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

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Abstract

Background: 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.

Aim of Study: To evaluate the efficacy of using recombinant tissue plasminogen activator in treatment of acute ischemic cerebral stroke showing its effect on morbidity and mortality.

Material and Methods: In this study, we searched Medline via PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from their inception till April 2020. The search retrieved 1806 unique records. We then retained 54 potentially eligible records for full-texts screening. Finally, 13 studies (No. of patients =7322 patients) were included.

Results: The overall effect showed that rtPA significantly increased the chance of being alive independent (mRS0-2) [OR=1.21 95% CI (1.05, 1.41); p=0.01]. Also increased the favorable outcomes (mRS 0-1) [OR=1.34 95% CI (1.12-1.60); p=0.001]. The risk of sICH increased [OR=3.93 95% CI (2.44, 6.35); p=0.00001] and the overall mortality showed no difference [OR=1.11 95% CI (0.90, 1.38); p=0.01]. The pooled studies showed no significant heterogeneity.

Conclusion: The evidence indicates that intravenous rt-PA increased the proportion of patients who were alive-with favorable outcome and alive and independent at final-follow-up. This benefit occurred despite an increase in the-number of early symptomatic intracranial hemorrhages and-dearly deaths. The overall mortality at the end of follow-up is not significantly increased.

Key Words: *Tissue plasminogen activator – Acute ischemic cerebral stroke.*

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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 **[1]**.

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 1990s 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 **[2]**.

The efficacy and safety of recombinant tissue plasminogen activator have been firmly established within 3 hours 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 **[3]**.

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 **[4]**.

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 [5].

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.

Material and Methods

We performed this systematic review and meta-analysis in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement. PRISMA and MOOSE are reporting checklists for Authors, Editors, and Reviewers of meta-analyses of interventional and observational studies. According to International committee of medical journal association (ICJME), reviewers must report their findings according to each of the items listed in those checklists [6].

The present review included studies that fulfilled the following criteria: Studies that included patients with acute ischemic stroke arriving to stroke unit as early as possible within 6 hours; studies that assessed the safety and effectiveness of recombinant tissue plasminogen activator (rt-PA, alteplase) for acute ischemic stroke; studies that compared those interventions with other interventions for acute ischemic stroke; studies that reported any of the following outcomes: In hospital mortality within 7 days, symptomatic intracranial hemorrhage, fatal intracranial hemorrhage, symptomatic edema, mortality at the end of follow-up, alive and favorable outcome (defined as modified Ranking Scale "mRS" or Oxford Handicap Score" OHS" 0-1) and alive and independent (defined as mRS or OHS 0-2) in addition to studies that were randomized controlled trials.

We excluded review articles, non-English studies, theses, dissertations and conference abstracts, and trials with unreliable date for extraction. In addition, we excluded trials that did not provide relevant clinical outcomes or in which the latest follow-up was less than 1 month after treatment.

Search strategy and screening:

An electronic search was conducted from the inception till April 2020 in the following bibliographic databases: Medline via PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science to identify relevant articles. We used different combinations of the following queries:

Stroke OR strokes OR cerebrovascular disorders and stroke OR Ischemic Cerebral Stroke. Thrombolytic therapy OR thrombolysis OR “thrombolytic therapy”OR tissue plasminogen activator OR tpa OR ttpa OR rtpa OR r-tpa.

Study design or publication types:

Randomized controlled trials OR “randomized controlled” OR “cluster randomized” OR “cluster randomization”.

Screening:

Retrieved citations were imported into End Note X7 for duplicates removal. Subsequently, unique citations were imported into an Excel sheet and screened by independent reviewers; the screening was conducted in two steps: Title and abstract screening, followed by a full-texts screening of potentially eligible records.

