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THROMBOLYSIS IN ACUTE ISCHEMIC STROKE

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Abstract:

Introduction: *A stroke can happen due to ischemia, or an embolic occlusion, or a hemorrhage, and is one of the major causes of devastating, prolonged neurologic morbidity and functional disability. Moreover, it is the leading cause of mortality globally. The current Stroke recommended protocols in management requires swift assessment and admission, alongside the administration of thrombolysis for acute ischemic stroke (AIS), prompt management by the specialists in a stroke unit, and early usage of aspirin in AIS and proper physiological monitoring.*

Aim of work: *In this review, we will discuss window period for effective management of ischemic stroke, and the methods of thrombolysis.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: stroke, acute ischemic attack, cerebrovascular accident, window period, intravenous thrombolysis, arterial thrombolysis, mechanical thrombolysis*

Conclusions: *Thrombolysis is at the leading edge of modern management of AIS, with significant evidence of its efficacy before the 4.5 h of the beginning of symptoms. Intravenous alteplase is the solely recommended and approved thrombolytic agent currently. nevertheless, the frequency of treated individuals is still somewhat low due to a number of burdens and failures in the optimal accomplishment of the treatment. Endovascular therapy in acute ischemic stroke has become a promising alternative for patients who are ineligible for intravenous thrombolysis or have failed in recanalyzing the occluded artery.*

Key words: *stroke, management if stroke, thrombolysis, alteplase*

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INTRODUCTION:

A stroke or Cerebrovascular Accident (CVA) is defined as the sudden loss of brain functioning zones, it is due to a disruption of supply of blood to the brain. A stroke can happen due to ischemia, or an embolic occlusion, or a hemorrhage, and is one of the major causes of devastating, prolonged neurologic morbidity and functional disability **[1]**. Moreover, it is the leading cause of mortality globally. reports from the World Health Organization (WHO), globally 15 million individuals suffer from CVA annually. from them, around 5 million die, while the other 5 million suffer some sort of permanent disability. 80% of the strokes happen in the low to middle income nations, where treatment is least obtainable **[2]**.

The current Stroke recommended protocols in management requires swift assessment and admission, alongside the administration of thrombolysis for acute ischemic stroke (AIS), prompt management by the specialists in a stroke unit, and early usage of aspirin in AIS and proper physiological monitoring. Thrombolysis for AIS the main and most successful intervention that can lower disability from stroke if administered within 3-4.5 hours after onset of ischemic stroke. Intravenous administration of recombinant tissue plasminogen activator (alteplase) in randomized controlled cases has shown improvements in functional disability, with a complete risk lowering percentage of 7%–13% compared to placebo; it then became the superior specific treatment recommended for acute management of ischemic stroke **[3]**. The effectiveness of treatment disappears rapidly, and risk of harm increases with time elapsed from symptom onset; hence the importance of need in swift diagnosis and treatment **[4]**.

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: stroke, acute ischemic attack, cerebrovascular accident, window period, intravenous thrombolysis, arterial thrombolysis, mechanical thrombolysis

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

Stroke risk factors

Risk factors have significant effects on the blood vessels in terms of its structure and function, thus affecting the flow of blood in it. Some risk factors are considered established ones as they alter structure of the vessel by causing atherosclerosis as well as stiffening of arteries, therefore causing them to be narrower, thicker, and also increase tortuosity of arterioles and capillaries. In the brain these variations lead to a decrease in resting cerebral blood flow (CBF) and significant changes in the regulation of blood flow **[5]**. The established risk factors include hypertension, aging, hypercholesterolemia, and diabetes. The alterations cause impairment in the crucial adaptive mechanisms that make sure that the brain is sufficiently perfused. The capacity of the endothelium to manage microvascular flow gets affected, while at the same time, the neuronal activity signaling to increase in blood flow is suppressed, creating a mismatch between the energy supply and demand of the brain tissue **[6]**.

