraindications to anticoagulants
Ongoing medication with anticoagulants
Cancer or other life-threatening diseases
Renal or hepatic failure
Pregnancy
Lack of informed consent from patients or relatives
Start of treatment with heparin beyond 6 h after stroke
Patients with undetermined or inconsistent lesions on initial computed tomographic scan

the study. Reasons for exclusion are listed in **Table 2**. The demographic characteristics and the risk factors of the enrolled patients are summarized in **Table 3**. Forty-five patients were included in the analysis. Their mean score on the CNS was 5.0 (range, 1.5 to 8.0) at hospital admission, 5.9 (range, 0.0 to 9.0) on day 1, and 6.4 (range, 0.0 to 10.0) on day 7. No direct or indirect signs of acute ischemia[18] on the baseline CT scan were noted in 41 patients (91.1%).

All patients underwent extracranial and transcranial ultrasound examinations. Eight patients underwent cerebral angiography on both carotid sides. Twenty-eight patients (62.2%) had obstructions of symptomatic arterial vessels: seven with obstructions of both extracranial internal carotid artery and middle cerebral artery stem, seven of internal carotid artery alone, four of carotid siphon, 10 of middle cerebral artery alone, and 17 with no detectable obstructions (but possibly obstructions of the middle cerebral artery branches, which are undetectable by ultrasounds[19]). All of the detected obstructions were occlusions, except two cases with tight stenosis of the extracranial internal carotid artery. All patients who underwent angiography had occlusion of the middle

Table 2. Primary Reasons for Exclusion on 360 Observed Strokes*

Reasons	No. (%)
Age	33 (10.5)
Stupor-coma	7 (2.2)
Recurrence of stroke	15 (4.7)
Referral time >5 h	147 (46.7)
Hemorrhages	28 (8.9)
Vertebro-basilar territory	25 (7.9)
Regression of signs and CNS score >8	7 (2.2)
Lacunar syndromes	13 (4.1)
Ongoing anticoagulants	4 (1.3)
Life-threatening disease or cancer	6 (1.9)
Start of heparin >6 h after stroke	27 (8.6)
No consistent lesion at CT scan	3 (0.9)
Total	**315**

*CNS indicates Canadian Neurological Scale; CT, computed tomographic.

Table 3. Patients' Characteristics (N=45)*

Sex	
M	26
F	19
Mean age, y (range)	68 (45–80)†
Hypertension, No. (%)	18 (40)
Smoker, No. (%)	10 (22.2)
Coronary heart disease, No. (%)	7 (15.5)
Diabetes, No. (%)	5 (11.1)
Side of infarction	
L	22
R	23
Mean CNS score at entry (range)	5.0 (1.5–8.0)‡
Atrial fibrillation at entry, No. (%)	16 (35.5)
Normal CT scan at entry, No. (%)	41 (91.1)
Symptomatic vessel obstructions, No. (%)	28 (62.2)
Mean time from stroke to heparin, min (range)	197 (60–360)§

*CNS indicates Canadian Neurological Scale; CT, computed tomographic.
†There were 22 patients older than 70 years.
‡There were 30 patients with a score lower than 6.5.
§There were 24 people who received heparin before 180 minutes from stroke.

Table 4. Clinical Results*

Mean CNS score (range)	
Day 1	5.9 (0.0-9.0)†
Day 7	6.4 (0.0-10.0)‡
Improved patients, No.	
Day 1	23
Day 7	29
Stable patients, No.	
Day 1	16
Day 7	8
Worsened patients, No.	
Day 1	6
Day 7	8
Deaths, No.	
Month 1	6
Month 6	11
Good outcome, No.	
Month 1	21
Month 6	21
Poor outcome, No.	
Month 1	24
Month 6	24
CT scan, No.	
Cerebral hematoma	2
Infarction	
≥3cm	25
<3cm	18
Stroke recurrence after 2 mo, No.	2

*CNS indicates Canadian Neurological Scale; CT, computed tomographic.
†There were 24 patients with a score lower than 6.5.
‡There were 19 patients with a score lower than 6.5.