Data extraction:

Data entry and processing were carried out using a standardized Excel sheet and reviewers extracted the data from the included studies. The extracted data included the following domains: (1) Summary characteristics of the included studies; (2) Baseline characteristics of studied populations; (3) Risk of bias domains; and (4) Study outcomes including "in hospital mortality within 7 days, mortality at the end of follow-up, symptomatic intracranial hemorrhage, fatal intracranial hemorrhage, symptomatic edema, alive and independent, alive with favorable outcomes". All reviewers' independently extracted data from the included studies and any discrepancies were solved by discussion.

Risk of bias assessment:

The quality of the retrieved RCTs was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (updated March 2011) using the quality assessment table provided

in the same book (part 2, Chapter 8, page 5). The Cochrane risk of bias assessment tool includes the following domains: Sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgment is categorized as 'Low risk', 'High risk' or 'Unclear risk' of bias [7].

Dealing with missing data:

The authors hold full responsibility for the accuracy of the provided data. All data was extracted and revised by the reviewers. If any of the data were not present, we tried to contact the author. And if the authors did not reply, we report it in the risk of bias selection.

Data synthesis and statistical analysis:

Based on the literature and clinical physicians opinion, we defined the outcomes as follows; (1) In hospital mortality within 7 days, (2) Symptomatic intracranial hemorrhage, (3) Fatal intracranial hemorrhage, (4) Symptomatic edema, (5) Alive and independent (mRS 0-2), (6) Alive with favorable outcomes (mRS 0-1), (7) Mortality at the end of follow-up.

Dichotomous outcomes was pooled as Relative Risk (RR) using Mantel-Hansel method. The random-effects method was used under the assumption of existing significant clinical and methodological heterogeneity. We performed all statistical analyses using Review Manager (RevMan) 5.3 or Open Meta-analyst for windows.

Assessment of heterogeneity:

We calculated the relative risk for dichotomous data. Firstly, the analysis was performed with a fixed-effect model and the heterogeneity was considered significant if the chi-square test was significant (p-value <0.01) or (the I-square >50.00%). The included studies showed low significance for heterogeneity.

Assessment of publication biases:

We intended to test for publication bias using funnel plots generated by RevMan software if any of the pooled analysis included more than 10 studies in the review [7].

Results

I- *Search results:*

In the present study, we searched Medline via PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from their inception till April 2020. The search retrieved 1806 unique records. We then retained 54 potentially eligible records for full-texts screening. Finally, 13 studies (No. of patients=7322 patients) were included.

I- *Characteristics of the included studies:*

Table (1): Summary characteristics of the included studies.

Study ID	Year Country	Study design	Number of patients	Dose	Control	Final follow-up
Mori et al.,	1992 Japan	Double-blind RCT	31	• 0.6mg/kg (34mg) or 0.9mg/kg (51mg)	• Placebo	1 month
JTSG	1993 Japan	Double-blind RCT	98	• 0.6mg/kg (34mg)	• Placebo	1 month
Haley et al.,	1993 USA	Double-blind RCT	27	• 0.85mg/kg	• Placebo	3 months
ECASS	1995 Europe	Double-blind RCT	620	• 1.1mg/kg (maximum 100mg)	• Placebo	3 months
NINDS	1995 USA	Double-blind RCT	624	• 0.9mg/kg (maximum 90mg)	• Placebo	3 months
ECASS II,	1998 Europe	Double-blind RCT	800	• 0.9mg/kg (maximum 90mg)	• Placebo	3 months
ATLANTIS A,	2000 USA	Double-blind RCT	142	• 0.9mg/kg (maximum 90mg)	• Placebo	3 months
ATLANTIS B,	2000 USA	Double-blind RCT	613	• 0.9mg/kg (maximum 90mg)	• Placebo	3 months
ECASS III,	2008 Europe	Double-blind RCT	821	• 0.9mg/kg (maximum 90mg)	• Placebo	3 months
Wang et al.,	2003 China	Double-blind RCT	100	• 0.9mg/kg (maximum 90mg)	• Open control	3 months
EPITHET,	2008 Australia	Double-blind RCT	101	• 0.9mg/kg (maximum 90mg)	• Placebo	3 months
IST-3	2012 International	Double-blind RCT	3035	• 0.9mg/kg (maximum 90mg)	• Placebo first 276 patients, open control thereafter	6 months
EXTEND	2019 USA	Open-label RCT	310	• 0.9mg/kg (maximum 90mg)	• Placebo	3 months

Table (2): Baseline characteristics of the included studies.

