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Acute Ischemic Stroke Treatments Beyond the Three-Hour Mark of

Tissue Plasminogen Activator

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Dedication

Thank you to my husband, Jonathan, and to my parents for all their love, encouragement, and support throughout my completion of this project and years of school.

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I would like to thank Professor Jay Peterson for his patience in working with me, helping me complete this massive project. His patience, time, assistance, and experience allowed me to complete something that I never would have accomplished based on my own knowledge or understanding. I would also like to thank Jolene Miller for all her assistance with research and formatting.

Table of Contents

Introduction

Stroke has increasingly become a challenge to society and medicine, as it is the number three cause of death in the United States, behind heart disease and cancer (American Heart Association [AHA], 2008). Each year approximately 780,000 Americans experience a new or recurrent stroke, meaning that someone has a stroke every 40 seconds (AHA). Every three to four minutes someone will die from a stroke, meaning that more than 160,000 people die from stroke annually (AHA). Over 75 percent of strokes occur in patients who have not previously experienced a stroke (AHA). Stroke also poses a challenge to the economy since patients are often left with residual physical and mental deficits, making stroke the leading cause of serious, long-term disability (AHA). In 2008 alone, the direct and indirect costs of stroke are expected to reach over $65.5 billion (AHA). Stroke becomes more prevalent with age, and as the nation's geriatric population continues to grow, the incidence of stroke will rise as well.

Etiology

A stroke is a sudden onset of neurologic deficit due to cerebrovascular disease which persists for a minimum of 24 hours. If symptoms resolve before 24 hours the episode is known as a transient ischemic attack (TIA). There are two main types of strokes: ischemic and hemorrhagic.

Ischemic stroke accounts for 87 percent of all strokes (AHA, 2008). It occurs when cerebral blood supply is insufficient and an inadequate amount of oxygen and nutrients is delivered to an area of the brain. The most common type of ischemic stroke happens when a cerebral artery becomes blocked by a mechanical obstruction from a thrombus or embolus. Systemic hypoperfusion can also result in ischemic stroke, with global, bilateral neurologic

symptoms and ischemic damage to other organs. Embolic or thrombotic occlusion of a cranial

blood vessel causes focal cerebral ischemia, inhibiting normal cellular brain function. This

ischemic area is still able to receive very minimal blood flow from collateral blood vessels.

Brain tissue surrounding this ischemic area becomes a transition zone between severely reduced

blood flow and adequately perfused tissue. This moderately oxygen deprived area is called the

penumbra, whose fate is influenced by how quickly and adequately blood flow is restored. The

quicker reperfusion therapy can be successfully initiated and completed, the larger the area of

salvageable penumbra and brain tissue, leading to a better patient outcome.

Thirteen percent of all strokes are hemorrhagic; 10 percent are due to intracerebral

hemorrhage and three percent are due to subarachnoid hemorrhage (AHA, 2008). Hemorrhagic

stroke commonly results from chronic hypertension and degenerative changes in cerebral

arteries; however it can occur in normotensive, younger individuals as well. The ensuing

intracerebral or subarachnoid bleeding occupies space within the brain, compressing brain tissue.

This compression interrupts normal brain function, leading to disturbance of respiratory centers

and other vital brainstem functions.

Diagnosis of Stroke

The hallmark symptom of a stroke is an acute loss of focal brain function, especially if

ischemic in nature. Common ischemic stroke symptoms include acute unilateral paralysis or

weakness within a region or entire side of the body; acute visual changes, dysphasia, delirium, or

ataxia. Hemorrhagic strokes may present with a severely painful headache, vomiting, and a

more gradual onset in intracerebral hemorrhage. Patient presentation alone often narrows the

differential diagnosis, with stroke, migraine, head trauma, brain tumor, postictal seizure, toxic-

metabolic disturbances, systemic infection, or conversion disorder being the most common. Obtaining a quick, but thorough patient history often narrows the differential even more, by ruling out a history of migraines, trauma, seizure disorder, drug abuse, or hyper-/hypoglycemia.

All patients suspected of having a stroke should have an emergent noncontrast CT scan or MRI to rule out intracranial bleeds or masses and to determine the area of injury, as this may guide treatment. Either imaging modality may be used, though CT scan is best if subarachnoid hemorrhage is suspected (Adams et al., 2007). Mandatory laboratory studies include electrocardiogram, complete blood count, basic metabolic panel, cardiac enzymes, and coagulation screen. Depending on patient history, additional laboratory studies may be warranted to further lessen the differential diagnosis.

Assessing Neurological Deficit After Stroke

Once a patient suffers a stroke several evaluation tools are used to assess neurological deficits and patient outcome. The most commonly used scale both in clinical practice and in research studies is the National Institutes of Health Stroke Scale (NIHSS). This 42 point scale assesses neurological function in 11 areas, including level of alertness, comprehension, and motor, sensory, visual, and language function (see Table 1). A score is calculated based on the patient's ability to complete certain commands. A lower score indicates a more normal level of function, such that a score of zero indicates normal function with no neurologic deficit, whereas a higher score indicates a greater neurological deficit. The Modified Rankin scale (mRS) measures functional capacity and the level of care a patient requires in completing activities of daily living (see Table 2). This simplified assessment scores patients from zero to six, where zero indicates the absence of symptoms and six indicates death. The Barthel index (BI) also

measures functional capacity, but this 100 point scale assesses patient function in 10 specific areas, verses the more general mRS (see Table 3). A score of 100 designates complete independence in all areas, whereas a score of zero indicates complete dependence. One of the less commonly used scales in stroke patient evaluation is the Glasgow outcome scale (GOS). This scale is a global assessment of function that helps determine patient recovery (see Table 4). A score of five indicates good recovery with a complete return to work or school, and a score of one equals death.

These scales allow practitioners to easily communicate regarding a patient's disability and may help with decisions regarding treatment initiation. No specific criteria have been established to suggest when practitioners should begin treatment, as two equivalent scores may indicate equivalent neurological deficits but not equivalent functional deficits. For instance, a stroke resulting in complete hemianopsia would equate to a score of 2 on the NIHSS, and the patient would never be able to drive again. However, such a low score may call for treatment, considering the significant functional deficit and low probability for improvement.

Treatment Goals in Ischemic Stroke

The initial goal of treatment in ischemic stroke is to maximize brain perfusion and collateral blood flow to the ischemic focus and surrounding penumbra (Finley Caulfield & Wijman, 2006). Treatment is most effective when initiated very early, as "time is brain." Stroke is a medical emergency which requires prompt diagnosis and management, but this is a challenge to achieve.

In order for the stroke chain of survival to even begin, the patient or an acquaintance must first recognize the symptoms. Though patients may be familiar with the symptoms of a

stroke, some are reluctant to seek treatment immediately due to denial or belief that the symptoms will resolve spontaneously. This is especially true if symptoms are fluctuating or patients have experienced a previous TIA which resolved quickly and without treatment. When patients who delay treatment finally seek it, a full recovery is less likely, as with each passing minute, more irreversible cerebral ischemic damage occurs.

After acute stroke symptoms are identified, the next step to treatment is transportation to a certified stroke center. Hospitals such as this are acknowledged by The Joint Commission for their compliance with national practice guidelines and standards and for their ability to treat stroke patients (Adams et al., 2007). These centers are more advanced in the acute management of stroke than non-certified hospitals, and current guidelines state that emergency medical services should bypass hospitals that do not have proper resources and go to the closest facility capable of treating acute stroke (Adams et al.). Timely delivery of a suspected stroke patient to a capable hospital will allow for a greater range of potential treatment options.

Once the patient presents to the hospital, they should immediately be assessed by the hospital stroke team or emergency department physician, if the stroke team has not yet arrived. The patient's airway, breathing, and circulation should be stabilized if necessary. A brief history and physical, including the NIHSS assessment, should follow. It is critical that an accurate timeframe of symptoms be established, including when the patient was last "normal" and without deficits, and if symptoms have worsened or improved since the initial onset of deficits. Next, a CT scan should be performed and labs analyzed to rule out other possible diagnoses. If it is determined that the patient is having a stroke, then treatment options should be analyzed. Most treatment options are dependent on the patient's time of symptom onset to time of therapy initiation, symptom severity, and past medical history. A discussion between the patient, their

family, and the physician weighing the risks and benefits of each acute ischemic stroke treatment for which the patient qualifies will ultimately determine the next step in the treatment plan.

