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What is the best first agent to give to a patient with acute ischaemic stroke? Aspirin, heparin, clopidogrel, cilostazol or dipyridamole?

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Evidence Based Medicine

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The International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST)

Why are these studies important and noteworthy?

The International Stroke Trial and Chinese Acute Stroke Trial were two landmark trials performed to assess the efficacy of aspirin in patients with acute stroke, within 48 hours of stroke onset. The role of aspirin in secondary prevention of serious vascular events was well established, but before these two trials there was no large scale randomized evidence on aspirin in acute ischaemic stroke.

The authors suggested that with several million people afflicted with ischaemic stroke every year, if only 10 or 20 per thousand could be saved from death or dependency, the overall impact would be huge. Pakistan is the sixth most populous country in the world with a population of over 120 million - translated into absolute numbers; these results have important implications for Pakistan.

IST also looked at the effect of heparin on death or dependency. The rationale was that heparin has a mechanism of action that is distinct from aspirin and so the combination might be more effective than either alone.

The balance of risk and benefit for heparin and aspirin was uncertain in acute stroke. Also, there was a wide variation in clinical practice, and a great uncertainty in the minds of many physicians regarding the safety and efficacy of these drugs.

There are in actual evidence based practice very few interventions that positively impact outcome after acute stroke and have a strong evidence base to support them. There still remains a large gap between available evidence and actual implementation.

Who were the participants?

CAST included 21106 patients from 413 hospitals in China. These were patients judged to be within 48 hours of the onset of symptoms of acute ischaemic stroke, and had no clear indication for or contraindication to aspirin, based on the physician's judgment. The fundamental criterion was that the responsible physician was uncertain whether aspirin treatment was indicated or not. A CT scan before randomization was mandatory only for patients who were comatose.

IST included 19435 patients from 467 hospitals in 36 countries. Amongst these were 229 patients from India, 9 from Japan, 140 from Singapore and 20 from Sri Lanka. The majority of patients were of European descent. These patients were also included within 48 hours of stroke onset, and CT was mandatory only for comatose patients.

Thus both studies had a simple design and a wide recruitment and certainly the impressive numbers to draw broadly relevant conclusions.

What was the intervention?

In CAST 10554 patients were randomly assigned Aspirin 160 mg per day, and 10552 were assigned matching placebo. Randomization was by prepacked, sequentially numbered trial envelopes, each containing calendar-packed aspirin or placebo, produced centrally.

IST was more complicated. Using a factorial design, half the patients were randomized to aspirin and half to 'avoid aspirin'. Similarly half were randomized to heparin, and half to 'avoid heparin'. Therefore of the 19,435 randomized, 4858 were randomized to 300 mg Aspirin only, 2432 to 300mg Aspirin and 5000 u heparin, 2430 to 300mg Aspirin and 12500 u of heparin, 2429 to 5000u of heparin only, and 2426 to 12500 u of heparin. 4860 were given neither heparin nor aspirin.

What was the outcome?

In CAST the participants were well matched in terms of age, mean times from onset of symptoms, blood pressures, gender, consciousness and stroke subtype. Patients were followed for up to 4 weeks and during this time, the proportional reduction in the odds of death in the aspirin group was 14% which was significant (p<0.01)and translated to an absolute difference of 5.4 fewer deaths per 1000 patients allocated to aspirin. For the endpoint of fatal and non-fatal recurrent stroke, the difference was not significant, however, it combined a significant reduction of 4.7 recurrent ischaemic strokes per 1000 with a non significant excess of 2.1 haemorrhagic strokes per 1000.

For the primary outcome of dead or dependant at discharge, there was a non significant trend favouring those allocated aspirin.

In IST also, the two groups were well matched. But IST differed from CAST in several respects. In CAST 63% were males, as opposed to 54% in IST, 72% were younger than 70 years as opposed to 39% in IST, 13% were drowsy or comatose as opposed to 23% in IST. Among aspirin allocated patients there were non-significantly fewer deaths within 14 days corresponding to 4 fewer deaths per 1000 patients. At six months, a smaller percentage seemed to be dead or dependant in the aspirin arm although this was again not significant. After adjustment for baseline prognosis however, the benefit from aspirin was significant. There were fewer recurrent ischaemic strokes within 14 days in the aspirin arm which was significant, and a non significant excess of haemorrhagic strokes was noticed. Heparin on the other hand showed significant reduction in recurrent ischaemic events in the initial 14 days, but this benefit was offset by a similar sized increase in haemorrhagic strokes.

What were the conclusions?

CAST and IST were two large trials in about 40,000 randomized patients. They show that immediate use of medium dose Aspirin (160 mg to 300 mg) produces a modest, but definite net reduction in early death or non fatal stroke. In these trials, aspirin caused about 2 haemorrhagic strokes per 1000 patients treated, but also prevented about 11 other strokes or deaths in hospital, corresponding to a net benefit or about nine deaths or non fatal strokes avoided for every 1000 patients treated for a few weeks.

As for Heparin, neither dose regimen in IST offered any clinical advantage. Subsequently, about 25 trials with 23,748 participants who received heparin or heparinoids for acute stroke have shown that it has no net benefit in improving outcomes from stroke regardless of dose, type of anticoagulant, and mechanism of stroke (embolic, posterior circulation etc). Therefore there is no evidence to support the use of heparin in acute ischaemic strokes.

None of the other agents have been tested in the acute setting; they have their place in secondary prevention.

How does this impact our clinical practice?

Before CAST and IST, there was no reliable evidence that early aspirin use in the dose of 160 mg to 300 mg in acute ischaemic stroke was safe and efficacious. Now, we know that with a cost effective treatment like a single dose of aspirin per day (Rs 1) we can prevent around nine deaths or non fatal strokes per 1000 patients treated. If this is translated into the numbers who can benefit from therapy, they would be in thousands. So when we have a patient with an acute stroke, who is non comatose — the best medicine is Aspirin at a dose of at least 150 mg. Heparin and heparinoids are of no established benefit.

Recommended Reading:

1. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischemic stroke. Lancet 1997; 349: 1569-81.

2. Chinese Acute Stroke Trial collaborative group. CAST: a randomized placebo controlled trial of early aspirin use in 21106 patients with acute ischemic stroke. Lancet 1997; 349: 1641-9.

3. Anticoagulants for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2008, Issue 4. Sandercock PAG, Counsell C, Kamal AK. Art. No.: CD000024. DOI: 10.1002/14651858.CD000024.pub3.

4. Antiplatelet therapy for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2008, Issue 3. Sandercock PAG, Counsell C, Gubitz GJ, Tseng MC. Art. No.: CD000029. DOI: 10.1002/14651858.CD000029.pub2.