Hypertension and diabetes, which are the most common risk factors, weaken the protective vascular mechanisms that stabilize blood flow to brain parenchyma in state of reduced blood pressure (cerebrovascular autoregulation), thus favoring the incidence of ischemia when intravascular pressure falls **[7]**. Such alterations in the vessels makes the brain susceptible and vulnerable to ischemia following any arterial occlusion since the development of collateral flow from neighboring adjacent non-ischemic vascular territories is impaired, which is extremely important for survival of the ischemic periinfarct zone. Beside vascular effects, other risk factors, such as diabetes and aging, enhances the intrinsic predisposition of cells of brain to injury, magnifying the damage to tissue which resulted initially by ischemia. However, the exact mechanism behind this effect is yet not well understood. Not much is understood about the interaction among the various types of stroke risk factors and how vascular effects are synergistic or additive. Moreover, it is also not known regarding the individual contribution of parenchymal and vascular factors to stroke risk **[8]**.

Pathophysiology of stroke

Because of large concentrations of the neurotransmitter-excitotoxin glutamate and the high intrinsic metabolic activity of the brain, the organ is especially susceptible to ischemic injury. This can happen either as a result of thrombosis that formed in the vessel or as a consequence of embolus occluding

the cerebral blood vessel. The embolus usually arises from the heart or through an atherosclerotic plaque which formed in the carotid artery or at the aortic arch. Even though neurological dysfunction presents within seconds to minutes of occlusion, the consequence of ischemic injury leading to cell death continues in steps for minutes or hours or days, which depends on the vulnerability of the specific part of brain and the contents of the cell. It depends more on the degree of residual perfusion **[9]**.

The way the blood vessels responds, in terms of perfusion, is important. It can be demonstrated by an example of vasodilatory molecules availability. A deficiency of endothelial NO results in worse stroke. The extent of damage massively depends on early restoration of blood flow, such as by clot lysis, resulting is lesser ischemic injury. This can be achieved by giving recombinant tissue plasminogen activator (tPA), which we will discuss in detail later in the article. Nevertheless, tPA is used in less than 10% of patients, and even more less often after 3 hours since the risk of bleeding into ischemic tissue rises **[10]**. Furthermore, tPA presents with other risks for example, injury to the blood brain barrier by matrix metalloproteinases activation. Combination treatments that enhance these effects may prolong the therapeutic window of tPA's while modifying the inconvenient effects of plasminogen activation of reperfusion therapy. Hypothetically, that has a potential to extend tissue viability for much longer **[11]**.

Intravenous thrombolytic agent and time window

In a new meta-analysis, which includes studies of urokinase, streptokinase and alteplase, therapy with thrombolytics showed significant benefits with stroke in terms of mortality or dependency, but the one agent or medication which was associated with superior and obvious benefit was alteplase. Henceforth, intravenous (IV) alteplase is the one agent given the license for AIS, the suggested dose being 0.9 mg alteplase/kg body weight (maximum of 90 mg), 10% of the overall dose administered as a starting IV bolus and the rest as an IV infusion over 60 min (given by the NINDS study criteria) **[10]**. The outcomes are influenced by differences in study design, the doses of thrombolytic agent administered, timing of thrombolysis and definition of hemorrhage **[12]**.

In the United Kingdom, the license for alteplase is constricted to a maximum 3 hours of the beginning of stroke in highly specific patients, by a specialist trained and experienced in the management of stroke, and in institutes with proper facilities for aftercare **[13]**. The guidelines from the American Stroke Association and European Stroke Organization (ESO) emphasizes the importance of thrombolysis as quick as possible after symptom onset, and have instructed the extended time window of 4.5 h. The National Stroke Foundation of Australia has a close recommendations for the use of alteplase in Australia and New Zealand, and a new update in 2010 has extended the time window for thrombolysis up to 4.5 h **[14]**.

