Failure of Heparin to Prevent Progression in Progressing Ischemic Infarction

E.C. Haley Jr., MD, N.F. Kassell, MD, and J.C. Tomer, PhD

Anticoagulation with heparin is frequently recommended for patients with progressing ischemic cerebral infarction, yet little data is available detailing the acute results of treatment with this agent. We report the results of continuous intravenous heparin treatment in 36 consecutive patients admitted with progressing ischemic infarction, all of whom had computed tomography scans to exclude the diagnosis of hemorrhage prior to treatment. Overall, 18 of 36 (50%) had continued neurologic worsening despite treatment. The incidence of further worsening was greater in carotid territory infarctions (14 of 19, 74%) than in either vertebrobasilar (2 of 8, 25%) or lacunar (2 of 9, 22%) infarctions ($p<0.05$, Fisher’s exact test). These observations suggest that additional controlled studies of the efficacy of heparin in progressing ischemic infarction are warranted. (Stroke 1988;19:10–14)

Although the use of anticoagulants in the treatment of ischemic cerebrovascular disease continues to be controversial, many experts believe that one circumstance in which anticoagulants are most likely to be of benefit is in progressing ischemic infarction or “stroke-in-evolution.” 1–3 The most common recommendation is for immediate anticoagulation with heparin (now usually by continuous intravenous infusion) followed by long-term oral anticoagulation with warfarin. However, to date there is very little data available detailing the acute or early benefits of heparin anticoagulation in this clinical setting. 4–5 We report prospectively accumulated observations on a consecutive series of patients admitted to the University of Virginia Medical Center during an 18-month period who met strict criteria for progressing ischemic infarction and who received heparin therapy.

Subjects and Methods

Criteria for entry into the study included the acute onset of a focal neurologic deficit, the clinical course of which suggested a vascular etiology; other causes were excluded. For ascertaining progressing stroke, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke Stroke Data Bank were used; progressing ischemic infarction was defined as an ischemic neurologic deficit that worsened or fluctuated due to neurologic causes after the patient was admitted to the hospital. Worsening was a change from the initial neurologic examination in at least one of the following: 1) a decrease of 2 or more points on the Glasgow Coma Scale, 6 2) a deterioration in limb power in a previously involved extremity, 3) new weakness in another part of the body, or 4) other new findings including aphasia, sensory deficit, or visual field abnormality. Extremity weakness was graded using the following scale: 5, none: holds limb against resistance; 4, mild: raises limb against gravity, but slight drift; decreased fine motor movements; 3, moderate: raises limb partially against gravity, but limb falls quickly; 2, severe: moves limb minimally; and 1, plegia: unable to move limb proximally or distally.

All patients had a computed tomography (CT) scan that excluded the diagnosis of intracerebral hemorrhage.

Patients with contraindications to heparin therapy and patients with profound deficits at the time of initiation of heparin treatment and who had not had prior fluctuation were excluded from the study.

After baseline neurologic examination, CT scan, and in some cases lumbar puncture, 3,000–5,000 units porcine heparin was administered as a rapid intravenous infusion, followed by a continuous infusion at 1,000 U/hr. The infusion rate was then adjusted to maintain the partial thromboplastin time (PTT) at 1·5–2 times control. Additionally, all patients received standard supportive medical care to maintain blood pressure, serum electrolytes, and oxygenation within normal limits. Serial neurologic examinations were then performed on a daily basis by one of the investigators during the patient’s hospitalization.

Patients were retrospectively grouped by vascular territory of the infarction (carotid, vertebrobasilar, or lenticulostriate [lacunar] groups) using standard clinical criteria supplemented in most cases by late CT documentation. Lacunar infarctions were defined by the onset of neurologic deficits compatible with one of the recognized lacunar syndromes, including pure motor hemiparesis, sensorimotor stroke, homolateral ataxia and crural paresis, or dysarthria-clumsy hand. 7–9 Follow-up CT scans were normal or showed small (<1.5 cm) areas of low density in deep brain structures in the territory of a single penetrating vessel, such as a lenticulostriate artery. Additionally, no proximal source of emboli was identified in the lacunar group.
In carotid territory infarctions, the presumed mechanism of infarction was determined based on all available clinical and laboratory data. Infarctions were classified as either large vessel atherothrombosis, artery-to-artery embolism, cardiogenic embolism, embolism of unknown source, or uncertain mechanism. Definitions for these entities may be found in Appendix 1.

Data were also collected on duration of symptoms prior to admission, duration of symptoms prior to heparin administration, and severity of deficits at the time of initiation of heparin treatment.

**Results**

From July 16, 1984, through January 13, 1986, 286 patients with ischemic cerebral infarctions were admitted to the University of Virginia Medical Center. Of these, 38 patients met the entry criteria for progressing ischemic infarction; two patients had profound deficits at the time of initiation of heparin therapy and were thus excluded from the analysis. The remaining 36 patients are reported. The mean period of observation was 27.5 (range 2–82) days. The duration of heparin treatment varied from 7 hours to 21 days (mean ± SD 6.3 ± 4.6 days).