Table 5. Causes of Death

Causes of Death	No. of Patients
1st month	
Cerebral hematoma	1
Stroke	4
Pulmonary embolism	1
6th month	
Pneumonia	2
Cardiac death	2
Pulmonary embolism	1

cerebral artery stem. Twenty-four patients (53.3%) had an abnormal electrocardiogram (16 had atrial fibrillation; eight had left ventricular hypertrophy). The heparin bolus increased the mean aPTT ratio from 0.91 (range, 0.77 to 1.05) to 3.46 (range, 0.98 to 7.0). The mean prothrombin time international normalized ratio went from 1.01 (range, 0.85 to 1.34) to 1.40 (range, 1.05 to 2.27). Four patients had no response to the bolus dose. Platelet counts declined to less than 100×10^9/L only in two patients (97×10^9/L and 89×10^9/L, respectively) by day 7. Neither patient had clinical evidence of adverse effects.

None of the patients died before day 4, when control CT scans were scheduled. Heparin was discontinued before the fifth day of stroke only in patients who developed hemorrhagic complications. The conditions of 23 patients (51.1%) were improved, 16 (35.5%) were stable, and six (13.3%) were worse by day 1. By

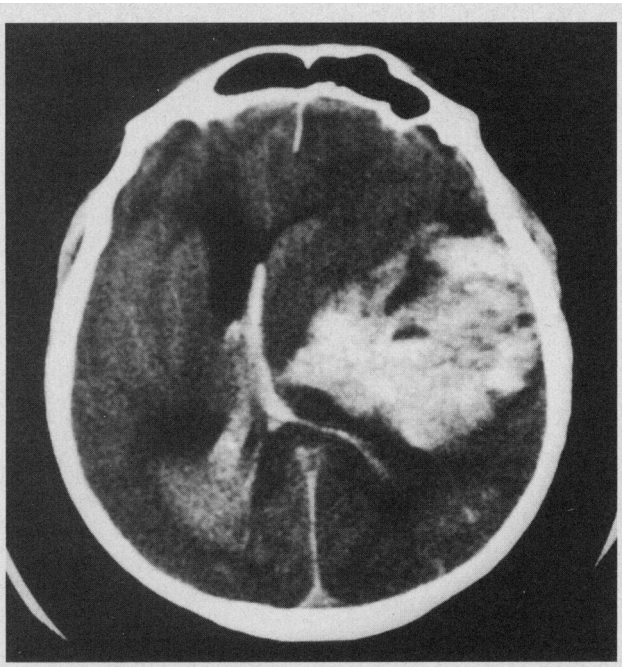

Figure 1. *Computed tomographic scan of patient 28 performed 24 hours after administration of heparin sodium bolus when the patient became comatose.*

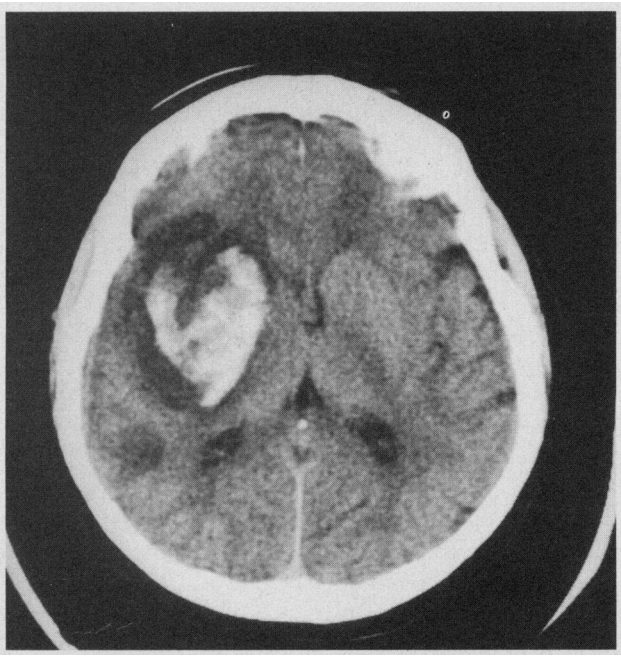

Figure 2. *Computed tomographic scan of patient 39 performed 48 hours after administration of heparin sodium bolus when the patient, after having a dramatic improvement of her right hemiparesis, became drowsy and hemiplegic.*

