THROMBOLYSIS IN THE TREATMENT OF ACUTE STROKE: IS THERE A ROLE FOR STREPTOKINASE WHEN TISSUE PLASMINOGEN ACTIVATOR IS NOT AVAILABLE?

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ABSTRACT

Every year 350,000 people suffer an acute stroke in Pakistan. Treatment of acute stroke has not improved significantly despite the availability of intravenous thrombolysis with tissue plasminogen activator (tPA). The drug is expensive and is offered to a selected few. Streptokinase (SK), a low cost alternative thrombolytic agent, is widely available in Pakistan and is utilized to treat patients with acute coronary syndromes. Streptokinase was tested in acute stroke in the 1980's and found to be ineffective in ischemic stroke. This is likely due to trial design flaws, rather than the drug itself. Factors that may have contributed to poor outcomes include a prolonged treatment window, inclusion of patients with established infarction on CT scan, failure to treat excessive arterial pressures, a fixed dose of streptokinase and concomitant use of antithrombotic medications. Given the lack of therapeutic alternatives we believe that a properly designed trial in appropriate patient population utilizing stricter inclusion criteria, including early treatment with a lower dose of SK is warranted.

Key Words: *Thrombolysis, Stroke, Streptokinase.*

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INTRODUCTION

Every year more than 15 million people suffer a stroke worldwide[1]. Stroke is the leading cause of chronic disability and the second most common cause of death[1]. The burden of stroke globally is highest in the developing world[2], where cost-effective treatments are urgently required. Thrombolysis with intravenous recombinant tissue plasminogen activator (tPA) is the only proven treatment for improving outcome in acute stroke[3,4] and results in an absolute benefit of 11% (probability of recovering to the level of functional independence), when treatment is initiated within 3 hours of onset[3]. Despite the fact that more than 80% of the stroke worldwide occurs in developing countries[5], treatment standards are highly variable and thrombolysis programs are rare[6]. Currently, thrombolysis is offered to only a handful of patients in Pakistan, for the most part in private hospitals where access to health care is often based on the financial capabilities of the patient. There is, therefore, an urgent need for an effective but affordable alternative thrombolytic agent like streptokinase that can be offered to patients across the country.

For review of the relevant literature, we used PubMed to focus on manuscripts where streptokinase (SK) was tested in the treatment of acute stroke. Published reports between 1965 and 2012 were reviewed. In addition, we also reviewed unpublished data with the principal investigators of the large randomized trials of SK in acute stroke. We also reviewed all published reports on the use of thrombolytic medications in acute stroke in Pakistan. Finally, we discussed current management of acute stroke with key opinion leaders on stroke management in Pakistan.

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The burden of stroke in Pakistan

While there are no large population based studies on the incidence of stroke in Pakistan, it is estimated that every year 350,000 new strokes occur in the country[7,8]. Approximately 70 percent of patients have ischemic stroke. Hypertension and diabetes are common risk factors. Early presentation to the hospital within 3 hours of onset of symptoms was recorded in 21% (1991-2001) to 28% (2006-2007) of patients in Karachi[9,10]. However thrombolysis was unfortunately offered to 1.5% of patients in selected private hospitals[11]. The high cost of the medication and organizational limitations to rapidly evaluate patients were common issues related to the low use of thrombolytic mediations.

Streptokinase and Acute Stroke

Streptokinase (SK) is a plasminogen activator, produced by various strains of streptococcal bacteria. It is used commonly in the treatment of acute coronary syndromes and has a profile similar to tPA with respect to both efficacy and safety[12,13]. There are four published clinical trials of SK in acute stroke including a pilot study in Glasgow, the Multi-centre Acute Stroke Trials (Italy; MAST-I and Europe; MAST-E) and the Australian Streptokinase (ASK) trial[14-17]. A meta-analysis of the 1,292 patients (653 randomized to SK and 639 to placebo) revealed no difference in the rates of death and severe disability (modified Rankin score ≥3) between the placebo and active arm of the studies[18]. There were significantly more hemorrhages observed in the SK arm of the studies. Symptomatic hemorrhagic transformation occurred at rates of 8-21% in these four trials[14-17]. A Cochrane systematic review however indicated that symptomatic hemorrhagic transformation rates are not significantly higher in SK patients, relative to tPA, notwithstanding the limitations of indirect comparisons[19]. The Cochrane review also indicated that differences in clinical outcome in the tPA and SK trials may not be solely related to the thrombolytic agents themselves. We need to carefully review the reasons why there was a higher risk of hemorrhage in these trials completed over 20 years ago. This is especially important if we are to re-evaluate SKs potential role in management of acute stroke. It is important to note here that we have considerable new knowledge on thrombolysis in acute stroke since the time of the 4 trials as thousands of acute stroke patients have been treated with tPA. Also, the rapid advances in imaging allows for unprecedented access to tissue viability of the brain in the hours following an acute stroke. We believe that these factors have improved our ability to select the patient most appropriate for thrombolysis. The following also needs consideration.