Overall, 18 of 36 patients (50%) continued to progress while receiving heparin. In those who progressed, the mean interval from initiation of treatment to development of the maximum fixed deficit was 55 (range 6–192) hours. Repeat CT scans were obtained soon after progression in 10 of these 18 patients, and in only one case (associated with intracerebral hemorrhage, see below) could progression of deficits be attributed to increasing mass effect or edema.

Of 19 patients with carotid territory progressing infarction, 13 continued to progress while receiving heparin. The degree of progression was frequently profound (Figure 1, top); 6 of the 13 (46%) developed their maximum deficits within 24 hours of initiation of heparin. One additional patient sustained an intracerebral hemorrhage into the infarcted territory while receiving heparin. His neurologic condition deteriorated markedly, and he required emergency evacuation of this intracerebral hematoma as a life-saving procedure. He was, therefore, considered to have progressed while on heparin. Neither the incidence nor the severity of progression was influenced by the mechanism of infarction. Of the 14 who progressed, 3 had large vessel atherothrombosis, 3 artery-to-artery emboli, 3 cardiogenic emboli, 1 an embolus of unknown source, and 4 uncertain stroke mechanisms. In the 5 who did not progress, 2 had large vessel atherothrombosis, 2 artery-to-artery emboli, and 1 a cardiogenic embolus.

In progressing vertebrobasilar infarction, 2 of 8 patients progressed further on treatment (Figure 1, middle). Both had basilar branch occlusion syndromes although neither had angiography to confirm the absence of vertebral or mainstem basilar occlusive disease. In the 6 who did not progress, 2 had angiographically documented mainstem basilar disease.

Similarly, 2 of 9 patients with lacunar infarction progressed.
progressed further while receiving heparin (Figure 1, bottom). Both had pure motor hemiparesis, and internal capsular lesions were documented on follow-up CT scans in each case. In the remaining 7 patients, 5 had pure motor strokes, 1 sensorimotor stroke, and 1 homolateral ataxia and crural paresis.

Pairwise comparison of the incidence of progression by vascular territory indicated a particularly high rate of treatment failure (74%) in patients with carotid territory infarctions. The differences were significant (p<0.05, Fisher's exact test).

Comparison of a number of clinical factors potentially related to early progression showed no significant difference between those who progressed and those who did not (Mann-Whitney test) (Table 1). The patients who did not progress tended to have had heparin started later after onset of symptoms than the patients who did progress. The severity of deficit at initiation of treatment was similar in both types of patients. Intravascular volume determined by the serum sodium concentration and the BUN/creatinine ratio and whole blood viscosity estimated from hematocrit were also similar in both types.

Bleeding complications occurred at a rate similar to that reported in other series.10,11 Five of 36 patients (13.9%) had complications severe enough to warrant discontinuation of treatment (Table 2). None had PTs outside the therapeutic range at the time of the complication and none were thrombocytopenic. Four had progressed, but major progression had already occurred before treatment was discontinued.

Discussion

In 1941, Hedenius12 reported the first series of patients to receive heparin for treatment of cerebrovascular disease. Spurred on by subsequent anecdotal reports of the ability of heparin to abort flurries of transient ischemic attacks (TIAs) in some patients, several studies were performed testing the use of anticoagulants in the treatment of TIA and ischemic infarction.12-28 Although most nonrandomized series reported benefit, favorable results from treatment were more difficult to show in randomized trials. For TIA no long-term benefit could be demonstrated for preventing future stroke or death, and for completed stroke the data suggested that anticoagulant-treated patients fared worse than untreated patients.29-31

However, the one circumstance in which anticoagulants appeared to confer the greatest benefit was in progressing ischemic infarction. Baker et al.15 in a cooperative study, reported 128 patients randomized to either anticoagulant or nonanticoagulant treatment. Heparin was administered intravenously in intermittent doses until therapeutic prothrombin times were established with oral agents. After an average follow-up of 13.4 months, progression of infarction was recorded in 21 of 67 controls (31.3%) compared with 8 of 61 anticoagulated patients (13.1%). Although the acute results of heparin treatment were not reported, when the data were examined after 1 month of follow-up, 10 instances of progression were recorded in the control group compared with 8 in the treated group. The putative benefits from anticoagulation, then, seemed to have been long-term rather than short-term. Moreover, even in the long-term, overall mortality was unchanged (17 of 67 controls died vs. 13 of 61 treated, \( \chi^2 = 0.1108, p = 0.739 \)).

Carter22 reported a randomized study of 122 patients believed to have progressing stroke. Major concerns remain regarding the methodology used in this study,29 and Sage32 has pointed out that, even after excluding patients with severe deficits at the time of treatment from the analysis, no significant difference in outcome between the control and treated groups was discernible (10 of 20 control vs. 17 of 22 treated patients improved or recovered, \( \chi^2 = 3.29, p > 0.05 \)).