Study ID	Year	Antithrombotic drug use	Age inclusion range	Stroke type	Exclusion criteria* for CT-defined ischemia	Time after stroke	Follow-up method (independent)
Mori et al.,	1992	• Avoid for 24h	• 18-80 years	• Carotid territory; ICA or MCA occlusion on angiography	• Visible infarction	• <6h	• At clinic (not stated)
JTSG	1993	• Avoid for 24h	• 18-80 years	• Carotid territory; ICA or MCA occlusion on angiography	• Visible infarction	• <6h	• At clinic (not stated)
Haley et al.,	1993	• Avoid intravenous heparin for several hours	• 18-80 years	• Any ischemic stroke	• None	• <3h	• At clinic (not stated)
ECASS	1995	• Aspirin or intravenous heparin not allowed; subcutaneous heparin allowed for <24h; thereafter, any antithrombotic allowed	• 18-80 years	• Carotid territory	• Visible infarction greater than a third of MCA territory	• 6h	• At clinic (not stated)
NINDS	1995	• Avoid for 24h	• 18-80 years†	• Any except very mild and very severe	• None	• 3h	• At clinic (masked independent clinician)
ECASS II,	1998	• Aspirin or intravenous heparin not allowed; subcutaneous heparin allowed for <24h	• 18-80 years	• Carotid territory	• Visible infarction greater than a third of MCA territory	• 6h	• At clinic (not stated)
ATLANTIS A,	2000	• Avoid for 24h	• 18-80 years	• Any except very mild and very severe	• None	• 6h	• At clinic (masked independent clinician)
ATLANTIS B,	2000	• Avoid for 24h	• 18-80 years	• Any except very mild and very severe	• Visible infarction greater than a third of MCA territory	• Most with in 5h	• At clinic (masked independent clinician)
ECASS III,	2008	• Avoid for 24h	• 18-80 years	• Any except very mild and very severe	• Visible infarction greater than a third of MCA territory	• 3.0-4.5h	• At clinic (masked independent clinician)
Wang et al.,	2003	• Avoid for 24h	• 18-80 years	• Any except very mild and very severe	• Any visible infarction	• 6h	• At clinic (not stated)
EPITHET,	2008	• Avoid for 24h	• 18-80 years†	• Any except very mild and very severe	• Visible infarction greater than a third of MCA territory	• 3-6h	• At clinic (not stated)
IST-3	2012	• Avoid for 24h; start aspirin at 24h unless contraindicated	• ≥ 18 years	• All subtypes	• Visible infarct only if it appears >6h after stroke-ie, incompatible with stated time after stroke	• 6h	• Centralized telephone or postal questionnaire (yes)
EXTEND	2019	• Avoid for 24h; start aspirin at 24h unless contraindicated	• ≥ 18 years	• Any except very mild and very severe	• Visible infarction greater than a third of MCA territory	• 6h	• At clinic (not stated)

Table (3): Risk of bias assessment.