Tissue plasminogen activator (t-PA), an endogenous, human serine protease exist in the intravascular space, the blood-brain interface and inside the brain parenchyma, has an important central role in the homeostasis of the coagulation cascade. It cuts down plasminogen to plasmin which breaks down fibrin-based clots. Regrettably , although it has extensive benefits a destructive effect on extracellular matrix and endothelial basal lamina can ensue leading to compromise of the blood-brain barrier and hemorrhage **[15]**. If used within the license, alteplase comes with a significant net decrease in death and disability after ischemic stroke regardless of a small but significant increase in the risk of intracerebral hemorrhage (ICH). The use of alteplase is restricted to fewer than 5% of AIS patients because of the restricted therapeutic window, inadequate awareness among society and professionals and undue worries about the risk of ICH **[16; 17]**.

Extending the window time

One major restriction in the use of thrombolysis in AIS is the restricted therapeutic time window. 3 hours therapeutic time window for alteplase use was licensed from the beginning of stroke symptoms in the majority of countries, based on NINDS trial criteria in 1995. Since then, two studies published in 2008 have demonstrated the benefit of alteplase up to 4.5 h after the onset of stroke symptoms.

The Third European Co-operative Acute Stroke Study (ECASS III) was a randomized controlled study of IV alteplase *versus* placebo administered 3-4.5 h after the beginning of stroke symptoms. This study found that symptomatic individuals treated with alteplase were remarkably more likely to have a favorable result (mRS score of 0 or 1) than those who were given placebo (52.4% versus 45.2%, respectively; OR, 1.34; 95% CI, 1.02-1.76; $p = 0.04$). While the rate of symptomatic ICH (sICH) was remarkably better in individuals treated with alteplase (2.4% *versus* 0.2%, $p = 0.008$), it was less *than* the rate seen in previous studies of patients given alteplase within 3 h of symptom onset, comprising the NINDS trial (6.4%). The all-cause death rate at 90 days was close between those treated with

alteplase and those treated with placebo (7.7% *versus* 8.4%, p = 0.68). The ECASS III trial excluded individuals with really severe stroke as assessed by clinical or imaging criteria, which may explain the lower sICH rate **[18]**.

The implemented safe treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) was a prospective, based on internet audit of over 700 clinical institutes in Europe that compared individuals treated with IV alteplase 0.9 mg/kg 3-4.5 h after stroke symptoms onset with individuals treated within 3 h of onset of stroke symptoms. This observational study found that post 3 months of treatment, individuals taking alteplase in both groups encountered similar rates of functional independence (modified Rankin score mRS of 0-2) (58% of patients treated 3-4.5 h after symptom onset *versus* 56.3% of those treated within 3 h, p = 0.42) and great recovery (mRS score of 0 or 1) (40.5% *versus*39.9%, p = 0.79) and the rates of symptomatic ICH (2.2% *versus*1.6%, p = 0.24) and mortality (12.7% *versus* 12.2%, p = 0.72) were same **[19]**.

This trial excluded patients that were above 80 years of age and those with an NIHSS score of > 25. These two trials supported the safety and efficacy of alteplase in AIS individuals that exceeded the 3 h window, up to 4.5 h after stroke symptoms onset. The ESO has updated its guidelines in January 2009 to extend the time limit for thrombolysis up to 4.5 h. The American Heart Association and American Stroke Association has released recommendations to increase the time window for thrombolysis in AIS to 4.5 h however, with more exclusion criteria including: age of > 80 years; current administration of oral anticoagulants (regardless of International Normalized Ratio [INR]); baseline National Institutes of Health Stroke Scale score of >20; and past history of both stroke and diabetes.

