شبكة المعلومات الجامعية

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بسم الله الرحمن الرحيم

HANAA ALY

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Systemic Recombinant Tissue Plasminogen Activator for Treatment of Acute Ischemic Cerebral Stroke; A Systematic Review

Thesis

Submitted for partial fulfillment of the master degree in General Intensive Care medicine

By

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Heba Abd-Elazeem Zalam

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LIST OF ABBREVIATIONS

Abb	Full Term
AIS	Acute ischemic stroke
AMI	Acute myocardial infarction
ASENT	Assessment of the Safety and Efficacy of a New Thrombolytic
BM	blood glucose
BP	blood pressure (mm Hg)
CI	confidence interval
CT	computed tomography
CVA	cerebrovascular accident
DIAS	Desmoteplase in Acute Ischemic Stroke Trial
DSPA α1	Desmoteplase alpha I
ECASS	European Cooperative Acute Stroke Study
FDA	food and drug administration
GCS	Glasgow Coma Scale
GUSTO	Global Utilization of Streptokinase and Tissue plasminogen activator for occluded coronary arteries.
IAT	intra-arterial thrombolysis
IMS	Interventional Management of Stroke
IST	International Stroke Trial 3
IV tPA	intravenous tissue plasminogen activator
M	Motor
MCA	middle cerebral artery
MD	mean difference
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
MRI	Multimodal magnetic resonance imaging

mRS	modified Ranking scale
NIDDS	National Institute of Neurological Disorders and Stroke Trial
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
ORG	Danaparoid Sodium a low molecular weight heparinoid
PE	pulmonary embolism;
PROACT II	Prolyse in Acute Cerebral Thromboembolism II
RR	relative risk
rt-PA	recombinant tissue plasminogen activator
rtPAs	Recombinant tissue plasminogen activators
sICH	symptomatic intracranial hemorrhage
SK	streptokinase
UK	urokinase
SMD	standardized mean difference
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
t-PA	tissue plasminogen activator
DALYs	Disability Adjusted Life Years
PITX2 gene	Paired-like homeodomain transcription factor 2

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INTRODUCTION

Cerebrovascular disease represents an enormous burden of disease and disability to mankind. The world health organization estimates that 15 million people worldwide suffer a stroke each year **(Mackay, 2004)**.

Because the vast majority of strokes are ischemic in etiology, the development of an effective treatment for clot dissolution was ground breaking. Recombinant tissue plasminogen activator was approved by the food and drug administration (FDA) in the mid 1990 s for the rapid lysis of ischemic stroke. The tissue plasminogen activator resulted in a clinically important and statistically significant reduction in stroke disability and has continued to be the most important achievement in medical treatment of stroke **(Barreto, 2011)**.

The efficacy and safety of recombinant tissue plasminogen activator have been firmly established within 3hours of symptom onset ; however, few patients are eligible for treatment in this time window . Expanding the time for treatment has been challenging, but new evidence has demonstrated a modest statistical improvement in selected patients when rt-pA is administered within 4.5 hours. **(Stemer and Lyden, 2010)**.

One of the main objectives in the treatment of acute cerebral ischemia is the rapid restoration or improvement of blood flow in an affected vascular territory. Recombinant tissue plasminogen activator has been recognized as a promising agent because of its endogenous origin, short half-life and high fibrin specificity, all of which promise to encouraging clinical results **(Keris et al., 2001).**

A study was done by the National Institute of Neurological Disorders and Stroke comparing the effect of using recombinant tissue plasminogen activator and placebo showed that, patients who received

rTPA were at least 30% more likely to have minimal or no disability at 3 months based on four assessment scales when compared to those placebo group. Symptomatic intracerebral hemorrhage within 36 hours occurred in 6.4% of rTPA patients versus 0.6% of placebo patients and mortality was similar in both groups at 3 months **(Marler et al., 2000).**

AIM OF THE WORK

This systematic review study was done to evaluate the efficacy of using recombinant tissue plasminogen activator in treatment of acute ischemic cerebral stroke showing its effect on morbidity and mortality.

Chapter (I)
Acute Ischemic Stroke

Stroke is ranked as the second leading cause of death worldwide with an annual mortality rate of about 5.5 million. Not only does the burden of stroke lie in the high mortality but the high morbidity also results in up to 50% of survivors being chronically disabled. Thus stroke is a disease of immense public health importance with serious economic and social consequences(***Katan and Luft,* 2018**).

A- Definition:

According to the definition proposed by the World Health Organization in 1970, "stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin(***World Health Organization,* 2018**).

Recently, a new definition of stroke that incorporates clinical and tissue criteria has been proposed by the American Stroke Association for the century. This definition is much broader and includes any objective evidence of permanent brain, spinal cord, or retinal cell death attributed to a vascular etiology based on pathological or imaging evidence with or without the presence of clinical symptoms(***Donkor,* 2018**).

B- Classification:

Generally, strokes can be classified into two major categories, namely, ischemic stroke and hemorrhagic stroke. Ischemic strokes account for about 80% of stroke cases while hemorrhagic strokes accounts for 20% but the actual proportions of stroke types depend on the population(***Chugh,* 2019**).

Data from a study involving 22 countries showed that the proportions of ischemic and hemorrhagic stroke in Africa were about 66% and 34%, respectively, compared to about 91% of ischemic stroke and 9% of hemorrhagic stroke in high-income countries. Recent data from the Stroke Investigative Research and Educational Network (SIREN) study in Nigeria and Ghana reported 68% of ischemic stroke and 32% of hemorrhagic stroke, which partly confirms the proportions of stroke subtypes in Africa (***Campbell et al.*, 2019**).

There are several sub classification schemes for ischemic stroke and the Trial of ORG (Danaparoid Sodium, A low molecular weight heparinoid) in Acute Stroke Treatment [TOAST] criteria is the most widely used. Based on the TOAST criteria, ischemic stroke can be grouped into five main pathological or etiological types (**Table 1**) (***Investigators.*, 1998**).