Study ID	Random sequence generation	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Selective reporting	Other
Mori et al.,	Low	Unclear	Low	Low	Unclear	Low	Unclear
JTSG	Low	Unclear	Low	Low	High	Low	Unclear
Haley et al.,	Low	Unclear	Low	Low	Unclear	Low	Unclear
ECASS	Low	Unclear	Low	Low	Unclear	Low	Unclear
NINDS	Low	Unclear	Low	Low	Unclear	Low	Unclear
ECASS II,	Low	Low	Low	Low	Unclear	Low	Unclear
ATLANTIS A,	Low	Unclear	Low	Low	Unclear	Low	Unclear
ATLANTIS B,	Low	Unclear	Low	Low	Unclear	Low	Unclear
ECASS III,	Low	Low	Low	Low	Unclear	Low	Unclear
Wang et al.,	Low	Low	Low	Low	Unclear	Low	Unclear
EPITHET,	Low	Low	Low	Low	Unclear	Low	Unclear
IST-3	Low	Low	Low	Low	Low	Low	Unclear
EXTEND	Low	Low	Low	Low	Low	Low	Unclear

II- *Meta-analysis results:*

1- *Symptomatic intracranial hemorrhage:*

Table (4): Meta-analysis for symptomatic intracranial hemorrhage.

Study	Symptomatic intracranial hemorrhage				Weight	Odds ratio M-H, random, 95%CI
	Experimental		Control			
	Event	Total	Event	Total		
Mori et al., 1992	2	19	1	12	3.2%	1.29 [0.10, 16.04]
Haley et al., 1993	0	14	1	13	2.0%	0.29 [0.01, 7.70]
JTSG 1993	4	51	5	47	8.2%	0.71 [0.18, 2.84]
NINDS 1995	20	312	2	312	7.6%	10.62 [2.46, 45.82]
ECASS 1995	62	313	20	307	19.5%	3.54 [2.08, 6.03]
ECASS II 1995	36	409	13	391	17.5%	2.81 [1.46, 5.38]
ATLANTIS B, 1999	21	307	4	306	11.1%	5.54 [1.88, 16.35]
ATLANTIS A, 2000	8	71	0	71	2.5%	19.14 [1.08, 338.32]
Wang et al., 2003	1	67	0	33	2.0%	1.51 [0.06, 38.11]
ECASS III, 2008	10	418	1	403	4.5%	9.85 [1.26, 77.32]
EPITHET 2008	4	52	0	49	2.4%	9.19 [0.48, 175.23]
IST-3 2012	104	1515	16	1519	19.5%	6.92 [4.07, 11.78]
Total (95% CI)	272	3548	63	3463	100.0%	
Overall effect		3.93 [2.44, 6.35]			Z=5.60 (p<0.00001)	
Heterogeneity:		I^2=43%			p=0.05	
Tau^2		0.23			Chi^2 = 19.44, DF=11	

Table (4) shows that:

12 studies reported the rates of Symptomatic Intracranial Hemorrhage. The overall effect showed that the rtPA increased the risk of sICH (odds ratio=3.93 95%CI [2.44, 6.35]; p<0.00001). The pooled studies showed no significant heterogeneity (p=0.05).

2- In-hospital mortality, fatal ICH and symptomatic edema (within 7 days).

Table (5): Meta-analysis for in-hospital mortality (within 7 days).

Study	In hospital mortality				Weight	Odds ratio M-H, random, 95%CI
	Experimental		Control			
	Event	Total	Event	Total		
IST-3 2012	163	1515	107	1520	55.7%	1.59 [1.23, 2.05]
Studies before 2012	82	1292	67	1208	44.3%	1.15 [0.83, 1.61]
Total (95% CI)	245	2807	174	2728	100.0%	
Overall effect		1.38 [1.01, 1.89]			Z=2.02 (p=0.13)	
Heterogeneity:		I^2=56%			p=0.04	
Tau^2		0.03			Chi^2=2.26, DF=1	

Table (6): Meta-analysis for fatal ICH.

Study	Fatal ICH				Weight	Odds ratio M-H, random, 95%CI
	Experimental		Control			
	Event	Total	Event	Total		
IST-3 2012	55	1515	7	1520	38.0%	8.14 [3.70, 17.94]
Studies before 2012	65	1844	14	1804	62.0%	4.67 [2.61, 8.35]
Total (95% CI)	120	3359	21	3324	100.0%	
Overall effect		5.77 [3.39, 9.81]				Z=6.47 (p=0.26)
Heterogeneity:		I^2=20%				p<0.00001
Tau^2		0.03				Chi^2=1.24, DF=1

Table (7): Meta-analysis for symptomatic edema.