Efforts have been made to extend the window of eligibility for thrombolysis by the usage of specialized CT or MRI perfusion imaging to spot viable penumbra. While desmoteplase, which is originated from vampire bat saliva, demonstrated great significance in safety and efficacy in pilot studies (DIAS1 **[20]** and DEDAS **[21]**), on a prolonged treatment window (3-9 h) the successive Phase III DIAS-2 study did not give out any benefit with the same 90-day clinical results in either the high- or low-dose group when compared with placebo, and growth mortality in the high-dose group (21% *versus* 5% low dose; 6% placebo) **[22]**. nevertheless, only 3 of 14 deaths in the high-dose group were demonstrating relatability to study medication. CT- or MR-based identification of the penumbra to support thrombolysis with tenecteplase in a small trial proved greater reperfusion and recanalization compared to alteplase moreover, neurological improvement **[23]**. For the time being, there is no evidence or demonstration to reinforce the standard use of thrombolysis over 4.5 h, which may be accompanied with net harm, as shown by a pooled analysis of the whole thrombolysis studies **[3]**.

Intra-arterial thrombolysis

Intra-arterial (IA) thrombolysis is included in the local delivery of thrombolytic agents, at or inside the thrombus, using neuro-interventional methods. Compared with intravenous treatment, IA therapy has the upper hand of giving a higher concentration of lytic agent transported to the clot target while decreasing the systemic exposure to drug. It has also the potential for superior efficacy with greater recanalization rates. This method also lets the mechanical disruption of the clot with the catheter or specific machines during the procedure. Disadvantages involves more time needed to start treatment, accessible only at specialized institutes, and mechanical manipulation inside potentially injured vessels. Combined IA and IV thrombolysis give the swiftness of initiation of IV and a trend to superior recanalization rates of isolated IA thrombolysis. Pro-Urokinase (pro-UK), urokinase (UK) and alteplase are the prime thrombolytic agents used in this type of procedures. Intra-arterial or mixed thrombolysis has been evaluated only in a minimized controlled study. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial shows the safety and efficacy of IA thrombolysis in individuals with an middle cerebral artery occlusion **[24]**.

Although the FDA and international regulatory agencies did not authorize a stroke labelling for pro-UK with a singular, small, phase III clinical trial, IA thrombolysis treatment is mostly given as an off-label treatment for stroke at tertiary institutes with a maximum of 6 hours since onset in the anterior circulation and up to 12-24 hours post onset in the posterior circulation. ESO 2008 & AHA/ASA 2007 guidelines advised intra-arterial treatment of acute MCA occlusion within a 6-hour time window as an alternative (Class II-I, Level B) and in individuals with disadvantages to the use of IV thrombolysis, such as recent surgery (Class II, Level C).

Mechanical thrombolysis

Mechanical thrombolysis includes the use of catheters to straightly convey a clot-disrupting or retrieval device to a thromboembolus that is occluding a cerebral artery. This method can improve

the rate and swiftness of recanalization and can lower the incidence of intracranial hemorrhage compared with intra-arterial pharmaceutical lytics. trial reports and small case series recommended that the use of intravascular devices for clot extraction in the endovascular therapy of ischemic stroke can be considered for individuals who are not thrombolytic candidates, such as those that have had a prior surgical procedure or are under anticoagulation therapy **[25; 26]**.

Thrombolysis in cardioembolic stroke

Cardioembolic stroke makes up one third of all ischemic strokes, and atrial fibrillation is the cardiac origin of emboli in 50% of them. Anticoagulation as a secondary prevention therapy of cardioembolic stroke subtype has surprisingly decreased the annual risk of stroke in these individuals and has ultimately changed their long-term survival **[27]**. Nevertheless, acute cardioembolic stroke is accompanied with great morbidity and mortality since it sometimes causes a devastating baseline neurological impairment, huge infarct volumes and a raised risk of hemorrhagic transformation, above all when stalled spontaneous or pharmacological-induced arterial recanalization happens **[28-30]**.

CONCLUSION:

Thrombolysis is at the leading edge of modern management of AIS, with significant evidence of its efficacy before the 4.5 h of the beginning of symptoms. Intravenous alteplase is the solely recommended and approved thrombolytic agent currently. nevertheless, the frequency of treated individuals is still somewhat low due to a number of burdens and failures in the optimal accomplishment of the treatment. Endovascular therapy in acute ischemic stroke has become a promising alternative for patients who are ineligible for intravenous thrombolysis or have failed in recanalizing the occluded artery.

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