The experiences of an acute stroke unit - implications for multicentre acute stroke trials

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Abstract

The suitability of 200 consecutive patients admitted to a newly established acute stroke unit was assessed for participation in two multicentre trials currently in their pilot phase: the International Stroke Trial of aspirin and heparin, and the Multicentre Acute Stroke Trial of streptokinase versus placebo. Of the 200 patients (74 men, 126 women, mean age 71 years), 96% had cerebral CT, and 94% had a final diagnosis of cerebrovascular disease. Overall, 50% of patients presented within 6 hours and 70% within 12 hours of the onset of ictus. A total of 113 patients (56.5%) were potentially eligible for trial treatment with aspirin/heparin. Only 9 patients (4.5%) were eligible for streptokinase treatment: 50% were excluded because they presented after 6 hours; 23% had a previous stroke with clinical sequelae and 23% had severe systemic illness. Forty eight per cent of patients had more than one exclusion criterion. The potentially high enrolment rates in trials of antithrombotic agents contrast with the restricted recruitment for trials of streptokinase, emphasising the need for multiple centres to achieve useful study enrolment.

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Recent advances in technology have improved diagnostic classification of stroke but treatment remains essentially supportive. Recent trials have shown no beneficial effect from specific therapies, such as corticosteroids,¹ naftidrofuryl² haemodilution³ and calcium antagonists.⁴⁻⁶ Ongoing drug studies with thrombolytic agents^{7,8} and neuroprotective drugs have recognised the importance of treating the acute stroke patient early; this is based on experimental evidence that neuronal ischaemia which persists for 4-6 hours results in irreversible cell death.⁹ Treatment within 90 minutes⁷ and 8 hours⁸ of the onset of neurological deficit is being achieved in current studies by streamlining admission and investigation. This contrasts with earlier studies in which treatment was administered up to 48 hours⁴ or even 7 days² after the ictus. An improved system of stroke care is required in the United Kingdom to explore the potential of these new treatments.¹⁰

As about 80% of acute stroke is the result of either a thrombotic or embolic process,

present research is evaluating the safety and benefits of antithrombotic, anticoagulant and thrombolytic therapy.

Two major multicentre trials which are in a pilot phase are a trial of aspirin and heparin in acute ischaemic stroke, the International Stroke Trial (IST), and a placebo-controlled study of thrombolytic therapy in patients with an acute middle cerebral artery territory infarction, the Multicentre Acute Stroke Trials (MAST) study. Fundamental differences exist in the enrolment criteria for these two trials. The IST is a randomised open trial into which thousands of patients must be enrolled to detect a moderate treatment effect. It is therefore designed to achieve maximum simplicity for all collaborators to maximise enrolment. In contrast, the enrolment criteria of the MAST study are by necessity more stringent. Firstly, treatment must be started within 6 hours for MAST compared with 48 hours for the IST. Secondly, a cerebral CT scan is essential before randomisation only in the MAST study to exclude a cerebral haemorrhage or non-vascular disorder.

We have explored the potential for participating in multicentre acute intervention trials in the first 200 patients admitted to our recently established acute stroke unit. Eligibility for treatment with thrombolytic drugs or with heparin and aspirin was assessed. Our findings have important implications for the design and feasibility of performing acute stroke trials in the United Kingdom.

Patients and methods

All patients with an acute neurological deficit of probable vascular origin within the preceding 48 hours, and without metabolic disturbance, trauma, or intoxication which could account for the presentation, are admitted to the 5 bed acute stroke unit which serves a population of 220 000 in the north west of Glasgow. There is no age limitation. Patients with known non-vascular neurological disease, recent head trauma, intoxication, or requiring intensive or coronary care, are not admitted.

All patients admitted during the first 10 months of operation of the unit were assessed for eligibility for study treatment with aspirin/heparin or thrombolytic drugs. The time of onset of neurological deficit was carefully noted during the period of study, and this and other information was prospectively

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recorded on data collection sheets. The latest available criteria for the International Stroke Trial and the Multicentre Acute Stroke Trial were used.

Results

A total of 200 patients (74 men, 126 women) aged 34 to 93 (median 71) years admitted in the first 10 months of operation of the unit were assessed.