The mainstay of treatment for patients who present to the hospital before three hours of symptom onset is intravenous (IV) tissue plasminogen activator (tPA). Despite the proven safety and efficacy of IV tPA, only one to three percent of stroke patients receive tPA (Gobin et al., 2004; Kim et al., 2006). The use in acute ischemic stroke treatment is largely limited by the three hour time window and exclusive patient criteria (see Table 5). This prohibits many patients from receiving tPA treatment, so extending this short timeframe past three hours has been a topic of great research interest. As time passes beyond three hours of stroke symptom onset, the risk of sustaining an intracranial hemorrhage from tPA treatment increases significantly, as demonstrated by the European Cooperative Acute Stroke Study (ECASS I) (Hacke et al., 1995). Between 16 and 19 percent of stroke patients present within three hours of stroke onset. Of these, only 14-32 percent arrive in the emergency room within two hours of onset, allowing sufficient time to evaluate the patient and confirm the absence of intracranial bleeding on CT scan (Adams et al., 2007).

Even if a patient arrives to the hospital within the three hour timeframe, many do not meet tPA's inclusion criteria (see Table 5). Only 10 percent of patients who meet the deadline are treated with tPA (Katz & Gobin, 2006). This is due not only to the extensive exclusion criteria, but also because many physicians are hesitant to use tPA, fearing the risk of intracranial hemorrhage, reocclusion, or neurotoxicity (Adams et al., 2007).

Methods

The following review of literature examined randomized controlled clinical trials that evaluated acute therapeutic treatments beyond three hours for acute ischemic stroke of thrombotic or embolic origin. Studies on the treatment of ischemic stroke due to systemic hypoperfusion were excluded, as the etiology and treatment of this pathology differs greatly.

The evaluated articles were published in English between 1995 and 2008, as 1995 heralded the landmark publication of the National Institute of Neurological Disorders and Stroke (NINDS) trial (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group [NINDS rt-PA Stroke Study Group], 1995). Treatment in the trials reviewed may have been initiated at any time after initial stroke symptom onset, but all studies must have treated patients beyond three hours. One exception to this criterion was made to allow inclusion of the NINDS trial, as this trial only involved treatment from zero to three hours after symptom onset.

Different modes of treatment application were examined, requiring different inclusion criteria for each mode. For all trials, they must have been multicenter, double-blind or open-label, placebo controlled, and a phase II or phase III study to be included in the literature review. However, an exception was made to these criteria to allow the inclusion of the Interventional Management of Stroke pilot studies which evaluated intra-arterial tPA. Including these trials provided information on a treatment mode which is currently practiced in acute ischemic stroke management, but for which no phase II or III trials have been completed. IV treatments must have been randomized, but randomization was not mandatory in trials evaluating intra-arterial and endovascular mechanical embolectomy treatments, as it was mandatory these trials be single-arm. Due to the invasive nature of these procedures, no control group was created and

therefore no randomization was utilized. Rather, these trials obtained their control information from previous studies which utilized the same drug.

Using the above criteria an extensive electronic search of articles was completed using MEDLINE, PubMed, and EBSCO databases.

Intravenous Tissue Plasminogen Activator

Since its US Food and Drug Administration (FDA) approval in June 1996 for acute ischemic stroke treatment within three hours of symptom onset, IV recombinant tissue plasminogen activator (rtPA or tPA) has been the mainstay of thrombolytic therapy (Adams et al., 2007). tPA activates plasminogen to form plasmin, a protease which cleaves fibrin, the major constituent of the thrombus or embolus obstructing the cerebral vasculature. Prior to the advent of tPA, heparin and aspirin were used as immediate therapy. The use of heparin as a sole treatment in acute ischemic stroke has been abandoned, as trials have failed to prove any benefit (International Stroke Trial Collaborative Group, 1997). Aspirin has shown to be of some clinical benefit when used for 14 days after stroke onset, but its efficacy as sole immediate therapy within the first hours of stroke onset is questionable (International Stroke Trial Collaborative Group). Neither heparin nor aspirin is currently used as a single immediate therapy, while both are used in conjunction with other thrombolytic medications.

National Institute of Neurological Disorders and Stroke Trial

The NINDS trial is the pivotal phase III trial which demonstrated the safety and efficacy of IV tPA in ischemic stroke treatment within three hours of symptom onset. This three hour cutoff was chosen based on pilot studies suggesting tPA's beneficial, yet limited timeframe (Brott et al., 1992; Haley et al., 1992; NINDS rt-PA Stroke Study Group, 1995). This randomized, double-blind, placebo-controlled, two-part study enrolled 624 patients who presented within three hours of the onset of significant neurological deficits and did not have signs of intracranial hemorrhage on CT scan. Patients received either placebo or IV tPA at 0.9 mg/kg of bodyweight (mg/kg), with a maximum dosage of 90 mg. Ten percent of the tPA was

administered as a bolus, followed by a constant infusion of the remaining 90 percent over 60 minutes (NINDS rt-PA Stroke Study Group).

The first part of the study investigated whether tPA had initial clinical efficacy. Forty seven percent of tPA patients and 39 percent of placebo patients met the primary outcome of improvement in NIHSS score by four or more points at 24 hours after treatment. No statistically significant differences were found between the two groups. Part two considered the risk versus benefit of tPA. Primary endpoints evaluated patient outcome at three months using the NIHSS, BI, mRS, and GOS. Based on the assessment scales, each outcome measure showed a statistically significant benefit in the tPA group over the placebo group, as tPA patients were at least 30 percent more likely to have minimal or no disability at three months (NINDS rt-PA Stroke Study Group, 1995).

Symptomatic intracranial hemorrhage was the greatest complication in the tPA group, occurring in 6.4 percent of treated patients and in only 0.6 percent of the placebo group (NINDS rt-PA Stroke Study Group, 1995). These patients tended to have more severe neurological deficits at baseline than the rest of the study group. Mortality rates were similar between the two groups (17 percent of tPA-treated patients and 21 percent of placebo-treated patients) (NINDS rt-PA Stroke Study Group). The study concluded that patients treated with tPA were 30 to 50 percent more likely than the control group to have a good neurological outcome at three months. Based on the positive results of pilot studies which established the timeline and the NINDS phase III trial results, IV tPA was approved by the FDA for treatment of acute ischemic stroke in patients presenting within three hours of symptom onset.

European Cooperative Acute Stroke Studies

ECASS I was a randomized, multicenter, double-blind, placebo-controlled trial that evaluated the safety and efficacy of IV tPA administration within six hours of stroke symptom onset (Hacke et al., 1995). In ECASS I, 620 patients with moderate to severe neurologic deficit were given either placebo or 1.1 mg/kg of bodyweight of tPA, with a maximum dosage of 100 mg. The median time to treatment was 4.3 hours.

The study's primary endpoints were BI and mRS scores at 90 days. In the group that adhered to protocol, no difference was found in primary outcome. When all patients were analyzed, including those who did and did not follow protocol, mRS scores were significantly better in the tPA group than in the placebo group (Hacke et al., 1995). The symptomatic intracranial hemorrhage rate in the tPA group was 20 percent, which was significantly higher than the placebo group (seven percent). These results were much higher than the NINDS study rate of hemorrhage (6.4 percent), which the authors concluded was likely a reflection of the higher tPA dose used in ECASS I versus the NINDS trial (Hacke et al., 2004).

Patients who were treated within the first three hours from symptom onset appeared to benefit from tPA, reflecting the NINDS study (Steiner et al., 1998). Regardless of this trend, no statistical significance was found in outcomes of the zero to three hour tPA group, potentially due to the small sample size of only 87 patients. In the three to six hour experimental group, mortality at 90 days was significantly lower in the placebo group (tPA 21 percent, placebo15 percent). However, tPA patients overall had a significantly shorter hospital stay than the placebo group (Hacke et al., 1995).

In ECASS II, patients were administered placebo or the same dosage of tPA that was used in the NINDS trial, 0.9 mg/kg of bodyweight with a maximum dosage of 90 mg, within six

hours of symptom onset (Hacke et al., 1998). ECASS II authors reported better CT-scan surveillance, potentially making patient eligibility more exclusive than ECASS I. Since greater brain edema correlates to a higher risk of hemorrhagic transformation, patients with cerebral swelling of an entire hemisphere on CT were excluded in ECASS I, whereas in ECASS II, patients were excluded if swelling exceeded 33 percent of the brain (Hacke et al.; von Kummer et al., 1997).