Study	Symptomatic edema				Weight	Odds ratio M-H, random, 95%CI
	Experimental		Control			
	Event	Total	Event	Total		
IST-3 2012	68	1515	42	1515	47.3 %	1.65 [1.11, 2.44]
Studies before 2012	237	1475	286	1451	52.7%	0.78 [0.64, 0.94]
Total (95% CI)	305	2990	328	2966	100.0%	
Overall effect		1.11 [0.53, 2.31]				Z=0.28
Heterogeneity:		I^2=91%				p=0.0007
Tau^2		0.26				Chi^2=11.37, DF=1

Tables (5-7) show that:

The overall effect estimates showed that the rt-PA increased the risk of in-hospital mortality (Odds ratio=1.38 [1.01, 1.89]; p<0.04), fatal ICH (Odds ratio=5.77 [3.39, 9.81]; p<0.0001) and symptomatic edema not significantly increased (odds ratio=1.11 [0.53, 2.31]: p=0.0007. The pooled studies showed no significant heterogeneity (p<0.01).

3- Modified ranking scale (0-2) (being independent and alive).

Table (8): Meta-analysis for modified ranking scale mRS (0-2) (being independent and alive).

Study	Modified ranking scale (0-2)				Weight	Odds ratio M-H, random, 95%CI
	Experimental		Control			
	Event	Total	Event	Total		
Mori et al., 1992	8	19	2	12	0.7%	3.64 [0.62, 21.36]
ECASS 1995	142	313	122	307	12.1 %	1.26 [0.92, 1.73]
ECASS II 1995	222	409	180	391	14.0%	1.39 [1.05, 1.84]
NINDS 1995	157	312	120	312	12.1 %	1.62 [1.18, 2.23]
ATLANTIS B, 1999	166	307	171	306	12.1 %	0.93 [0.68, 1.28]
ATLANTIS A, 2000	7	71	15	71	2.2%	0.41 [0.16, 1.07]
Wang et al., 2003	53	67	22	33	2.3%	1.89 [0.74, 4.81]
ECASS III, 2008	278	418	248	403	13.6%	1.24 [0.93, 1.65]
EPITHET 2008	24	52	20	49	3.2%	1.24 [0.56, 2.73]
IST-3 2012	554	1515	534	1520	21.4%	1.06 [0.92, 1.23]
Extend 2019	56	113	48	112	6.2%	1.31 [0.77, 2.22]
Total (95% CI)	1667	3596	1482	3516	100.0%	
Overall effect		1.21 [1.05, 1.41]				Z=2.56
Heterogeneity		I^2=40%				(p=0.01)
Tau^2		0.02				Chi^2=16.80, DF=10

Table (8) showed that the rtPA significantly increased the chance of being independent and alive (mRS 0-2) (odds ratio=1.21 [1.05, 1.41] p= ,01).

4- Modified ranking scale (0-1) (favorable outcomes).

Table (9): Meta-analysis for modified ranking scale mRS (0-1) (favorable outcomes).

