Intravenous Alteplase 3-6 Hours Versus 0-3 Hours in Acute Ischemic Stroke, an Egyptian Based Study

Thesis

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Essam Mohamed Ezzaat Ali

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Abb.	Full term
ACA	*Anterior cerebral artery*
ACOM	*Anterior communicating artery*
ADC	*apparent diffusion coefficient*
AHA	*American heart association*
AHA/ASA	*American Heart Association / American Stroke Association*
AIS	*Acute ischemic stroke*
ATLANTIS	*The Alteplase Thrombolysis for Acute Non Interventional Therapy in Ischemic Stroke*
BA	*Basilar artery*
BABO	*Basilar artery atheromatous branch occlusive disease*
BP	*Blood pressure*
CBC	*Complete blood count*
CBF	*Cerebral blood flow*
CPP	*Cerebral perfusion pressure*
CSD	*Cortical spread depression*
CSF	*Cerebrospinal fluid*
CT brain scan	*Computed tomography brain scan*
CTA	*Computed Tomography Angiography*
DEDAS	*Dose Escalation study of Desmoteplase in Acute ischemic Stroke*
DIAS	*Desmoteplase in Acute Ischemic Stroke*
DSPA1	*D rotundus salivary plasminogen activator alpha-1*
DWI	*diffusion weighted image*
ECASS	*The European Cooperative Acute Stroke Study*

List of Abbreviations (Cont...)

Abb.	Full term
EHRA-ESC	*European Heart Rhythm Association / European Society of Cardiology*
ESR	*Erythrocyte sedmintation rate*
FDA	*Food and Drug administration*
FDP	*Fibrin degradation products*
FLAIR	*Fluid-attenuated inversion recovery*
GBD	*Global Burden of Disease*
ICA	*Internal carotid artery*
ICH	*Intra-cerebral hemorraghe*
IST-3	*The third International Stroke Trial*
IV	*Intravenous*
LDL-C	*Low-density lipoprotein cholesterol*
MAP	*Mean arterial blood pressure*
MCA	*Middle cerebral artery*
MRI	*Magnetic resonance image*
mrs	*Modified Rankin Scale*
NIHSS	*National Institutes of Health Stroke Scale*
NINDS	*The National Institute of Neurological Disorders and Stroke*
OSA	*Obstructive sleep apnea*
PAO	*Proximal arterial occlusion*
PCA	*Posterior cerebral artery*
PCIS	*Posterior circulation ischemic stroke*
PCOM	*The posterior communicating artery*
PIDs	*Peri-infarct depolarizations*
REGARDS	*Reasons for Geographic and Racial differences in Stroke*

List of Abbreviations (Cont...)

Abb.	Full term
rt-PA	*Recombinant Tissue Plasminogen Activator*
SITS	*The Safe Implementation of Thrombolysis in Stroke*
SK	*Streptokinase*
TIA	*Transient ischemic attack*
UFH	*Unfractionated heparin*
UK	*Urokinase*
VA	*Vertebral artery*

INTRODUCTION

Stroke is the number 4 cause of death and a leading cause of long-term disability in the united states.Roughly 6.8 million Americans 20 years and older have had a stroke, and an additional 4 million individuals are projected to have a stroke by the year 2030 ***(Go et al., 2014)***. About 780,000 strokes are estimated to occur annually in the United States ***(Rosamond et al., 2008).***

87% of all strokes are ischemic (e.g., due to large arterythrombosis or cardiogenic embolism). As a result, much attention has been focused on developing treatment strategies for this stroke subtype.

In Egypt, the most populated nation in the Middle East, the overall crude prevalence rate of stroke is high (963/100,000 inhabitants). The official national statistics indicate that diseases of the circulatory system, including stroke, are the primary cause of death in Egypt ***(Abdullah et al., 2014)***.

Alteplase (recombinant tissue-type plasminogen activator; rt-PA), is a serine protease produced by recombinant DNA technology. The molecule consists of a single polypeptide chain of 527 amino acids which is chemically identical to human endogenous t-PA. Promotes thrombolysis by converting plasminogen to plasmin; plasmin degrades fibrin and fibrinogen ***(Collen et al., 1989)***.

The Food and Drug Administration (FDA) approval in June 1996 of intravenous recombinant tissue-type plasminogen activator (rt-PA) for patients with acute ischemic stroke treated within 3 hours of symptom onset marked a historic first step in treating this devastating disease. This approval was primarily based on the results of the National Institute of Neurologic Disorders (NINDS) trials.

Recanalization documented within 6 hours of onset tends to be strongly associated with good clinical outcomes, with a 4- to 5-fold increase in the odds of good final functional outcome ***(Chalela et al., 2007).***

In June 2012, Sandercock and colleagues published a meta-analysis of 12 intravenous rtPA trials that had enrolled 7012 patients up to 6 hours from symptom onset. The results confirmed the benefits of intravenous rtPA administered within 6 hours from symptom onset. Utilization of reperfusion therapies for stroke remains <1% in Egypt. Among contributing factors are country-specific problems such as poor public and physician awareness, the affordability of the drugs, and availability of experienced personnel and resources.

Aim of the Work

To assess safety and effectiveness of IV alteplase given 3-6 hours versus 0-3 hours after acute ischemic stroke

Chapter 1

ISCHEMIC STROKE

Definition

Stroke is defined as an episode of focal neurologic(brain, retina, spinal cord) dysfunction (even if less than 24 h duration) in which the autopsy, computed tomography (CT) brain scan, or magnetic resonance imaging (MRI) brain scan shows features consistent with focal brain infarction or hemorrhage ***(Easton et al., 2009)***. Ischemic stroke is responsible for about 80% of all strokes intra cerebral hemorrhage (ICH) for 15% and subarachinoid hemorrhage (SAH) for 5% ***(Moinuddin et al., 2015)***.

Epidemiology

Stroke is the number 4 cause of death and a leading cause of long-term disability in the United States. Roughly 6.8 million Americans 20 years and older have had a stroke, and an additional 4 million individuals are projected to have a stroke by the year 2030 ***(Go et al., 2013)***. About 780,000 strokes are estimated to occur annually in the United States ***(Rosamond et al., 2008)***.

The importance of addressing stroke through well-devised epidemiologic studies was underscored by the Global Burden of Disease 2013 Study ***(GBD, 2013)***.

The GBD 2013 used world mapping to visualize stroke burden and its trends in various regions and countries using epidemiologic measures of age-standardized incidence, mortality, prevalence, disability-adjusted life years, and years lived with disability associated with stroke from 1990 to 2013 ***(Feigin et al., 2015)***.

Their findings showed that the absolute number of people affected by stroke substantially increased across all countries in spite of dramatic declines in age-standardized incidence, prevalence, mortality rates, and disability. Population growth and aging have played an important role in the observed increase in stroke ***(Feigin et al., 2015)***.

The prevalence of non-fatal stroke in Egypt is 5.6 per 1,060 populations. This prevalence lies within the lower range of that recorded in developing countries (5-10 per 1,000). This is similar to that found in India (5.5 per 1,000), but higher than recorded in Saudi Arabia (1.8 per 1,000) ***(El-Talawy et al., 2013)***.

Risk factors of stoke

When we examine persons with stroke, we often find risk factors. Although one may look for "the cause," or the direct mechanism of stroke, such as atherosclerotic plaque or embolic source, common risk factors contribute a significant extent to the underlying processes that lead to strokes. Treatment of risk