day 7, the conditions of 29 patients (64.4%) were improved, eight (17.8%) were stable, and eight (17.8%) were worse. Two patients (4.4%) had homolateral recurrence of stroke between 2 and 3 months after the qualifying stroke. At both 1 and 6 months, functional outcomes were rated as good in 21 patients (46.7%) (**Table 4**). Six patients (13.3%) died within the first month and another five (11.1%) within 6 months, for a total of 11 deaths (24.4%). The timing and causes of death are outlined in **Table 5**.

Table 6. Statistical Results (Univariate Analysis)*

	OR (95% CL)	
	1st Month	6th Month
Predictors of Death		
Age	NS	NS
Sex	NS	NS
Side of infarction	NS	NS
Hypertension	NS	NS
AF on ECG	NS	NS
LVH on ECG	NS	10.0 (1.6, 73.3)
Heparin start	NS	NS
CNS		
At entry	NS	NS
At day 1	NS	NS
Lesion size on CT	NS	22.0 (2.3, 152.9)
Vessel obstruction	NS	10.3 (1.1, 90.9)
PT INR	NS	NS
aPTT ratio	NS	NS
Platelet count	NS	NS
Predictors of Poor Outcome		
Age	NS	NS
Sex	NS	NS
Side of infarction	NS	NS
Hypertension	NS	NS
AF on ECG	NS	NS
LVH on ECG	NS	NS
Heparin start		
CNS	NS	NS
At entry	8.0 (1.2, 21.5)	5.2 (1.2, 26.9)
At day 1	3.8 (1.0, 17.1)	5.0 (1.2, 22.2)
Lesion size on CT	35.7 (5.1, 178.5)	12.5 (2.5, 70.3)
Vessel obstruction	4.3 (1.0, 19.7)	8.1 (1.7, 42.3)
PT INR	NS	NS
aPTT ratio	NS	NS
Platelet count	NS	NS

**OR indicates odds ratio; CL, confidence limits; AF, atrial fibrillation; ECG, electrocardiogram; LVH, left ventricular hypertrophy; CNS, Canadian Neurological Scale; PT INR, prothrombin time international normalized ratio; aPTT, activated partial thromboplastin time; CT, computed tomography; and NS, not significant.*

Table 7. Statistical Results (Logistic Regression Analysis*

	OR (95% CL)	
	1st Month	6th Month
CNS Score		
At entry	NS	NS
At day 1	NS	NS
Lesion size on CT	35.7 (6.1, 207.5)	9.6 (2.1, 44.3)
Vessel obstruction	NS	5.8 (1.2, 27.8)

**OR indicates odds ratio; CL, confidence limits; CNS, Canadian Neurological Scale; CT, computed tomography; and NS, not significant.*

Cerebral hematomas, which were associated with clinical worsening, were observed in two patients (4.4%) (**Figure 1** and **Figure 2**). One of them died by day 5. Extracranial bleeding occurred in six patients (13.3%): in four it was in the gastrointestinal tract; in one, in the genitourinary tract; and in one it was subcutaneous. None of the hemorrhages was life-threatening or required blood transfusion. All hemorrhages occurred within 48 hours of receiving the bolus dose.