Study	Modified ranking scale (0-1)				Weight	Odds ratio M-H, random, 95%CI
	Experimental		Control			
	Event	Total	Event	Total		
Mori et al., 1992	6	19	2	12	0.9%	2.31 [0.38, 13.96]
ECASS 1995	112	313	90	307	12.0%	1.34 [0.96, 1.88]
ECASS II 1995	165	409	143	391	13.7%	1.17 [0.88, 1.56]
NINDS 1995	133	312	83	312	12.0%	2.05 [1.46, 2.87]
ATLANTIS B, 1999	146	307	144	306	12.7%	1.02 [0.74, 1.40]
ATLANTIS A, 2000	11	71	15	71	3.5%	0.68 [0.29, 1.62]
Wang et al., 2003	38	67	7	33	2.9%	4.87 [1.86, 12.77]
ECASS III, 2008	219	418	182	403	14.1 %	1.34 [1.02, 1.76]
EPITHET 2008	18	52	12	49	3.5%	1.63 [0.69, 3.88]
IST-3 2012	363	1515	320	1520	17.9%	1.18 [1.00, 1.40]
Extend 2019	40	113	33	112	6.8%	1.31 [0.75, 2.30]
Total (95% CI)	1251	3596	1031	3516	100.0%	
Overall effect		1.34 [1.12, 1.60]			Z=3.25 (p=0.001)	
Heterogeneity:		I^2=52%			p=0.02	
Tau^2		=0.04			Chi^2=20.99, DF=10	

Table (9) showed that rt-PA increased the overall effect of favorable outcomes (mRS 0-1) (odds ratio=1.34; 95% [1.12, 1.60]). The pooled studies showed no significant heterogeneity (p=0.001).

5- All mortality.

Table (10): Meta-analysis for all mortality.

Study	All mortality				Weight	Odds ratio M-H, random, 95%CI
	Experimental		Control			
	Event	Total	Event	Total		
Mori et al., 1992	2	19	2	12	1.0%	0.59 [0.07, 4.85]
Haley et al., 1993	1	14	3	13	0.8%	0.26 [0.02, 2.85]
JTSG 1993	3	51	4	47	1.7%	0.67 [0.14, 3.17]
NINDS 1995	54	312	64	312	14.4%	0.81 [0.54, 1.21]
ECASS 1995	69	313	48	307	14.2%	1.53 [1.01, 2.29]
ECASS II 1995	43	409	42	391	12.7%	0.98 [0.62, 1.53]
ATLANTIS B, 1999	33	307	21	306	9.4%	1.63 [0.92, 2.90]
ATLANTIS A, 2000	16	71	5	71	3.5%	3.84 [1.32, 11.15]
Wang et al., 2003	5	67	3	33	1.9%	0.81 [0.18, 3.60]
ECASS III, 2008	32	418	34	403	11.1%	0.90 [0.54, 1.49]
EPITHET 2008	13	52	7	49	3.8%	2.00 [0.72, 5.53]
IST-3 2012	408	1515	407	1515	25.6%	1.00 [0.85, 1.18]
Total (95% CI)	679	3548	640	3459	100.0%	
Overall effect		1.11 [0.90, 1.38]			Z=1.01 (p=0.031)	
Heterogeneity:		I^2=36%			p=0.01	
Tau^2		=0.04			Chi^2=17.15, DF=11	

Table (10) showed that all mortality increased in only two studies of the studies included in our meta-analysis, but the overall effect of rt-PA after pooling all the results of all the included studies was no difference in between the two groups, the drug group and the placebo group odds ratio=1.11 95%CI [0.90, 1.38] the pooled studies showed no significant heterogeneity p=,01.

Discussion

Acute Ischemic Stroke (AIS) is a medical emergency, affecting 795,000 people in the United States each year. The global burden of AIS on society continues to rise with increasing incidence, in part due to increasing longevity [8].

Stroke treatment is a continuum that begins with the rapid identification of symptoms and treatment with transition to successful rehabilitation. Therapies for AIS may vary based on anatomic location, interval from symptom onset, and coexisting health conditions. Successful therapy requires a seamless systematic approach with coordination from pre-hospital environment through acute management at medical facilities to disposition and long-term care of the patient [9].

Recombinant tissue plasminogen activators (rtPAs) are produced using genetic engineering techniques through mutations in the DNA sequence of native rTPA. These new therapeutic agents exhibit longer half-lives than native rTPA, allowing convenient bolus dosing, enhanced fibrin specificity, and higher resistance to in activation-by PAI-1 [10].