We report early observations on an anecdotal series of 36 consecutive patients with progressing ischemic infarction all treated with heparin in a standardized fashion by continuous intravenous infusion. CT scan excluded the diagnosis of intracerebral hemorrhage in all patients prior to treatment. Despite these precautions, 50% of patients continued to deteriorate neurologically during heparin treatment. PTT > 1.5 times control were documented in all cases. Additionally, in only 1 patient could the neurologic worsening be attributed to causes other than further progression of ischemic infarction. That patient sustained an intrace-

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<thead>
<tr>
<th>Table 1. Comparison of Clinical Parameters Possibly Leading to Progressing Infarction</th>
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</thead>
<tbody>
<tr>
<td>Carotid territory infarction</td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Clinical parameter</td>
</tr>
<tr>
<td>Duration of symptoms prior to admission</td>
</tr>
<tr>
<td>Interval from admission to heparin treatment</td>
</tr>
<tr>
<td>Total duration of symptoms before heparin treatment</td>
</tr>
<tr>
<td>Degree of deficit at initiation of heparin</td>
</tr>
<tr>
<td>Serum sodium (meq/l)</td>
</tr>
<tr>
<td>BUN/creatinine ratio</td>
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<tr>
<td>Hematocrit (vol %)</td>
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Data as median (range in parentheses) for duration, interval, and total duration in hours; mean ± SD for the other parameters. No significant differences between progression and no progression groups, Mann-Whitney test.
rebral hemorrhage, perhaps related to the anticoagulant treatment.

Patients with carotid territory infarctions were particularly at risk for further progression despite heparin treatment compared with patients with vertebrobasilar or lacunar infarctions. This finding has implications not only for developing alternative therapeutic approaches, but also for design of future randomized trials. Specifically, the response of progressing infarction to medical therapies may differ depending on the vascular territory involved and the underlying pathophysiology. For example, patients with lacunar infarctions may represent a special subset. The territory of infarction in these cases is small, and the frequency of a leisurely or fluctuating onset may be higher than in patients with large vessel infarctions. The reason is unclear. To some extent, patients with lacunar infarctions may have a better prognosis than patients with large vessel infarctions, even without treatment, although a third of patients with lacunar infarcts are not independent after a year. However, it must be recognized that with current methods it is often very difficult to ascertain with certainty early in the course, that an evolving neurologic deficit is definitely a lacunar infarction. For example, pure motor hemiplegia, in addition to being related to capsular infarctions, has been described as accompanying large subcortical infarctions associated with middle cerebral artery stem disease and even small cortical infarctions. In the current series, all patients with progressing deficits were treated uniformly with heparin, and although an evolving lacunar infarction may have been suspected clinically, all were confirmed by follow-up CT scanning.

Aside from the vascular territory involved, no other clinical variable examined in this study (Table 1) predicted progression during heparin therapy. Angiography, however, was performed in only 14 of the 38 patients. Additional angiographic data might have been extremely useful in predicting progression or response to heparin.

We recognize that the findings of an anecdotal series cannot be interpreted with the weight of a controlled clinical trial. Nevertheless, the disappointingly high rate of early progression of ischemic deficits seen in this series is similar to that reported in placebo or untreated groups published previously. That heparin might not be effective in all patients with progressing stroke is to be expected considering that the clinical picture of a progressing ischemic neurologic deficit can have a multiplicity of causes.

Our data suggest that further controlled studies of heparin's efficacy in patients with progressing ischemic infarction are warranted. Results from a randomized trial at McMaster University found no benefit from heparin treatment in a group of patients with incomplete infarctions who had been stable for at least 24 hours. Future studies should incorporate similar modern methodology for conducting clinical trials and should include data assessing the underlying vascular anatomy and physiology so that subgroups of patients who may or may not benefit from treatment can be more readily identified. Moreover, planning for these studies should take into account the development of low molecular weight heparin compounds (heparinoids) that potentially may be safer and more efficacious than currently available preparations.

In the interim, given the presently available data it does not seem reasonable to require heparin-treated controls in clinical trials of innovative treatments for progressing stroke. Alternative approaches to this problem should be considered but should also undergo rigorous, randomized clinical testing before being accepted as standard therapy.

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Appendix 1. Clinical Criteria Determining Carotid Territory Stroke Mechanism

Large vessel atherothrombosis. Stepwise or stuttering onset of entry neurologic deficit; may have history of TIAs. Clinically, region of brain involvement not consistent with cortical branch occlusion. Angiography shows large vessel occlusion without evidence of distal emboli. CT scan demonstrates infarction in watershed zones or in entire territory of occluded vessel.

Artery-to-artery embolism. Abrupt or rapid onset of entry neurologic deficit; may have history of TIAs. Angiography or ultrasonography shows embolic source in carotid or vertebrobasilar system. If carotid occlusion and distal branch emboli both demonstrated, classified as artery-to-artery embolism.

Cardiogenic embolism. Abrupt or rapid onset of entry neurologic deficit. Definite cardiac source of embolus identified, preferably with angiographic or noninvasive exclusion of large artery source.

Embolism of unknown source. Abrupt onset of neurologic deficit; angiographic documentation of embolic material. No identifiable source of embolus established.

Uncertain mechanism. Despite exhaustive search, no cause for entry deficit identified, or full diagnostic evaluation not clinically appropriate, or evaluation refused by patient.
References


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