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

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Background Our purpose was to assess the feasibility and risk of performing a double-blind placebo-controlled study of low-molecular-weight heparin in the treatment of acute ischemic stroke.

Summary of Report Fifty-five patients were treated within 48 hours of stroke onset. Pretreatment computed tomography was performed to rule out cerebral hemorrhage. Fraxiparine (6000 IU per day) was given subcutaneously for 7 days. No adverse reaction was encountered during the treatment period. At 3 months, 26 patients were independent, 21 moderately disabled, 4 severely disabled, and 4 dead.

Conclusions It would be safe and practical to conduct a clinical trial on the use of Fraxiparine in the treatment of acute ischemic stroke. (Stroke. 1994;25:684-685.)

Key Words • cerebral infarction • heparin

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 by controlled clinical trials 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. 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 hypertensive 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). 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. An-
thrombotic agents may act by limiting clot propagation,
promoting clot lysis, preventing recurrence, and facilitat-
ing 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, includ-
ing the International Stroke Trial, which is currently
investigating the effects of heparin and aspirin in the
acute setting.2
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 hepar-
in, 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 experi-
ments.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. 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
subtypes among Chinese living in Hong Kong: the Shatin Stroke
5. Hirsch J. Overview of low molecular weight heparins and heparin-
6. ten Cate H, Henry CP, Bütler HR, ten Cate JW, Magnani HN. Use of a heparinoid in patients with hemorrhagic stroke and thrombo-
10. The American Nimipidine Study Group. Clinical trial of nimo-
11. Angeleri F, Scarpino O, Martinazzo C, Mauro A, Magi M, Pel-
llicioni G, Rapas G, Bruno R. GM1 ganglioside therapy in acute
infarct with intravenous glycerol: a double-blind placebo-
13. Massey EW, Bütler J, Davis JN, Adams HP Jr, Marler JH, Goldstein LB, Alberts M, Bruno A. Large-dose infusions of hepar-
14. Chesterman CN, Chong BH. Uses of heparin. BMJ. 1993;306:
871-872.
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