The primary endpoint was a score of zero or one on the mRS at 90 days. 54.3 percent of tPA patients and 46.0 percent of placebo patients reached this outcome, which was not found to be statistically significant (Hacke et al., 1998). Patients were divided by treatment time between zero to three (158) and three to six hours (642) as in ECASS I. In ECASS II, no statistically significant differences were found in outcome between either of the treatment groups and the placebo groups. The authors note that one factor involved was the small sample size in the zero to three hour onset-to-treatment interval. Overall symptomatic intracranial hemorrhage occurred 2.5 times more frequently in the tPA groups, reflecting similar outcomes in the ECASS I and NINDS trials. Overall mortality at 90 days was lower in ECASS II (tPA 10.3 percent, placebo 10.5 percent) than ECASS I (tPA 22.4 percent, placebo 15.8 percent) or NINDS (tPA 17 percent, placebo 21 percent), which the authors expressed was likely due to ECASS II patients having less severe neurological deficits due to patient selection criteria (Adams et al., 2007; Hacke et al.; NINDS rt-PA Stroke Study Group, 1995).

Results of ECASS II demonstrated that tPA efficacy may not depend on administration within three hours of stroke symptom onset, although the study was not powered to detect this as the zero to three hour group was so small. Further research was recommended by the authors to determine tPA's efficacy when administered up to six hours after ischemic stroke symptom

onset. ECASS III is currently in progress and will further evaluate the three to six hour treatment time.

Alteplase ThromboLysis for Acute Non-Interventional Therapy in Ischemic Stroke

The Alteplase ThromboLysis for Acute Non-Interventional Therapy in Ischemic Stroke (ATLANTIS) trial was the third large randomized trial evaluating IV tPA treatment past three hours of symptom onset. It was a multicenter, randomized, placebo-controlled, double-blind study that evaluated tPA use after three to five hours of ischemic stroke symptom onset. Patients were given placebo or 0.9 mg/kg of intravenous tPA, with a maximum of 90 mg (Clark et al., 1999). ATLANTIS was stopped prematurely when an interim analysis showed poor efficacy and that treatment was unlikely to be beneficial.

The primary endpoint was excellent neurologic recovery at 90 days, defined as a score of zero to one on the NIHSS. Thirty four percent of tPA patients and 32 percent of placebo patients met this endpoint, showing no significant tPA benefit (Clark et al., 1999). Patients treated with tPA had a higher hemorrhage rate than the placebo group (7.0 percent versus 1.1 percent, respectively), which is similar to findings in the NINDS trial (6.4 percent). The authors of the trial wrote that data may demonstrate symptomatic intracranial hemorrhage is not increased if tPA is administered up to five hours after stroke symptom onset (Clark et al.; NINDS rt-PA Stroke Study Group, 1995). Mortality rates at 90 days were not significantly different (tPA 11.0 percent and placebo 6.9 percent) (Clark et al.). Because no statistical significance was found in 90 day neurologic recovery or mortality rates, the authors concluded that the use of tPA beyond three hours was not supported by this study and further research needed to be conducted.

Intra-arterial Tissue Plasminogen Activator

Interventional Management of Stroke Studies

The NIH Interventional Management of Stroke (IMS) Studies evaluated the feasibility, efficacy, and safety of combined IV and local IA tPA thrombolysis. IA thrombolysis offers a different route of tPA administration, which potentially creates another option for ischemic stroke patients who do not qualify for or who have failed traditional IV thrombolysis. The IMS studies are based on the Emergency Management of Stroke (EMS) Bridging Trial, a pilot study in which 35 patients with acute ischemic stroke presenting within three hours of symptom onset were treated first with IV tPA or placebo, followed by IA tPA within six hours of symptoms if on angiography the vessel remained occluded. Seventy percent of patients required IA tPA therapy. Of these, 54 percent achieved arterial recanalization, compared to 10 percent of the placebo and IA tPA group (Lewandowski et al., 1999). No statistically significant difference was found in neurological outcome between the two groups, but the EMS trial did demonstrate the feasibility of combined IV and IA tPA treatment.

IMS I was the second pilot study investigating combined IV and IA tPA. The open-labeled, single-armed trial evaluated 80 patients who presented within three hours of stroke symptom onset who were treated with 0.6 mg/kg of IV tPA over 30 minutes, followed by IA tPA within five hours if an occlusion was still demonstrated on angiography, compared to the six hour limit in EMS (IMS Study Investigators, 2004). Results were compared to the control arm of the NINDS tPA Stroke Trial. Mortality at three months was not statistically different than the NINDS placebo or tPA arm, nor was the primary outcome (MRS of zero or one at three months) (IMS Study Investigators; NINDS rt-PA Stroke Study Group, 1995). The rate of symptomatic hemorrhage was similar between the IMS and NINDS study groups, but asymptomatic

hemorrhage rates were significantly higher in the IMS study group (IMS Study Investigators; NINDS rt-PA Stroke Study Group).

IMS II was the third major pilot study investigating combined IV and IA tPA, evaluating 81 subjects. The treatment protocol was identical to IMS I except that while the microcatheter delivered IA tPA, low-intensity ultrasound was transmitted within the clot to accelerate thrombolysis (IMS II Trial Investigators, 2007). IMS II patients treated with IV and IA tPA had a statistically significant better functional outcome at three months than the NINDS placebo group (IMS II Trial Investigators; NINDS rt-PA Stroke Study Group, 1995). Results of IMS II confirmed EMS and IMS I findings, as three month mortality and symptomatic intracranial hemorrhage rates in patients treated with tPA were not statistically different from the NINDS trial study group (IMS II Trial Investigators, 2007; IMS Study Investigators, 2004; Lewandowski et al., 1999; NINDS rt-PA Stroke Study Group).

Potential advantages of IA thrombolysis over IV thrombolysis include increased recanalization rates, improved accuracy of diagnosis, treatment of patients between three to six hours after symptom onset, and the ability to treat major intracranial vessel occlusions, which are less likely to dissolve with IV thrombolysis (Adams et al., 2007; Albers, Amarenco, Easton, Sacco, & Teal, 2004; Blakeley & Llinas, 2007). Infusion of a thrombolytic locally or regionally also allows for a lower dose of drug, leading to an increase in patient safety by decreasing the risk of bleeding (Albers et al.; Blakeley & Llinas). Despite these advantages, the administration of IA thrombolysis requires qualified neurological and vascular interventional radiologists at large hospitals with the capacity to perform emergent angiography (Blakeley & Llinas). Assembling a team to carry out a cerebral angiography to locate the occlusion and determine collateral circulation then positioning a microcatheter for IA tPA delivery takes time as well,

delaying treatment when time is of the essence. For this reason an IV thrombolytic is commonly initiated before the IA thrombolyic. IA thrombolysis is best indicated in patients with a proven large vessel occlusion who are not candidates for or who have failed IV thrombolysis, making its use increasingly common (Blakeley & Llinas).

July 2006 marked the beginning of IMS III, a phase III, randomized, multicenter, open-label trial planning to enroll 900 patients. The study will again compare IV tPA initiated within three hours of stroke symptom onset with adjuvant IA tPA to traditional IV tPA treatment. IMS III will use ultrasound with IA tPA infusion as a potential treatment option as in IMS II, however it will also include the use of the Merci Retrieval System, a mechanical embolectomy device approved by the FDA in 2004.

Intravenous Streptokinase

Intravenous streptokinase is a fibrinolytic that works through a similar mechanism as tPA, activating plasminogen to form plasmin. Its use has previously been substantiated for the treatment of myocardial infarction (Second International Study of Infarct Survival Collaborative Group, 1988), which in the 1990's led to investigations to explore its use in the treatment of acute ischemic stroke. To date, three major trials have evaluated this possibility. These studies were randomized, multicenter, placebo-controlled trials that were terminated early due to safety concerns (Donnan et al., 1996; Multicenter Acute Stroke Trial - Europe Study Group [MAST-E Study Group], 1996; Multicentre Acute Stroke Trial - Italy Group [MAST-I Group], 1995).