1. *The Dose of Streptokinase in the SK trials:* Dose finding studies were not completed in stroke patients. The dose of SK was 1.5 million units as a single bolus in all four trials. The dose was based on that used in myocardial infarction trials. In dose-finding studies of tPA in ischemic stroke, it was found that hemorrhagic complications developed at doses lower than those used for acute coronary syndrome treatment[20,21]. A lower dose of SK in stroke also appears appropriate. In the MAST-E trial, early death, related primarily to hemorrhagic complications, was more common in low weight patients, who would have received a relatively higher dose on a per kg basis[22].

2. *The use of concomitant Antithrombotic Agents:* The combination of SK with other anti-thrombotic medications may have contributed to the higher risk of hemorrhages in the SK trials. Heparin was administered to 31% of patients in all trials, the majority of whom were in the MAST-I and MAST-E studies[18]. Heparin use in the MAST-E trial was left to the discretion of the investigators, but was administered to 65% of patients in the SK group at least once during the acute hospital admission. Although heparin use within 24 hours was much less frequent, an association with the very high 21.2% incidence of hemorrhage cannot be excluded[22]. The use of Aspirin (ASA) with SK in two of the trials potentially led to an increased risk of hemorrhagic transformation[23,24]. The addition of ASA to SK in the MAST-I trial was associated with a more than two-fold increased risk of hemorrhagic transformation and death[20]. In addition, the ASA-SK combination was associated with a 10% symptomatic hemorrhage rate in this trial[16]. In contrast, patients treated with SK alone developed symptomatic hemorrhage in 6% of cases, identical to the rate seen in the NINDS tPA trials[25].

3. *Inappropriate Patient Selection with Established Infarction on brain imaging:* Imaging studies are essential to rule out hemorrhage and to detect early signs of ischemic stroke. A careful review of the SK trials, shows that many patients had evidence of early infarction on their diagnostic CT scans[26]. Such patients would not be treated with tPA because of the high risk of complications. A post-hoc analysis of the MAST-E trial indicated early ischemic changes were present in 75.7% of patients who

subsequently developed hemorrhage[27]. CT changes were associated with a three-fold increase in the risk of hemorrhage. Patients with extensive early ischemic changes have therefore been excluded from the more recent thrombolytic trials and current guidelines do not recommend thrombolysis in these patients[4,28,29].

4. *Prolonged Time to Treatment:*

   The time to treatment is an important determinant of response to therapy. Of 1 293 patients enrolled in SK trials, only 304 were treated within 3 hours of onset. Meta-analyses indicate that in patients treated with SK within 3 hours of symptom onset, there was a trend to lower rates of death/severe disability at 90 days[14,18].

5. *Uncontrolled Hypertension*:

   Elevated systolic blood pressure is associated with an increased risk of hemorrhagic transformation following thrombolysis[30]. In the Australian Streptokinase Trial, systolic BP >165 mmHg at the onset of treatment was associated with a 25% increase in the rate of major hemorrhagic trans-formation[31]. Combination of the high blood pressure with evidence of early infarction on CT likely contributed synergistically to the increased rates of bleeds detected in the SK trials.

6. *Stroke Severity:*

   Evidence from recent meta-analysis of large studies and databases has shown that patients with large strokes do not respond well to thrombolysis[31].