Clinically silent hemorrhagic infarctions were detected on the second CT scan in four patients (8.9%). A CNS score of less than 6.5 at study entry (P=.0084) and at day 1 (P=.0503), obstruction of large vessels (P=.0498), and a brain lesion 3 cm in diameter or greater at initial CT scan (P<.0001) were associated with poor outcomes at 1 month. A CNS score of less than 6.5 at study entry (P=.0194) and at day 1 (P=.0024), obstruction of large vessels (P=.0049), and a brain lesion 3 cm in diameter or greater (P=.0005) were also associated with poor outcomes at 6 months. Mortality alone during the first month was unrelated to any investigated variable, whereas death by the sixth month was related to left ventricular hypertrophy on electrocardiogram (P=.009), CNS score of less than 6.5 at day 1 (P=.0018), and arterial obstruction (P=.0349) (**Table 6**). Hemorrhagic complications were unrelated to any coagulation parameters.

After multivariate analysis (**Table 7**), infarct size at initial CT scan was the only independent predictor of both 1-month (P<.0001) and 6-month (P=.002) outcomes, and large vessel status was an independent predictor of 6-month outcome (P=.0235). The number of deaths was insufficient to perform multivariate analysis for mortality alone.

COMMENT

Despite the findings of several studies,[4-10] the risks-benefits of heparin anticoagulation therapy for ischemic stroke remain to be ascertained. Our prospective pilot study does not have a control group, but to our knowledge it is the largest study, to date, to report experiences with early administration of heparin. It demonstrates that immediate heparin treatment for acute ischemic stroke in the anterior circulation can be applied to a sizeable population of patients.

No patients or relatives refused treatment, probably because of the neurological severity of early referred strokes and the consequent request for treatment. While some authors[20] suggest that heparin therapy not be started prior to 48 hours after stroke to avoid hemorrhagic transformations, our results do not indicate that immediate anticoagulation therapy with heparin is extremely dangerous. Bleeding occurred in 17.8% (8/45) of our patients, but only in 4.4% (2/45) was it cerebral. These rates were insignificantly higher than those previously found.[5,6,8] The case fatality rate was 50% (23/45) for heparin-related cerebral hematoma in our study, the same as reported with delayed treatment.[5,8] Hemorrhages were seen early after initiation of treatment, both in our series and in others',[5,8] suggesting that these complications may be unrelated to the timing of treatment and to the use of a bolus. No predictor of hemorrhagic complications could be found, as already stated.[8] Clinically silent hemorrhagic transformations were observed in a percentage of patients lower than that reported in a prospective CT study of ischemic cerebral infarction.[21] A decrease in platelet count was rare: our cases were classifiable as type I thrombocytopenia, which is usually benign,[22] and there were fewer cases than expected.[23] Homolateral recurrence of stroke was equally rare and occurred late after treatment. Thus, the short-term course of heparin did not lead to any strokes associated with heparin withdrawal, probably because of the protective effects of the later administration of aspirin.[24]

Efficacy of our treatment schedule is difficult to evaluate. As for outcome, the only reported series of untreated patients referred in the first 6 hours of stroke onset is, to our knowledge, by Fieschi et al,[13] who observed deaths in 25% of their patients and favorable outcomes in 32.5% at 30 days after stroke. No data on long-term mortality and self-sufficiency are available. Our 30-day outcomes would seem to be better, but selection bias cannot be excluded. As for clinical course in the first hours of treatment, an improvement rate in the first day such as was observed in our study was also observed in a limited series of untreated patients with stroke,[25] which again is scarcely comparable. Among the studies on heparin treatment for stroke, only one study observed results similar or better than ours. In that study,[5] heparin was initiated within 48 hours of stroke, and the authors suggested that good outcomes could be dependent on the interval between stroke onset and treatment, being more frequent in patients treated within 12 hours. Therefore, early treatment could be crucial. However, statistical analysis suggests that better outcomes are associated with smaller infarct size and large vessel patency, as would be expected in patients with stroke. Thus, to ascertain efficacy of immediate heparin treatment for acute stroke, a large randomized controlled trial is needed.

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