Multicenter Acute Stroke Trial – Europe

In the Multicenter Acute Stroke Trial, Europe study group (MAST-E), patients with moderate to severe ischemic middle cerebral artery (MCA) infarcts presenting within six hours of symptom onset were treated with placebo or 1.5 million units of IV streptokinase over one hour (MAST-E Study Group, 1996). The administration of concomitant IV heparin or aspirin within 48 hours in either group was permitted, at the discretion of the investigators (MAST-E Study Group). It was anticipated that six-hundred patients would be enrolled in the study, but only 310 patients had been enrolled when recruitment was stopped because of an increase in mortality due to intracerebral hemorrhage (MAST-E Study Group).

Primary safety outcomes were mortality at 10 days and cerebral hemorrhage. The study was terminated when the 10 day mortality rate of the streptokinase group reached 34 percent, which was significantly higher compared to 18 percent mortality in the placebo group (MAST-E Study Group, 1996). The rate of asymptomatic cerebral hemorrhage was also higher in the

streptokinase group (45.3 percent) than the placebo group (41.3), and symptomatic hemorrhages were more likely to be fatal in the streptokinase group. A post-hoc analysis found that patients who had hemorrhagic transformation had significantly more atrial fibrillation, diabetes mellitus, no heparin use, streptokinase use, and early CT signs (Jaillard et al., 1999). The primary efficacy outcome was a combination of death and a mRS greater than three at six months after treatment. At six months, 79.5 percent of the streptokinase group and 81.8 percent of the placebo group were dead or disabled, which was not statistically significant (MAST-E Study Group). The authors concluded that MAST-E did not demonstrate IV streptokinase to be beneficial in acute ischemic stroke.

Multicentre Acute Stroke Trial – Italy

The Multicentre Acute Stroke Trial, Italy study group (MAST-I) used a randomized open-label protocol to treat patients who presented within six hours of stroke symptom onset with 1.5 million units of IV streptokinase over one hour, 300 mg of buffered aspirin once daily for 10 days, both, or neither (MAST-I Group, 1995). The combination of streptokinase and aspirin has been demonstrated to produce twice the benefit of either used alone in the treatment of acute myocardial infarction, and investigators hoped that the same would serve in acute stroke treatment (Ciccone, Motto, Aritzu, Piana, & Candelise, 1998; Fibrinolytic Therapy Trialists' Collaborative Group, 1994). Unlike MAST-E, IV heparin administration for stroke treatment was not permitted for 10 days (MAST-I Group). 1,500 patients were anticipated to enroll in MAST-I, but recruitment stopped at 622 patients when the trial was suspended due to an excess of 10-day mortalities.

The primary outcome measurement was mortality or a mRS score greater than three at six months. This was met in 63 percent of the streptokinase group and 65 percent of the placebo group, demonstrating no statistical significance in respect to the primary outcome (MAST-I Group, 1995). Patients in the streptokinase group had a significantly higher rate of death within the first 10 days after treatment (27 percent) than patients who received placebo (12 percent). A post hoc analysis of MAST-I demonstrated that the combination of streptokinase and aspirin put patients at an increased rate of early death, as it significantly increased early mortality from day three to day 10 (Ciccone, Motto, Aritzu, Piana, & Candelise, 2000; MAST-I Group).

Australian Streptokinase Trial

The third major IV streptokinase study for ischemic stroke treatment was the Australian Streptokinase Trial (ASK). Patients presenting within four hours of stroke symptom onset were administered placebo or 1.5 million units of IV streptokinase over one hour (Donnan et al., 1996). One hundred mg of aspirin was given within four hours of streptokinase administration. Patients were randomized according to their time of presentation after stroke symptom onset. Seventy patients received treatment within three hours and 270 received treatment beyond three hours. Only 340 of the projected 600 patients were recruited before the study was prematurely terminated after the Safety Monitoring Committee found the mortality rate was significantly higher among patients who received treatment beyond three hours of stroke symptoms.

The ASK primary outcome measure was a combined mortality and BI score of less than 60 three months after treatment (Donnan et al., 1996). There was a significant difference in primary outcome of the streptokinase group treated within three hours of symptom onset versus patients treated after three hours, with a significantly better outcome towards earlier therapy.

The primary outcome did not demonstrate any statistically significant difference between the placebo group or treatment group. Patients treated with streptokinase after three hours of symptoms had almost twice the risk of death as those treated with placebo (43 and 22 percent, respectively), though the authors were not clear as to if this was significant. A statistically significant hematoma rate was found between the treatment group (13.2 percent) and placebo group (3.0 percent). ASK failed to demonstrate a significantly better outcome at three months in patients treated with streptokinase within three hours (34.1 percent) versus placebo (51.7 percent).

Intravenous Desmoteplase

Desmoteplase (recombinant desmodus rotundus salivary plasminogen activator alpha-1)

is a very fibrin specific recombinant form of tPA found in vampire bat saliva (Hacke et al., 2005;

Lapchak & Araujo, 2007). This compound has higher in vivo and in vitro activity plus a longer

terminal half life (2.8 hours) than tPA (approximately 5 minutes), and unlike tPA it does not

have any neurotoxic effects (Bringmann et al., 1995; Grandjean, McMullen, & Newschwander,

2004; Hacke et al.; Lapchak & Araujo). Due to these desired properties, investigators

hypothesized desmoteplase would be an effective acute ischemic stroke treatment, being more

specific for acute thrombus than tPA and potentially safer past the three hour timeframe (Hacke

et al.).

Desmoteplase in Acute Ischemic Stroke

The Desmoteplase in Acute Ischemic Stroke study (DIAS) was a randomized, double-

blind, placebo-controlled, dose-finding, phase II trial (Hacke et al., 2005). The purpose was to

determine the safety and efficacy of various doses of IV desmoteplase in acute ischemic stroke

patients with a perfusion/diffusion mismatch on MRI who were treated within three to nine hours

from symptom onset. The purpose of perfusion/diffusion mismatch in the patient selection

protocol was to determine viability of the penumbra. Once the trial began, concerns arose

regarding the safety endpoint, causing the study to be performed in two parts. The initial

protocol treated 47 randomized patients with placebo or fixed doses of desmoteplase at 25, 37.5,

or 50 mg. This approach resulted in an excessive amount of symptomatic intracranial

hemorrhage in the desmoteplase group (26.7 percent), leading to termination of part one and

modifications in dosage for part two. Part two enrolled 57 patients treated with placebo or weight-adjusted doses of desmoteplase at 62.5 mcg/kg, 90 mcg/kg, or 125 mcg/kg.

Safety endpoint for both parts was symptomatic intracranial hemorrhage. Part one had a rate of 26.7 in the experimental group, part two a 2.2 percent rate, with no symptomatic intracranial hemorrhage occurring in the placebo groups (Hacke et al., 2005). No data is provided by the authors as to whether this finding was statistically significant. The efficacy endpoints were the rate of reperfusion on MRI after four to eight hours and clinical outcome at 90 days, measured by a NIHSS less than one, mRS less than two, and BI less than 75. A statistically significant reperfusion rate of 71.4 percent occurred in the 125 micrograms per kilogram (mcg/kg) group, compared to 19.2 percent with placebo. Perfusion rates were not statistically significant in the 62.5 mcg/kg and 90 mcg/kg groups versus placebo (23.1 percent, 46.7 percent, and 19.2 percent, respectively). There was no significant difference in clinical outcome at 90 days in the 62.5 mcg/kg group (13.3 percent) or 90 mcg/kg group (46.7 percent) versus placebo (22.2 percent); however a statistically significant positive effect was found in the 125mcg/kg group (60.0 percent) compared to placebo.

In patients treated with desmoteplase, reperfusion on MRI was achieved in 54.3 percent of the three to six hour group, and in 40.0 percent of the six to nine hour group (Hacke et al., 2005). DIAS authors concluded that the use of MRI perfusion/diffusion mismatch in patient selection criteria may be more important than duration of symptoms in predicting therapeutic response, as 38.3 percent of patients treated with desmoteplase between three to six hours of symptom onset had a favorable 90 day clinical outcome, which was comparable to those treated at six and nine hours (39.3 percent).

The Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trial was a phase II trial of 38 patients which occurred after DIAS and further investigated the use of weight-adjusted doses of desmoteplase in patients with a perfusion/diffusion mismatch on MRI treated three to nine hours after stroke symptom onset (Furlan et al., 2006). Protocol was similar to DIAS except only the 90 mcg/kg and 125 mcg/kg doses were evaluated against placebo. The 62.5 mcg/kg dosage was not evaluated due to its poor outcomes in DIAS. DEDAS echoed the findings of DIAS, demonstrating that desmoteplase at dosages of 90 and 125 mcg/kg is a safe treatment in patients selected by perfusion/diffusion mismatch on MRI treated three to nine hours after ischemic stroke symptom onset. No symptomatic intracranial hemorrhages occurred in any of the groups. Non-significant asymptomatic intracranial hemorrhage was observed at similar rates in the treatment groups versus placebo (35.7 percent of 90 mcg/kg, 40.0 percent of 125 mcg/kg, and 12.5 percent of placebo). At 90 days, one patient had died in each study group.

Reperfusion at four to eight hours after desmoteplase administration was not statistically significant versus placebo, and occurred in 18.2 percent of the 90 mcg/kg group, 53.3 percent of the 125 mcg/kg group, and 37.5 percent of the control group (Furlan et al., 2006). Good clinical outcome at 90 days occurred in 28.2 percent of the 90 mcg/kg group, 60.0 percent of the 125 mcg/kg group, and 25.0 percent of the placebo group. No statistical significance was found in clinical outcome, but the 125 mcg/kg group did appear to be the more successful dosage. The results of DIAS and DEDAS show a promising future for desmoteplase in first line ischemic stroke treatment due to its high fibrin specificity (Blakeley & Llinas, 2007).

DIAS-2, a phase III trial further evaluating the 90 mcg/kg and 125 mcg/kg dosing was recently completed and presented at the XVI European Stroke Conference. Protocol was identical to DIAS, except for the use of CT perfusion/diffusion imaging instead of MRI (Hacke,

2007 May 29-Jun 1). No data on the trial is available for analysis, as the results have not yet

been published.

Intra-arterial Pro-urokinase

Prolyse in Acute Cerebral Thromboembolism Trials

Prolyse in Acute Cerebral Thromboembolism (PROACT) was a 180 patient, phase II, randomized, double-blind, multicenter trial conducted to evaluate the safety and efficacy of direct IA recombinant pro-urokinase (pro-UK) in treating symptomatic middle cerebral artery (MCA) occlusion within six hours of symptom onset (del Zoppo et al., 1998). Pro-UK, also called Prolyse, is a precursor of urokinase. It is activated at the thrombus surface to produce a thrombolytic effect. Heparin augments the function of prolyse by stimulating tPA release from the vascular endothelium (Furlan et al., 1999). In this trial, MCA occlusion was chosen as the study group as it is the most common site of thromboembolism in patients with severe stroke of less than six hours duration (del Zoppo et al., 1992). Forty patients were randomized at a two to one ratio to be treated with an IA infusion of six mg/kg pro-UK or placebo over two hours at the site of occlusion (del Zoppo et al., 1998). Both groups also received IV heparin for four hours.

The primary efficacy outcome was complete recanalization of the MCA after two hours of IA infusion, confirmed by angiography (del Zoppo et al., 1998). This was met in a statistically significant 57.7 percent of the pro-UK group versus zero of the placebo group. Symptomatic intracranial hemorrhage within 24 hours after treatment was used as the primary safety outcome. No statistical significance was found, as symptomatic intracranial hemorrhage occurred in 15.4 percent of pro-UK patients and 7.1 percent of placebo patients. No statistically significant difference was found between placebo and pro-UK groups in functional outcome at 90 days, which the authors felt was due to the small number of patients studied.

PROACT I served as an introductory study to PROACT II, a phase III trial. PROACT II was also a randomized, multicenter trial that treated 180 patients within six hours of symptom

onset, and was open-label with a blinded follow-up (Furlan et al., 1999). The dose of IA pro-UK in PROACT II was increased from the six mg/kg to nine mg/kg to try to improve recanalization while still minimizing symptomatic intracranial hemorrhage. IV heparin was again given to both the control and study groups for four hours after angiographic confirmation of an MCA occlusion.

In PROACT II, the primary efficacy outcome of an mRS of two or less at 90 days after treatment was found statistically significant with forty percent of pro-UK patients and 25 percent of placebo patients achieving this goal (Furlan et al., 1999). Recanalization was achieved in 66 percent of the study group, compared to only 18 percent of the control group, and was also statistically significant. The primary safety outcome of symptomatic intracranial hemorrhage within 24 hours of treatment was not found to be statistically significant, as it occurred in 10 percent of pro-UK patients and two percent of placebo patients. The authors concluded that despite this trend in increased symptomatic intracranial hemorrhage, treatment with pro-UK was beneficial. The authors calculated that for every seven patients treated with IA pro-UK, one patient will benefit.

Merci Retrieval System

In August 2004, the Merci Retrieval System X-series (Concentric Medical Inc., Mountain View, CA) became the first FDA approved device indicated for acute ischemic stroke treatment,via percutaneous thromboembolectomy. The system consists of three parts: the Merci Retriever, the Merci Microcatheter, and the Merci Balloon Guide Catheter (Gobin et al., 2004). The Merci Retriever is a flexible wire with five helical loops of decreasing diameter made of nitinol memory wire. The Merci Microcatheter keeps the Merci Retriever straight while navigating the cerebral vasculature. The Merci Balloon Guide Catheter, a 9-french catheter with a lumen and balloon at its tip to collect the clot, stops blood flow near the clot to reduce the risk of thrombus fragmentation and embolization to a previously uninvolved territory. Once the Merci system reaches the thrombus, the helical loops of the Retriever are released into the thrombus. The clot is then ensnared inside the helical Retriever by performing up to seven revolutions of the Retriever. After the thrombus has been completely ensnared, the Retriever and Microcatheter are withdrawn into the Balloon Guide Catheter lumen and removed by hand suction with a syringe. The balloon is deflated and angiography can be performed to confirm vessel recanalization. If the entire clot was not removed with upon the first attempt, up to six attempts with the Merci System has been recommended (Katz & Gobin, 2006).

Mechanical embolectomy may be advantageous over chemical embolectomy since no thrombolytic drug is needed, reducing the rate of hemorrhagic side effects and prolonging the therapeutic time window. Therefore, indications for mechanical embolectomy are more broad and inclusive than for tPA (see Table 6).

Mechanical Embolus Removal in Cerebral Ischemia

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial explored the safety and efficacy of the Merci Retrieval System to recanalize large obstructed cerebral arteries when utilized within eight hours of ischemic stroke symptom onset (Smith et al., 2008). This phase II, prospective, single-arm, non-randomized trial enrolled 164 patients from 25 centers. Eligibility included patients who presented before three hours of stroke symptom onset but did not meet eligibility requirements for tPA, symptom onset between three and eight hours prior to treatment, and occlusion of a treatable vessel.

Once the procedure began, patients were given a 3,000 unit bolus of heparin and patients were not permitted to receive other thrombolytics throughout the procedure unless the thrombus was not removed within six passes of the Merci Retriever. If the clot was not removed within six passes or if distal embolization occurred, administration of intra-arterial thrombolytics was allowed (Smith et al., 2008). IA tPA was used to treat device failures in 14 cases and distal occlusions in 17 cases. Procedural complications included device fracture (3.2 percent of the 341 devices used), embolization of a previously unoccluded vessel (2.1 percent of cases), vascular dissection (2.8 percent of cases), intracranial vascular perforation (4.3 percent of cases), and subarachnoid hemorrhage (2.1 percent of cases).

Because MERCI was a single-arm study, the control arm used for statistical analysis was the spontaneous recanalization rate from PROACT II (Furlan et al., 1999; Smith et al., 2008). 57.3 percent of occlusions were recanalized using the Merci Retrieval System, showing statistical significance compared to the PROACT II placebo arm (18 percent) (Furlan et al.; Smith et al.). Overall the trial had a 69.5 percent recanalization rate with the Merci Retreival System and adjunctive IA tPA (Smith et al.). The rate of symptomatic intracranial hemorrhage

was 9.8 percent, which was similar to PROACT II (10 percent) and slightly higher than NINDS (6 percent) and IMS (6 percent) trials (Furlan et al.; IMS Study Investigators, 2004; NINDS rt-PA Stroke Study Group, 1995; Smith et al.). Patient mortality in MERCI was higher than other trials at 39 percent, however patient eligibility was based on occlusion of a large intracranial vessel, which naturally creates a more severe stroke and higher patient mortality (Smith et al.).

