Pilot Study of Low-Molecular-Weight Heparin in the Treatment of Acute Ischemic Stroke

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Ischemic stroke accounts for approximately 85% of all strokes in the West and 70% in the Orient. Established methods of prevention include antiplatelet agents, oral anticoagulants, and carotid endarterectomy. For the acute episode, however, there is currently no treatment that has been conclusively proven to be beneficial. Heparin has been a popular choice of many physicians for decades, but its usefulness has never been established, and its potential for causing hemorrhage continues to arouse caution.

Recent clinical studies in venous thrombosis suggest that low-molecular-weight heparins and heparinoids (LMWH) may cause less bleeding than unfractionated heparin for an equivalent antithrombotic effect, as well as being more bioavailable and simpler to administer. In the treatment of ischemic stroke, in which hemorrhagic transformation of the infarct (HTI) is a major concern, LMWH could have similar advantages.

In an open pilot study, we gave one such compound to patients admitted to hospital with proven cerebral infarction. The objectives of this pilot study were to gain experience in the recruitment of patients, administration of the treatment protocol, and observation for adverse reactions and to assess whether there was any excess mortality or serious morbidity associated with the treatment.

Subjects and Methods

We screened adult patients <80 years old who were admitted to the Prince of Wales Hospital, Hong Kong, with a diagnosis of acute stroke. Eligible patients had onset of symptoms less than 48 hours previously and computed tomography that ruled out cerebral hemorrhage. Patients with sustained hypertension (systolic >180 or diastolic >120 mm Hg), active bleeding disorder, major confounding neurological or systemic illness, recent operation, or known hypersensitivity to heparin and those who were already on anticoagulants were excluded. Informed consent was obtained from either the patient or his or her next of kin, and the protocol was approved by the Ethical Sub-Committee of the Faculty of Medicine, Chinese University of Hong Kong.

A preparation of LMWH (Fraxiparine) was given subcutaneously at a fixed dosage of 7500 ICU ("Institut Choay" units, equivalent to 3000 international units) every 12 hours for 7 days. During this period, patients were monitored for signs of bleeding and other adverse reactions. The major end points were mortality and functional outcome at 3 months after the stroke, the latter being assessed according to a simplified Rankin scale ("Appendix").

Venous blood samples were drawn from randomly selected patients 3 hours after the previous subcutaneous injection of LMWH on day 3 and day 7 of treatment. Anti-factor Xa (anti-Xa) activity was assayed photometrically with the Coatest LMW Heparin/Heparin Kit (Kabi Diagnostica, Nyköping, Sweden).

Results

Among the 55 patients who satisfied the inclusion and exclusion criteria, there were 29 men and 26 women whose mean age was 64 years (range, 30 to 80 years). All patients were of Chinese origin. Thirty-two patients (58%) gave a history of hypertension, 12 (22%) of diabetes mellitus, and 6 (11%) of previous stroke, and 6 (11%) were found to be in atrial fibrillation on admission. Based on clinical and radiological criteria developed for the Shatin Stroke Registry, 33 patients had a cortical or subcortical infarction, 17 a lacunar infarction, and 5 a brain stem or cerebellar infarction. The mean ± SD of plasma anti-Xa activity was 0.53 ± 0.29 U/mL on day 3 (n=25) and 0.51 ± 0.31 U/mL on day 7 (n=18).

All but three patients finished the 7-day course of LMWH treatment. There was no myocardial infarction, pulmonary embolism, clinical bleeding, or other adverse reaction in any patient during this period. Two patients elected to stop treatment on day 4 and day 6, respectively, both on the grounds that they had recovered completely from their stroke. One patient died on day 5; her autopsy showed a large right cerebral hemisphere infarct with herniation but no sign of hemorrhagic transformation. Three more patients died after the treatment period: one of neurological damage from the...
initial stroke on day 9, one of pneumonia and sepsis on day 13, and one of recurrent stroke on day 15.

At 3 months after their stroke, 26 patients (48%) were independent, 21 (38%) moderately disabled, 4 (7%) severely disabled, and 4 (7%) dead.

In the group of 25 patients whose plasma anti-Xa activity was measured on day 3, 11 could be considered as having had a subtherapeutic level (ie, <0.4 U/mL).6 Of these 11 patients, 6 were independent at 3 months, compared with 8 of 14 patients whose levels were above 0.4 U/mL. The difference was not significant (χ² test, P = .78).

Discussion

Since the aim of the main study would be to investigate a treatment that might be applicable to the generality of ischemic strokes, patients with the entire spectrum of stroke severity and infarct origin were included. Antithrombotic agents may act by limiting clot propagation, promoting clot lysis, preventing recurrence, and facilitating revascularization. Early intervention with such agents might limit the volume of brain damaged by ischemia and thereby reduce the consequent death and disability. The therapeutic window of 48 hours was to some extent arbitrary, but it is in keeping with the time limit set by many previous and ongoing stroke therapy trials, including the International Stroke Trial, which is currently investigating the effects of heparin and aspirin in the acute setting.7

We have chosen a preparation of LMWH that has been shown to be as effective and safe as unfractionated heparin in the treatment of deep vein thrombosis.8 After the deep vein thrombosis experience, in which fixed-dose subcutaneous Fraxiparine was found to have the same effect as adjusted-dose intravenous unfractionated heparin,9 we selected a fixed-dose rather than an adjusted-dose regimen. We checked plasma anti-Xa activity to establish the mean level achieved in our patients, rather than as an indicator for dose adjustment. The level in individual patients showed a wide variation, but the mean on two occasions remained constant at 0.5 U/mL. This is within the range (0.4 to 0.8 U/mL) that has been considered therapeutic on the basis of animal experiments.6 In the context of human stroke, we have not found that a “subtherapeutic” level was associated with a substantially poorer prognosis. In the main study, we plan to compare a high dose of 20 000 ICU per day with a low dose of 10 000 ICU per day to determine whether dosage variation affects clinical outcome.

Our 3-month mortality rate of 7% is lower than the 30-day case fatality rate of 20% for unselected cerebral infarcts admitted to our hospital previously.1 It is also lower than the mortality rates reported by several recently completed stroke therapy trials that recruited patients up to 48 hours after the onset10-12 and is no greater than the 3-month mortality rate of another pilot study that gave the LMWH (ORG 10172) by adjusted-dose intravenous infusion to 57 patients within 24 hours of onset.13 Furthermore, we did not encounter any significant adverse reactions during treatment with Fraxiparine. In addition, Fraxiparine may be given subcutaneously without laboratory monitoring, making it simple to use.8 We conclude that it would be safe and practical to conduct a larger trial of Fraxiparine in the treatment of acute ischemic stroke.

In this pilot study, three of four deaths occurred shortly after the treatment period, and at least one was from recurrent stroke. It may be postulated that the treatment period of 7 days was inadequate, so we have extended it to 10 days in the main trial. So that our results can be compared directly with those of the International Stroke Trial, we have also increased the follow-up period to 6 months in our main study.

Uncertainty remains concerning the prevalence of HTI in ischemic stroke patients, whether treated by heparin, LMWH, or neither. It is also not clear to what extent HTI leads to changes in mortality or morbidity. In our main study, which is placebo-controlled, we have incorporated repeat computed tomography at the end of treatment on every patient so that the prevalence and effect of HTI in different therapeutic groups can be contrasted.

Appendix

A Simplified Rankin Scale

Independent, Rankin 0 or 1: little or no disability to interfere with lifestyle.
Moderate, Rankin 2 or 3: disability restricting lifestyle or preventing independent existence.
Severe, Rankin 4 or 5: disability requiring frequent or constant attention.

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References

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