The interval from onset to admission ranged from 30 minutes to 56 hours (median 4.75 hours) in the 114 cases in whom onset was accurately determined. In 49 cases time of onset could not be determined precisely. In 28 cases this was because patients awoke with the deficit. In these cases the time of going to sleep was recorded; the median time from “onset” to admission in this group was 6 hours 15 minutes (range 2 hours to 72 hours). In a further 22 dysphasic or unconscious patients no accurate history was available. The median interval from when the patient was last known to be well to admission was 7 hours (range 2 hours 30 minutes to 50 hours). In the remaining 36 patients no reasonable estimate of time of deficit onset could be made. Overall, 50% of patients definitely presented within 6 hours, 62% within 8 hours and 70% within 12 hours of first onset of symptoms.

CLINICAL PRESENTATION

There was a history of a previous cerebrovascular event in 70 patients (35%); 46 (23%) had residual deficit and 24 (12%) had made a full functional recovery. Clinical diagnosis according to the classification scheme of Bamford *et al*¹¹ was of partial anterior circulation syndrome (PACS) in 92 cases (46%), and of total anterior circulation syndrome (TACS) in 54 cases (27%). Lacunar infarction (LACI) was diagnosed in 31 cases (15.5%), and posterior circulation infarction (POCI) in 11 cases (5.5%). In the remaining 12 cases (6%), 5 had post-ictal paresis, 3 had non-organic hemiparesis and 4 had non-neurological disease.

CT FINDINGS

Cerebral CT was performed in 193 cases (96%) at a median of 23 hours after onset of deficit (range 1 to 120 hours). It was abnormal in 154 cases (77%). In 32 cases (16%) there was intracranial bleeding (21 primary intracranial haematoma, 5 subarachnoid haemorrhage, 5 haemorrhagic change within infarction, and 1 arterio-venous malformation). Thirteen of the 32 cases (40%) with evidence of intracranial haematoma had been receiving long term aspirin therapy.

Table 1 Exclusion from entry to the International Stroke Trial in 200 patients admitted to an acute stroke unit

Exclusion criteria	Number (%)	Excluded
Not clinical ischaemic stroke	12	(6%)
Not admitted within 48 hours	6	(3%)
On longterm aspirin	37	(18.5%)
On longterm warfarin	7	(3.5%)
Not living independently	26	(13%)
Contra-indication or allergy to aspirin	6	(3%)
Conscious level not normal or drowsy	18	(9%)
Coma and CT evidence of haemorrhage	9	(4.5%)

A total of 100 cases (50%) showed recent cerebral infarcts; 13 of these were lacunar infarcts, 5 were major hemisphere lesions with oedema and midline shift. Two patients had intracerebral tumour (one meningioma, one secondary deposits from undiagnosed bronchial carcinoma).

POTENTIAL ENROLMENT TO ASPIRIN/HEPARIN STUDY

The number of patients excluded according to enrolment criteria of the IST are shown in table 1. Overall, 113 patients (56.5%), would have been eligible (fig, left). The commonest single exclusion factors were preceding aspirin treatment (18.5% of patients) and functional dependence (13%). In 23 cases (11.5%) aspirin had been prescribed for TIA or stroke, in 8 cases (4%) for cardiac disease and in 4 cases (2%) for both. In 23 cases (11.5%) aspirin was the single exclusion criteria from the IST. A recent protocol modification permits entry of patients previously prescribed long term aspirin, where clinical uncertainty over the need for continuation of aspirin exists. Only 6 patients (3%) were excluded because clinical deficit had an onset more than 48 hours before potential treatment.

POTENTIAL ENROLMENT TO STREPTOKINASE STUDY

Only 9 patients (4.5%) would have been eligible for streptokinase treatment as part of this study (fig, right). The reasons for exclu-

Figure Eligibility and number of exclusion criteria for drug trial entry in 200 patients admitted to an acute stroke unit. (left) Over half of the patients were potentially suitable for entry to the IST; (right) only 4.5% of patients were suitable for entry to the MAST. There were often multiple reasons for excluding patients from the study. IST = International Stroke Trial of aspirin and heparin; MAST = Multicentre Acute Stroke Trial of intravenous streptokinase.

Table 2 Exclusion from entry to the Multicentre Acute Stroke Trial in 200 patients admitted to an acute stroke unit.