A prospective "real world" trial of the Merci Retrieval System has been completed in a single center with 25 patients. Patient selection and treatment mimicked the MERCI protocol, with the exception that some patients were treated within three hours of stroke symptom onset and some were also treated with carotid angioplasty and stenting (Devlin, Baxter, Feintuch, & Desbiens, 2007; Smith et al., 2005). The overall recanalization rate (56 percent) was consistent with primary results of MERCI, as was the overall mortality rate (36 percent) (Devlin et al.; Smith et al.). Successful reperfusion provided a significant improvement in neurological outcome at three months (Devlin et al.). Of the 34 Merci devices used in the study, one fractured within an intractable MCA lesion which was retained by the patient and caused no additional symptoms. Safety analysis of the Merci Retrieval System was also similar, as the one fractured device was not statistically different than the fracture rate in primary MERCI results (Devlin et al.; Smith et al.).

The Merci Registry is an ongoing project with the purpose of assessing real world application of the Merci Retriever in treating acute ischemic stroke. Started in 2007, there is no maximum number of participants to enroll, and no deadline is currently in place. At this time there are no plans to publish current results.

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

Platelet glycoprotein IIb/IIIa receptor antagonists such as abciximab and triofiban show promise in increasing the rate of spontaneous recanalization in ischemic stroke, and their use has already been substantiated in myocardial infarction (Bellandi, Maioli, Leoncini, Toso, & Dabizzi, 2006; Lavi et al., 2005). Binding of the platelet glycoprotein IIb/IIIa receptor to fibrinogen leads to platelet accumulation and thrombus formation. Platelet glycoprotein IIb/IIIa antagonists bind to these receptors and inhibit platelet-dependent thrombus formation (Furlan et al., 2000).

Abciximab in Emergent Stroke Treatment Trial

Abciximab, a monoclonal antibody platelet glycoprotein IIb/IIIa receptor antagonist, was tested in the phase II, randomized, double-blind, dose-escalation Abciximab in Emergent Stroke Treatment Trial (AbESTT-I). Four hundred patients were treated within 24 hours of stroke symptom onset with placebo or 0.25 mg/kg IV bolus abciximab, followed by a 12 hour continuous infusion of abciximab at 0.125 mcg/min (Abciximab Emergent Stroke Treatment Trial Investigators [AbESTT Investigators], 2005). No statistical significance was found in functional outcome (mRS score of zero or one) at three months (48.5 percent of abciximab patients, compared to 40 percent of the placebo group). Symptomatic intracranial hemorrhage within five days of treatment was also not statistically significant between the experimental group (3.6 percent) and control group (1 percent).

The phase III AbESTT-II trial again used an IV bolus of 0.25 mg/kg of abciximab followed by a 12 hour continuous infusion at 0.125 mcg/minute to evaluate abciximab in treating patients in three cohorts: zero to five hours, five to six hours, and zero to three hours (Adams et al., 2008). The

study aimed to enroll 1800 patients but was terminated prematurely after 808 patients. Thirty three percent of placebo and 32 percent of the zero to five hour treatment group had a favorable outcome at three months. After only five days of enrollment 5.5 percent of abciximab patients treated within five hours and 0.5 percent of placebo patients had symptomatic or fatal intracranial hemorrhage. An unfavorable benefit-risk profile was found, and neither safety nor efficacy was demonstrated.

Future Directions in Acute Ischemic Stroke Treatment

Advances in science and technology have brought great developments in acute stroke treatment, and more advances are currently being trialed and perfected. Not all research efforts have been developments in therapeutic management. In recent years much attention has been directed towards imaging and its impact on acute stroke treatment. For years computed tomography (CT) has been the primary diagnostic brain imaging study for suspected stroke patients (Adams et al., 2007). Magnetic resonance imaging may soon replace CT as the "gold standard," especially when evaluating patients using multimodal MRI. More sophisticated neuroimaging improves the selection of patients who can be effectively treated with reperfusion therapies by identifying penumbras with salvageable brain tissue and those with low risks of hemorrhagic transformation. Even more importantly, it may identify patients who would benefit from recanalization therapy beyond the three hour time window (Finley Caulfield & Wijman, 2006).

A patient's chance of successful recanalization after three hours of symptom onset appears to largely depend on the ischemic penumbra and its perfusion-diffusion mismatch, or amount of decreased perfusion compared to the amount of preserved diffusion (Adams et al., 2007). Multimodal MRI includes perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI). PWI determines the residual hemodynamic status of ischemic brain regions. DWI better visualizes regions difficult to see on T1 or T2 weighted images, while also permitting early visualization of ischemic areas within minutes of symptom onset (sensitivity 88 to 100 percent, specificity 95 to 100 percent). The multicenter Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study demonstrated that patients with a diffusion-perfusion mismatch were more likely to have early recanalization from IV tPA

between three and six hours after stroke symptom onset, as results were statistically significant (Olivot et al., 2008). The study also concluded that patients without a diffusion-perfusion mismatch did not benefit from IV tPA beyond three hours, and that large DWI regions created a higher risk for hemorrhage when reperfusion was attempted.

Neuroprotective strategies have also become a large focus of stroke research. These agents diminish the underlying mechanisms of neuronal damage during brain ischemia, and are best used in the ambulance or at non-stroke certified hospitals, where the time-consuming transfer to a stroke center is necessary. Many agents have failed to cross over from the lab to clinical application due to limitations in trial design. An example of this is IV NXY-059, a free radical trapping agent given within six hours of stroke symptom onset. The Stroke Acute Ischemic NXY-059 Treatment (SAINT I) trial enrolled 1700 patients and showed a statistically significant improvement in outcome for the treatment group. SAINT II enrolled more patients, but results were much less promising. Patients in the control group and treatment groups showed no difference in neurological outcome when treated within six hours of stroke onset (Shuaib et al., 2007). IV magnesium given within two hours of stroke symptom onset and high-dose albumin with five hours are also currently being investigated as neuroprotective agents in the Field Administration of Stroke Therapy – Magnesium (FAST-MAG) and Albumin in Acute Stroke (ALIAS), respectively. Transcranial laser, antioxidants, and anti-inflammatory drugs are also currently being investigated (Lapchak & Araujo, 2007).

Hypothermia may be one of the more promising methods of neuroprotection. An increase in core temperature has been found in approximately 25 percent of ischemic stroke patients, promoting the inflammatory response, increasing excitotoxic amino acids, and increasing the metabolic demand to an already ischemic region (Citerio et al., 2006; Finley

Caulfield & Wijman, 2006). When initiated early, mild to moderate hypothermia (2-5° C below

normal brain temperature) reduces ischemic damage (Finley Caulfield & Wijman). The

randomized, multicenter Intravascular Cooling for the Treatment of Stroke-Longer window

(ICTuS-L) is an ongoing study evaluating hypothermia with IV tPA within six hours of stroke

onset (Finley Caulfield & Wijman).

Discussion

Intravenous Tissue Plasminogen Activator

The NINDS study demonstrated the safety and efficacy for IV tPA given within three hours of acute ischemic stroke symptom onset (NINDS rt-PA Stroke Study Group, 1995). Although patients treated with IV tPA were found to have a higher rate of symptomatic intracranial hemorrhage, the life-saving benefits of tPA outweigh this risk. Based this positive information, IV tPA was approved by the FDA for treatment of acute ischemic stroke in patients presenting within three hours of symptom onset. A three hour time limit on approved use was imposed due to NINDS pilot studies, however ECASS I and ECASS II confirmed the three hour mark as being ideal (Hacke et al., 1995; Hacke et al., 1998; NINDS rt-PA Stroke Study Group).