Although, intravenous rTPA for AIS showed a significant increase insurvival free of disability, there is still a discrepancy within the published literature regarding the role of rTPA in the setting AIS [11].

Thus, we performed the present systematic review and meta-analysis to assess the efficacy and safety of intravenous rTPA when given up to 6h after stroke for important early and late outcomes.

In the present study, wese arched Medlinevia PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from their inception till April 2020. These archretrieved 1806 unique records. We then retained 54 potentially eligible records for full-texts screening. Finally, 13 studies (No. of patients=7322 patients) were included.

1- *In-hospital Mortality, fatal intracranial hemorrhage, and symptomatic intracranial hemorrhage:*

Intravenous rTPA improves outcome in selected patients with AIS when given within 4.5 hours from onset. Despite its efficacy, the use of alteplase is limited by the risk of hemorrhagic complications, particularly symptomatic intracranial hemorrhage (sICH). The risk of sICH varies on thebasis of patient population and the definition of sICH used but general lyranges from 2% to 7%. The sICH can lead to fatal hemorrhage and death [12].

Our study revealed that, in patients received rTPA within 6 hours from the onset of stroke, the risk of sICH increased significantly in the rTPA group compared to no thrombolysis group. The overall effect showed that rt-PA increased the risk of sICH (OR=3.93 95% CI [2.44-6035]; p <0.00001). The pooled studies showed no significant heterogeneity (p=0.05). In addition, the risk of in hospital mortality increased (OR=1.38 [1.01-1.89]; p<0.04).

Also our study revealed that rTPA increase the risk of fatal ICH (OR=5.77 [3.39-9.81]; p<0.0001) and have no significant effect on symptomatic edema (OR=1.11 [0.53-2.31]; p=0.0007) the pooled studies showed no significant heterogeneity (p<0.01).

In agreement with our findings, Wardlaw and colleagues [13] assessed all the evidence from randomized trials for rTPA in acute ischemic stroke in an updated systematic review and meta-analysis. In up to 12 trials (7012 patients), the risk of sICH, death, and fatal ICH increased significantly in the rTPA group.

Likewise, Sandercock and colleagues [11] conducted the third International Stroke Trial (IST-3) that aimed to determine whether awider range of patients might benefit up from rtPA to 6h from stroke onset. In this international, multicenter, randomized, open-treatment trial, patients were allocated to 0.9mg/kg intravenous recombinant-tissue plasmino genactivator (rTPA) or to control. 3035 patients were enrolled by 156 hospitals in 12 countries. More deaths occurred within 7 days in the rTPA group (163 [11 %]) than in the control group (107 [7%], adjusted OR 1.60, 95% CI 1.22-2.08, p=0.001; absolute increase 37/1000, 95% CI 17-57).

Similarly, in another meta-analysis, Wardlaw and colleagues [13] aimed to determine whether, and in what circumstances, thrombolytic therapy might be an effective and safe treatment for acute ischemic stroke. The authors included 27 trials, involving 10,187 participants. About 44% of the trials (about 70% of the participants) were testing intravenous rt-PA. Thrombolytic therapy increased the risk of sICH (OR 3.75, 95% CI 3.11 to 4.51) and early death (OR 1.69, 95% CI 1.44 to 1.98; 13 trials, 7458 participants). Early death after thrombolysis was mostly attributable to intracranial hemorrhage.

Davis and colleagues **[14]** prospectively and randomly assigned 101 patients to receive alteplaseorplacebo 3-6 hafteronse to fischemic stroke. Herisk of sICH, death, and fatal ICH increased significantly in the rtPA group.

2- Follow-up mortality:

In the present study, 13 studies reported the rate so fall mortality. Only two studies of the included studies showed that all mortality at the end of follow-up was increased in rt-PA group (ECASS 1995, ATLANTIS 2000). The other 11 studies showed no difference between rt-PA and placebo group including the largest sample sized and the most weighted study estimated by Rev Man, (IST 2012). But the overall effect after pooling all the results of the 13 studies showed that there is no difference in between the two groups, rt-PA group and placebo group (OR1.11 95%CI [0.90, 1.38]). The pooled studies showed no significant heterogeneity (p=,01).