In the SK trials, many patients enrolled had severe strokes. In the MAST-E trial, 51% of patients were drowsy prior to randomization, indicating large strokes, with a worse prognosis and reduced likelihood of a response to reperfusion therapy[15]. Poor patient selection of severe strokes may also have contributed to the poor outcome in the SK trials.

Should we consider a safety study with SK in Pakistan?

Given the available data from the four SK trials it is highly unlikely that it will be shown to be superior to tPA, either in terms of safety profile or clinical efficacy. A placebo-controlled trial of SK in ischemic stroke patients in developed countries therefore cannot be justified as tPA is approved for treatment of acute stroke. The only justification for further study of this drug in acute stroke is the lack of availability of tPA in developing countries which for the most part is related to its cost. Furthermore we do not anticipate the development of a generic version of tPA, given the recombinant technology required to produce it. While negotiations with manufacturers for more affordable drug pricing in developing countries have been successful in other diseases, such as HIV, this has not yet occurred in the area of fibrinolytics.

In developing countries, medications must be purchased by the patient/family. The cost of 100 mg of tPA may be as high as USD 2,200 [Rs 200,000 approximately][33]. This is beyond the financial capabilities of most people in the developing world. In contrast, SK is less than 1/10th the cost of tPA[34,35] (35-50 USD [Rs 4000] at sites in Pakistan; personal communications Adnan Khan). SK is also widely available, as it is used to treat acute coronary syndrome patients.

The need for an economical alternative to tPA therefore justifies additional thrombolysis trials in centres where tPA is unavailable. Even if SK is ultimately shown to be less efficacious than tPA, the lower cost per Quality Adjusted Life Year (QALY), would justify its use. The safety of the SK has to be established and at the very least some evidence of a signal of efficacy shown, before larger studies are undertaken.

How do we ensure that safety is not compromised in a future study?

There have been significant advances in trial designs and imaging of acute stroke patients since the original trials of SK were completed. It is critical that any future SK trial not simply be a replication of those completed in the past, which will most certainly produce similar results. If SK is to be demonstrated to be safe and effective in ischemic stroke, optimization of both trial design and implementation will be required.

Trial Design for a future study

We believe that the most important issues that need to be addressed in a new trial design are evaluation of a much shorter treatment window and a lower, weight-based dose of SK. Although thrombolysis is effective up to 4.5 hours after symptom onset[3], the relative efficacy of this treatment decreases with time. In an initial safety study a shorter time window of 3 hours from onset of symptoms will help ensure fewer hemorrhagic complications. This will also allow for judging the efficacy signal.

A careful review of the literature suggests that the SK dose used in previous trials may have contributed to the relatively high hemorrhagic complication rate, particularly in patients with lower body weight. The optimal dose of SK is

Table 1: Proposed Inclusion/Exclusion Criteria for Future Streptokinase Trials

Inclusion Criteria
• Ischemic stroke
• Informed consent
• Treatment can be initiated within 3 hours of onset or time last
• 18-80 years of age
• NIHSS 4-22
Exclusion Criteria
• Symptom onset >3 hours prior to treatment initiation
• Extensive hypo-attenuation on NCCT (ASPECTS =7)
• Systolic BP >180 mmHg prior to treatment
• Treatment with any anticoagulant (NB: prior use of antiplatelets is acceptable)
• Blood glucose >11.1 mmol/L
• Surgery within 3 months
• Any history of intracranial bleeding
• Acute coronary syndrome within 3 months
• Known secured or unsecured cerebral aneurysm or arteriovenous malformations
• Previous treatment with streptokinase
• Known coagulopathy of any kind
• Platelet count <100 000/Kl

unknown and ideally, a careful dose finding study with tiered stopping rules should be completed prior to any future trial. The time and expense of such a study are a challenge in developing countries, with limited resources for investigator driven initiatives such as this.

We propose utilization of weight-adjusted doses of SK (15 000 units/kg), with a maximum of 1 million units. This maximum dose is 2/3 of that used to treat acute coronary syndromes (1.5 million units). We believe that this lower dose together with better patient selection will lead to fewer hemorrhagic complications.