ECASS I, ECASS II, ATLANTIS, and the IMS studies further evaluated the administration of IV tPA, but expanded the time limit to five to six hours after symptom onset. ECASS I results of the zero to three hour group supported the NINDS trial, but no statistical significance was found in the three to six hour group compared to placebo (Hacke et al., 1995). ECASS II again found no difference between the control and experimental group when treating patients from zero to six hours, but overall mortality was lower in ECASS II than ECASS I (Hacke et al., 1995; Hacke et al., 1998). ECASS II had a more stringent inclusion protocol though, so patients had less severe neurological deficits, which would naturally result in lower mortality (Hacke et al., 1998). ATLANTIS was stopped early due to safety concerns, while there was also no significant differences in outcome between the control and experimental groups (Clark et al., 1999).

These trials reveal that IV tPA administration beyond three hours of symptom onset has promise, though more research needs to be completed. Each of these trials had different patient

eligibility requirements, severity of neurological deficits in patients, and treatment protocols, therefore making direct comparison difficult. Despite inconclusive results, these studies did not reveal increased symptomatic intracranial hemorrhage rates when IV tPA is administered beyond three hours of symptom onset (Clark et al., 1999; Hacke et al., 1995; Hacke et al., 1998; IMS II Trial Investigators, 2007; IMS Study Investigators, 2004; NINDS rt-PA Stroke Study Group, 1995).

Further research is needed to determine the exact cutoff time for safe and efficacious IV tPA administration. The Third International Stroke Trial (IST-3) is an ongoing trial that will aid in solving this dilemma. The study's purpose is to determine whether administration of IV tPA within six hours of acute ischemic stroke symptom onset increases the proportion of independent survivors at 6 months (Sandercock et al., 2008). Currently the world's largest thrombolysis trial with over 1,000 patients enrolled, IST-3 aims to enroll over 6,000 patients. Such a large patient enrollment will provide further insight into what ways comorbidities such as previous stroke, diabetes, and heart disease influence stroke treatment outcome.

Intra-arterial Tissue Plasminogen Activator

IMS I and II both found that patients had a better outcome when treated with IA tPA within five hours of symptom onset versus placebo (IMS II Trial Investigators, 2007; IMS Study Investigators, 2004). The combination of IV and IA tPA administration up to six hours after ischemic stroke symptom onset, though not FDA approved, is currently being used in clinical practice at some advanced stroke centers and appears very promising. Like IV tPA, additional research is needed to determine IA tPA's safety and efficacy, as well as exact treatment protocols for IA tPA administration as a chief or adjuvant therapy. Results of the currently ongoing phase

III IMS III trial are highly anticipated, with the expectation that this trial will provide further guidance in the safest, most efficacious application of IA tPA.

Intravenous Streptokinase

IV streptokinase has shown safety and efficacy in treating acute myocardial infarction, but the MAST-E, MAST-I, and ASK trials proved deleterious effects when streptokinase is used in acute ischemic stroke treatment (Donnan et al., 1996; MAST-E Study Group, 1996; MAST-I Group, 1995; Second International Study of Infarct Survival Collaborative Group, 1988). Both MAST-E and MAST-I found that IV streptokinase administered up to six hours after ischemic stroke symptom onset resulted in greater mortality than when treating with placebo (MAST-E Study Group; MAST-I Group). The ASK trial tested IV streptokinase up to only four hours after stroke symptom onset, but it was also stopped early due to the high rate of mortality in streptokinase treated patients (Donnan et al.). IV streptokinase was initially proposed as an acute ischemic stroke treatment due to its success in the management of myocardial infarction, but the above clinical trials have disproved this notion, as IV streptokinase does not appear to be a viable treatment option in acute ischemic stroke.

Intravenous Desmoteplase

DIAS and DEDAS evaluated the use of perfusion-diffusion mismatch on MRI with IV desmoteplase administration in patients treated three to nine hours after stroke symptom onset (Furlan et al., 2006; Hacke et al., 2005). In both studies, patients had a higher reperfusion rate than placebo, but statistical significance was found only in the 125 mcg/kg group. Favorable 90 day outcomes were greater in the desmoteplase groups of both studies as well, but again,

statistical significance was only found in the 125 mcg/kg group of DIAS (Furlan et al.; Hacke et al.). The results of DIAS and DEDAS demonstrated the safety of desmoteplase, while also demonstrating the efficacy of perfusion-diffusion mismatch on MRI and its potential role in acute ischemic stroke treatment. Based on these trials, the future of acute ischemic stroke treatment may be based on neuroimaging and perfusion-diffusion mismatch.

Intra-arterial Pro-urokinase

PROACT I and II examined the safety and efficacy of IA pro-UK when given within six hours of stroke symptom onset (del Zoppo et al., 1998; Furlan et al., 1999). Recanalization rates were significantly greater in the pro-UK groups than the placebo groups in both PROACT I and II (del Zoppo et al.; Furlan et al.). Despite these convincing results, due to the limited number of multicenter, randomized, placebo-controlled studies evaluating IA thrombolysis in acute ischemic stroke treatment, no FDA approved IA thrombolytic exists, nor have guidelines been established for its usage (Blakeley & Llinas, 2007). Another disadvantage to IA thrombolysis is the need for an on-call, experienced surgical team and the necessary surgical equipment, limiting its prospective use to only advanced medical centers.

Merci Retrieval System

The MERCI trial studied the safety and efficacy of mechanical embolectomy in treating acute ischemic stroke up to eight hours after symptom onset. Recanalization rates were greater compared to the PROACT II placebo arm and were statistically significant (Smith et al., 2005). Symptomatic intracranial hemorrhage rates were slightly lower than many other studies, but patient mortality was higher.

The FDA approval of the Merci Retrieval System was a huge stride in medical technology, but its approval did not come without debate. Despite the fact that recanalization is the single most powerful treatment for ischemic stroke, recanalization with the Merci System is very costly. The system itself costs approximately $4,000, plus the cost of the surgical procedure and the specific compatible angiography equipment (Katz & Gobin, 2006). Not only is the cost of the procedure or equipment of concern, but the hospital staffing of an on-call interventional neuroradiologist also adds another lofty expense, making Merci's use unfeasible even at many primary stroke care centers. Recanalizing proximal occlusions is often challenging, but the Merci Retrieval System does this quite well (Saver, 2006). Unfortunately, for reasons mentioned above, the Merci device is not yet widely used. Patients with occlusions that may be managed by the Merci Retrieval System may not be able to receive treatment solely because no facilities within the regional area use the system. The Merci Retrieval System may be a medical breakthrough in acute ischemic stroke treatment, but its real-world practicality is not currently present.

Considering the substantial incidence of ischemic stroke, its high rate of morbidity and mortality, and the economic costs it places on society, new treatments for stroke are much desired. Over 100 compounds are currently being studied for the treatment of ischemic stroke (Lapchak & Araujo, 2007). The most crucial need is a safe, efficacious treatment for ischemic stroke patients presenting beyond the three hour time window. The greater a time window for a given stroke treatment, the more human lives can be promoted, and the more money can be generated for pharmaceutical companies. Despite this lucrative scheme, experts fear drug companies may be near the end of their rope, frustrated by repeated trial failures (Garber, 2007; Weinberger, 2006).

Conclusion

Treatment of ischemic stroke is a great challenge, as the method must have a high recanalization rate, low rate of intracranial hemorrhage, no neurotoxicity, a low rate of complications in its administration, a small side effect profile, economical feasibility, and financial practicality. The search to find this ideal treatment for patients with acute ischemic stroke who present past three hours of their symptom onset is still ongoing.

As shown by the Merci Retrieval System, an FDA approved treatment is only beneficial if it can be made available to the general population, rather than only to patients living in proximity of a few highly advanced medical facilities. Further, patients living in rural areas are rarely afforded multiple treatment options as there may not be a primary stroke center in the area. These patients are taken to community hospitals that do not necessarily have a wide array of cutting-edge treatments. At the proper dose, IV desmoteplase has shown to be an excellent treatment option in acute ischemic stroke, and its regular use may be in the near future. Even though desmoteplase has shown its efficacy when patient selection is guided by perfusion-diffusion mismatch, less advanced medical facilities may not have this MRI technology. IA pro-UK is another promising alternative whose use is limited by its need for a surgical team and stroke specialist experienced in IA cerebral drug administration, as is the Merci Retrieval System. Practitioners await the results of IMS III, to gain greater insight on combined IV and IA tPA. Another successful trial evaluating IA tPA may lead to its FDA approval, but for now practitioners must use expert judgment and knowledge gained from previous trials to guide them in which patients are best fit for its usage.