3- Functional outcomes at the end of follow-up:

The modified Ranking scale (mRS) is a measure of global disability that is commonly used as a functional outcome for stroke studies. The mRS was designed to assess poststroke recovery levels and the wording of the original scale assumesa comparison with the pre-stroke state **[15]**.

Our study revealed that the overall effect estimates showed that the rtPA significantly increased the chance of being independent and alive (mRS 0-2) (OR=1.21 [1.05, 1.41] p=,01)) and favorable outcomes (mRS 0-1) (OR=1.34; 95% [1.12, 1.60]). The pooled studies showed no significant heterogeneity (p=0.001).

Conclusion:

The evidence indicates that in travenous rt-PA increased the proportion of patients who were alive with favorable outcome and alive andindependent at final follow-up. This benefitoccurred despite an increase in the number of early symptomatic intracranial hemorrhages and early deaths. The overall mortality at the end of follow-up is not significantly increased.

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منشط بلازمينوجين الآنسجة المؤتلف لعلاج السكتة الدماغية الحادة: مراجعة منهجية

المقدمة: تم تصنيف السكتة الدماغية على أنها السبب الرئيسى الثانى للوفاة على مستوى العالم بمعدل وفيات سنوى يبلغ حوالى ٥.٥ مليون. لا يكمن عبء السكتة الدماغية فى معدل الوفيات المرتفع فحسب، بل يؤدى إرتفاع معدلات الإعتلال أيضاً إلى إصابة ما يصل إلى ٥٠٪ من الناجين بإعاقة مزمنة.

الهدف من الدراسة: لتقييم فعالية إستخدام منشط البلازمينوجين النسيجى المؤتلف فى علاج السكتة الدماغية الإقفارية الحادة مع توضيح تأثيره على معدلات الإعتلال والوفيات.

المواد والطرق: فى هذه الدراسة، تم البحث فى مواقع Medline عبر PubMed و SCOPUS و Web of Science وسجل كوكرين المركزى للتجارب الضبطية (CENTRAL) و Google Scholar منذ نشأته حتى أبريل ٢٠٢٠. وقد إسترجع البحث ١٨٠٦ سجلاً فريداً. ثم إحتفظنا ب ٥٤ سجلاً يحتمل أن تكون مؤهلة لفحص النصوص الكاملة. أخيراً، تم تضمين ١٣ دراسة (عدد المرضى = ٧٣٢٢ مريضاً).

النتائج: أظهر التأثير الكلى أن rtPA زاد بشكل كبير من فرصة البقاء على قيد الحياة بشكل مستقل، كما أدى إلى زياة النتائج الإيجابية، على الرغم من أن الحقن الوريدى rt-PA لـ AIS أظهر زيادة كبيرة فى النجاة بدون إعاقة، فلا يزال هناك إختلاف فى الدراسات المنشورة فيما يتعلق بدور RT-PA فى ضبط AIS. وهكذا، قمنا بإجراء المراجعة المنهجية الحالية والتحليل الوصفى لتقييم فعالية وسلامة الحقن الوريدى rt-PA عند إعطائه حتى ٦ ساعات بعد السكتة الدماغية للحصول على نتائج هامة مبكرة ومتأخرة.

الخلاصة (الإستنتاج): تشير الدلائل إلى أن الحقن الوريدى يزيد من نسبة المرضى الذين كانوا على قيد الحياة مع نتائج أيجابية وعلى قيد الحياة ومستقلين فى المتابعة النهائية. حدثت هذه الفائدة على الرغم من الزيادة فى عدد حالات النزيف داخل الجمجمة المبكرة والوفيات المبكرة. لم يتم زيادة الوفيات الإجمالية فى نهاية المتابعة زيادة كبيرة.