We also suggest more stringent inclusion /exclusion criteria (Table 1). During this phase of study, it is important to use more conservative patient selection criteria than are currently recommended in clinical practice[4]. Thus, patients normally treated with tPA in experienced stroke centres, such as the very elderly (i.e. >80 years) and those taking warfarin (i.e. those with INR values <1.5) should be excluded from initial studies of SK. Similarly, a very conservative approach to early ischemic infarct signs on CT scan would appear to be the most prudent approach to establishing the safety of SK.

Optimizing Trial Implementation

For the reasons mentioned above, study site selection will be very important to the success of any future SK study program. The study can only be completed in hospitals where tPA is not currently being used to treat acute stroke patients. To be eligible to participate in the study, prospective study centres must have physicians who have expertise in the case of stroke care and have organized stroke care pathways in place. This ideally includes admission to a multi-disciplinary stroke unit. Centres with higher stroke patient volumes are ideal, as this is associated with concentration of expertise.

Care of stroke patients must be consistent with current treatment guidelines, including vital sign monitoring for a minimum of 24 hours[4]. In addition, more specific post-treatment measures aimed at reducing complications related to SK are recommended. Blood pressure (BP) control is a major determinant of hemorrhagic complications of thrombolysis[36]. Paradoxically, patients must also be observed closely for evidence of hypotension in response to SK treatment. Hypotension was reported in a small number of patients in MAST-I

(1.9%) and MAST-E (0.6%), but a significant number in the ASK trial (20%)[17-20]. Although this was not definitively associated with worse clinical outcome in any of the studies, there is a theoretical concern that this may result in decreased cerebral perfusion pressure, thereby exacerbating ischemia. For this reason, patients treated with SK should all be treated with an established intravenous therapy regimen aimed at ensuring euvolemia.

The success of a study where acute stroke patients are being treated has several essential components. The most important aspect for success is development of a system that rapidly identifies a potential study candidate and where there is immediate access to expedited CT scanning. Given the prognostic value of imaging evidence of early infarct signs, investigators must have experience with interpretation of acute CT scans in ischemic stroke patients. In addition, centralized grading of CT scans in order to assess compliance with inclusion/exclusion criteria is advisable.

FUTURE DIRECTIONS

We have initiated planning of an open label safety and feasibility trial of SK in acute ischemic stroke patients i.e., Asia Africa Streptokinase In Stroke Trial (AASIST). The primary aim of this Trial is to establish the safety of SK in strictly selected ischemic stroke patients (Table 1). The trial is being conducted in experienced high volume stroke centres. We plan to do a two-phase study. The first phase of the AASIST study is an open label feasibility and safety study of acute treatment with SK (randomized to 15 000 units/Kg) in 100 ischemic stroke patients within 3 hours of onset. The primary study aim is to demonstrate the feasibility and safety of SK based thrombolysis in ischemic stroke patients. It is hypothesized that treatment with SK in appropriately selected patients will be associated with a hemorrhagic transformation rate similar to that of tPA. The primary outcome of this study is a safety endpoint, specifically the frequency of symptomatic hemorrhagic transformation evident on CT images 24 hours after treatment. A priori stopping rule has been established based on the upper limit of symptomatic hemorrhagic transformation rates following tPA administration in previous randomized controlled trials and phase IV studies (approximately 8%)[28,36]. Symptomatic intracerebral hemorrhage will be defined according to accepted criteria used in previous stroke thrombolysis trials, in particular the second European Cooperative Acute Stroke Study (ECASS II)[23,31]. If the safety of SK using these more stringent inclusion/exclusion criteria can be established, a larger randomized controlled trial is planned. The final design and sample size of this second phase will be based on the results of the safety study.

SUMMARY

Fifteen years since the pivotal NINDS tPA trial, there is no doubt that thrombolytic reperfusion therapy is a highly effective treatment for acute stroke. Current treatment guidelines have not facilitated thrombolysis or acute stroke care programs in most developing country medical centres. This is for the most part related to the high cost of tPA. Demonstrating the safety, and ultimately efficacy, of SK in a carefully selected patient population will make acute stroke treatment feasible for patients who currently receive no therapy.

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CONTRIBUTORS

AS conceived the idea & initiated the study. All the authors contributed significantly in the write up of the review that resulted in the submitted manuscript.