The best treatment for eligible patients presenting within three hours of ischemic stroke symptom onset is IV tPA. The ease of IV administration allows treatment to be completed at the

most rural of healthcare facilities and without the guidance of a neurologist. For patients who present up to six hours after symptom onset or who still have not recanalized after IV tPA treatment, IA tPA is currently the treatment of choice. More advanced centers with the capability to use the Merci Retrieval System or who are able to enroll patients in stroke treatment trials should take clot location, patient presentation, and patient comorbidities into account before choosing an acute treatment. All current treatments present some level of risk to the patient. These risks must be weighed against the patient's neurological deficits and the chance for recovery. In the worse case scenario, when a patient does not qualify for any available treatments, the best management may be a strict medical care protocol in a neurological intensive care unit. Physician Assistants help to fulfill such protocols by extending the role of the physician, providing more efficient patient care and monitoring. Outside of recanalization and cerebral reperfusion, some of the most important factors in long-term patient outcome include prevention of further clot formation; intensive physical, occupational, and speech therapy; and a reduction of hospital-acquired infections such as pulmonary and urinary tract infections (Adams et al., 2007).

Advances in acute ischemic stroke treatment have certainly been made, but no treatment has been determined to be the "gold standard" in acute ischemic stroke treatment past three hours of symptom onset. All of the pharmacologic and mechanical treatments reviewed in this paper call for further research, as so many studies differ in patient selection criteria, neurological deficit severity, penumbra size, drug dosage and administration protocol, and allowance of other thrombolytics to be administered and in what timeframe or duration.

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Table 1

National Institutes of Health Stroke Scale

Item Number	Title	Responses and Scores
1a	Level of consciousness	0 = Alert 1 = Drowsy 2 = Obtunded 3 = Coma/unresponsiveness
1b	Orientation questions (two)	0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly
1c	Responds to commands (two)	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task
2	Gaze	0 = Normal horizontal movements 1 = Partial gaze palsy 2 = Complete gaze palsy
3	Visual fields	0 = No visual field defect 1 = Partial hemianopsia 2 = Complete hemianopsia 3 = Bilateral hemianopsia
4	Facial movement	0 = Normal 1 = Minor facial paralysis 2 = Partial facial weakness 3 = Complete unilateral paralysis
5	Motor function arm a. left b. right	0 = No drift 1 = Drift before 10 seconds 2 = Falls before 10 seconds 3 = No effort against gravity 4 = No movement
6	Motor function leg a. left b. right	0 = No drift 1 = Drift before 5 seconds 2 = Falls before 5 seconds 3 = No effort against gravity 4 = No movement
7	Ataxia	0 = Absent 1 = Ataxia in one limb 2 = Ataxia in both limbs
8	Sensory	0 = Normal 1 = Mild sensory loss 2 = Severe sensory loss
9	Language	0 = Normal 1 = Mild aphasia 2 = Severe aphasia 3 = Mute or global aphasia

10	Articulation	0 = Normal 1 = Mild dysarthria 2 = Severe dysarthria
11	Extinction or inattention	0 = Normal 1 = Mild (loss 1 sensory modality) 2 = Severe (loss 2 modalities)

Note. From "Measurements of Acute Cerebral Infarction: A Clinical Examination Scale," by B.

Thomas, H. P. Adams, C. P. Olinger, J. R. Marler, W. G. Barsan, J. Biller, et al., 1989, *Stroke*,

20(7), 864-870.

Table 2

Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Note. From "Interobserver Agreement for the Assessment of Handicap in Stroke Patients," by J. C. van Swieten, P. J. Koudstaal, M. C. Visser, H. J. A. Schouten, and J. van Gijn, 1988, *Stroke*, *19*(5), 604-607. Used with permission.

Table 3

The Barthel Index

Activity	Responses and Scores
Feeding	0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
Bathing	0 = dependent 5 = independent (or in shower)
Grooming	0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
Dressing	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
Bowels	0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
Bladder	0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
Toilet Use	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)	0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent
Mobility (on level surfaces)	0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
Stairs	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent
Total (0 – 100):	

Note. From "Functional Evaluation: the Barthel Index," by F. I. Mahoney and D. Barthel, 1965,

Maryland State Medical Journal, 14, 56-61. Used with permission.

Table 4

Glasgow Outcome Scale

Score	State	Comments
1	Dead	
2	Vegetative State	Unable to interact with environment, unresponsive
3	Severe Disability	Able to follow commands, unable to live independently
4	Moderate Disability	Able to live independently, unable to return to work or school
5	Good Recovery	Able to return to work or school

Note. From "Assessment of Outcome After Severe Brain Damage," by B. Jennett and M. Bond,

1975, *Lancet*, *1*(7905):480-4. Used with permission.

Table 5

Indications and Contraindications for the Use of Recombinant Tissue Plasminogen Activator

(tPA) in Patients with Ischemic Stroke

Indications for tPA (Patient must meet all criteria)
Diagnosis of an ischemic stroke causing a neurologic deficit
Symptom onset clearly defined, and within 180 minutes of treatment initiation
CT scan does not show any evidence of intracerebral hemorrhage, or signs of early infarct
Neurologic deficit must not be minor, isolated, or clearing spontaneously
Patient is > 18 years of age
Patient or family understands the potential risks and benefits
Contraindications for tPA (Patient must meet no criteria)
Current oral anticoagulant use
Elevated activated partial thromboplastin time (aPTT) if heparin received in previous 48 hours
Prothrombin time ≥ 15 seconds
Blood pressure > 185 mmHg systolic or > 110 mmHg diastolic, or aggressive treatment required to meet these limits
Platelet count ≤ 100,000 mm^3
Blood glucose concentration ≤ 50 mg/dL or ≥ 400 mg/dL
Prior stroke within 3 months
History of previous intracranial hemorrhage
Head trauma within 3 months
Myocardial infarction within 3 months
Major surgery within the preceding 14 days
Gastrointestinal or genitourinary hemorrhage within 21 days
Evidence of acute trauma (fracture) or active bleeding on physical examination
Arterial puncture at a non-compressible site in within previous 7 days
Seizure at stroke onset
Use tPA With Caution
NIHSS > 22, especially in an elderly patient

Note. Adapted from "Guidelines for the Early Management of Adults With Ischemic Stroke" by

H. P. Adams, G. J. del Zoppo, M. J. Alberts, D. L. Bhatt, L. Brass, A. Furlan, et al., 2007,

Circulation, 115(20), 1655-1711; and "Tissue Plasminogen Activator for Acute Ischemic

Stroke" by National Institute of Neurological Disorders and Stroke rt-PA Stroke Study

Group, 1995, *New England Journal of Medicine, 333*(24), 1581-1587.

Table 6

Indications for the Use of the Merci Retrieval System in Patients with Ischemic Stroke

Indications for Thrombectomy with the Merci Retrieval System
Presentation after 3 hours of symptom onset
Presentation within 3 hours of symptom onset, but with contraindications to IV tPA
Significant neurological deficit
Failure to regain neurological deficits after systemic thrombolysis
No sign of hemorrhage on imaging
Angiographically visible occlusion located in an accessible vessel such as the internal carotid, middle cerebral, vertebral, basilar, or posterior cerebral artery

Note. Adapted from "Merci Retriever in Acute Stroke Treatment" by J. M. Katz and Y. P.

Gobin, 2006, *Expert Review of Medical Devices, 3*(3), 273-280.

Abstract

Objective: Intravenous tissue plasminogen activator (tPA) is the mainstay treatment for patients presenting within three hours of ischemic stroke symptom onset, though many patients are not candidates for its use. This review examined recanalization treatments for patients presenting beyond three hours from symptom onset. **Method:** Clinical trials published in English between 1995 and 2008 were identified using MEDLINE, PubMed, and EBSCO. **Results:** A review of the literature revealed few feasible options in treating patients with acute ischemic stroke beyond three hours of symptom onset due to poor patient outcomes or prohibitive costs. Practitioners await results from ongoing trials, like the IMS III evaluating intra-arterial tPA. ECASS I, ECASS II, ATLANTIS, ASK, MAST-E, MAST-I, AbESTT I and AbESTT II revealed mostly disappointing results. **Conclusion:** Future research is needed due to varying trial outcomes and the considerable need for treatments options in patients presenting past three hours of ischemic stroke symptom onset.