Exclusion criteria	Number	(%) Excluded
Not clinical ischaemic stroke	12	(6%)
Not clinically MCA territory	11	(5.5%)
Lacunar syndrome	31	(15.5%)
Not admitted within 6 hours	100	(50%)
Previous CVA with clinical sequelae	46	(23%)
Other serious systemic illness	45	(22.5%)
Symptoms resolving completely	9	(4.5%)
Very mild deficit	27	(13.5%)
Peptic ulcer or bleeding tendency	13	(6.5%)
On warfarin	7	(3.5%)
Streptokinase in past 6 months	1	(0.5%)
Potentially pregnant	2	(1%)
Hypertensive	12	(6%)
Haemorrhage on CT	32	(16%)

sion from MAST are shown in table 2. One hundred patients (50%) were excluded because of presentation beyond 6 hours, or uncertainty over timing. In 42 patients (21%), entry was precluded because the clinical diagnosis was of lacunar syndrome (15.5%) or posterior circulation infarction (5.5%).

Discussion

Disappointing patient recruitment rates is a common feature of trials evaluating new therapies in acute ischaemic stroke. To ensure patient homogeneity, restrictive recruitment criteria have been used, but this has compromised enrolment. In a trial of naftidrofuryl in acute cerebral infarction, only 100 of 980 patients screened (10.2%) were entered into the study.² Only 7.4% of 3058 patients screened were entered into a trial of intravenous heparin for acute partial thrombotic stroke.¹² In a multicentre trial of a calcium antagonist in acute stroke, only one of 192 patients (0.5%) screened over 2 years was enrolled.¹³ These figures argue convincingly that critical evaluation of any new therapy requires a large coordinated multicentre study.

Our results show different potential recruitment rates for two major multicentre trials, the IST and MAST studies. In the MAST study, exclusion criteria are greater in number and more restrictive than the IST study. This reflects the greater perceived risk of thrombolytic treatment, its proposed mode of action and specific contraindications to streptokinase. Certain exclusion criteria are incontrovertible (recent streptokinase treatment, active peptic ulceration and recent surgery) but few patients (7%) were excluded on this basis. When other individual exclusion criteria were removed, potential enrolment was increased: treating patients with lacunar syndrome would increase enrolment from 4.5% to 10.5%. Lacunar infarction thus was the only exclusion criterion in 12 cases (6%); treating these patients might not be appropriate, however, in view of the different pathophysiological mechanisms in this group. The upper time limit for treatment of 6 hours is the most restrictive, and was the only criterion excluding 40 patients (20%). Increasing time to entry to 8 hours as in another ongoing

study⁷ would increase the enrolment from 4.5% to 8% of patients. A limit of 12 hours would allow treatment in 11%, and of 24 hours would allow treatment in 17%. Stratification for time could be incorporated into this larger study. By including all anterior circulation infarcts (including lacunar syndrome) within 24 hours of onset of deficit, 23% of patients would be eligible for randomisation.

Allowance for time required for investigation and randomisation has not been made in the above calculations and would reduce enrolment further. Streamlined admission, CT, and treatment within 90 minutes of deficit appears possible;⁷ cerebral angiography has also been performed within 8 hours in other centres.¹⁴ We estimate a processing time (including CT) of one hour, which would exclude a further 3 patients (1.5%), reducing total enrolment in the MAST study from 4.5% to 3%.

The rationale behind the IST study is that overall improvements in quality of life may be achieved by moderate reductions in mortality and morbidity by a simple treatment given to a large proportion of patients. The exclusion criteria are accordingly minimally restrictive, although 12 patients (6%) with haematoma on CT did not have impaired conscious level and would have been enrolled in centres with late or no access to CT scanning. Whilst a subgroup analysis of the pilot study is planned to address the safety of including such patients, our own policy is that trial entry should be dependent on exclusion of haematoma by early CT scanning.

We have not estimated the number of patients who would decline to participate in the above trials. Local experience shows patient consent rate of approximately 66% in clinical trials (GT McInnes, personal communication) but this does not take into account the difficulties of obtaining consent from or on behalf of debilitated patients within strict time limits.

Our calculated low rate of recruitment for the thrombolytic trial has been matched by subsequent experience in a local pilot study with similar entry criteria to MAST, in which 7 of 183 patients during 11 months were treated with streptokinase/placebo within 6 hours of onset of deficit. Nevertheless, this rate of recruitment would exceed the anticipated enrolment in the MAST study of 600 patients from 60 centres within two years. We would have been unable to achieve this before reorganisation of our stroke care service and we therefore support an improved system of stroke care in the United Kingdom.¹⁰ Screening and entry of patients into both the IST and MAST studies simultaneously should be possible. Entry into the MAST study would preclude entry into the IST for only 2.5% of patients therefore making little impact on the numbers of patients entered into the latter trial. These trials should answer important issues about the medical management of acute ischaemic stroke.

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