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

Waleed M. Abd El-Mageed MD; Rania M. Mohamed MD; Mohamed M. Mohamed; Essam M. Ezzaat Ali

Anesthesia Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Essam.ezzaat@yahoo.com

Abstract: Background: Stroke is a devastating disease with increasing incidence and prevalence due to population aging. The most effective approach in acute stroke therapy is still under discussion, but it appears reasonable to get the vessel recanalized to save penumbra tissue. Intravenous alteplase is FDA approved within 4.5 hours of acute ischemic stoke onset. Some studies extend the window to 6 hours. Methods: This was a prospective open-label randomized controlled clinical trial will be conducted on 60 patients with acute ischemic stroke (AIS); to compare safety and effectiveness of Alteplase given 3-6 hours versus 0-3 after acute ischemic stroke. The 60 AIS patients were classified according to time of Alteplase infusion into 2 independent groups. 0-3 Alteplase "group A" (30 patients). 3-6 Alteplase "group B" (30 patients). Results: Our study revealed Highly significant shorter time of onset of symptoms, in A group; compared to B group. Significant decrease in NIHSS score in A group; compared to B group; during the post-infusion measurements. Non-significant decrease in mrs score in A group; compared to B group; during the post-infusion measurements. We found that, there is significant decrease in mortality in A group; compared to B group. We also found that, there is non-significant difference as regards parenchymal hemorrhages, between the 2 groups. Alteplase infusion therapy within the first 3 hours of stroke onset, convey a great benefit regarding improvement of NIHSS and mrs scores, along with decreased mortality and intracranial hemorrhage rates, as compared with 3-6 hours Alteplase infusion. The 3-6 hours group can benefit from IV thrombolytic by proper selection of patients. Conclusion: Our data suggested that, Alteplase infusion therapy within the first 3 hours of stroke onset, convey a great benefit regarding improvement of NIHSS and mrs scores, along with decreased mortality and intracranial hemorrhage rates, as compared with 3-6 hours Alteplase infusion. The 3-6 hours group can benefit from IV thrombolytic by proper selection of patients.
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1. 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.

2. Patients and methods

Patients

This Prospective open-label controlled clinical trial was carried out from 1 October 2017 to 1 June 2018, including sixty patients admitted to Cairo Governorate hospitals Approval of the ethical committee of AinShams university was obtained before the start of patient's recruitment.

Patients were included in the study according to the following criteria: Age, 18 -80years old, clinical diagnosis of ischemic stroke, causing a measurable neurological deficit (defined as impairment of language, motor function, cognition, gaze, or vision, or as neglect), and onset of symptoms of ischemic stroke within 6 hours of initiation of treatment with the study drug: "time of onset" of stroke is defined as that point at which a change in the baseline neurological function occurred. If that time is not known, eg, the patient awakens from sleep with new symptoms, the last time the patient was observed to be neurologically intact must be considered the time of onset.

Exclusion criteria:

Clinical

Absolute contraindications:

1. Coma, severe obtundation, fixed eye deviation, or complete hemiplegia.
2. History of stroke within the previous 6 weeks.
3. Previous known intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, arteriovenous malformation, or aneurysm.
4. Clinical presentation suggestive of subarachnoid hemorrhage, even if initial computed tomographic scan is normal.
5. Hypertension, defined as systolic blood pressure ≥185 mm Hg or diastolic blood pressure ≥ 110 mm Hg on repeated measures prior to study entry or requiring aggressive (eg, intravenous antihypertensive) treatment to reduce blood pressure to within these limits.
6. Presumed septic embolus.
7. Presumed pericarditis or presence of either ventricular thrombus or aneurysm related to recent acute myocardial infarction.
8. Recent (within 30 days) surgery or biopsy of a parenchymal organ.
9. Recent (within 30 days) trauma with internal injuries or ulcerative wounds.
10. Recent (within 90 days) head trauma.
11. Any active or recent (within 30 days) hemorrhage.
12. Known hereditary or acquired hemorrhagic diathesis, eg, activated partial thromboplastin time or prothrombin time greater than normal; unsupported coagulation factor deficiency; or oral anticoagulant therapy with prothrombrin time greater than normal.
13. Pregnancy (positive HCG test), lactation, or parturition within the previous 30 days.
14. Baseline lab values: glucose less than 50 mg/dL or greater than 400 mg/dL; platelet count less than 100 000/μL.
15. Other serious, advanced, or terminal illness.
16. Any other condition that the investigator feels would pose a significant hazard to the patient if recombinant tissue-type plasminogen activator therapy were initiated.
17. Current participation in another research drug treatment protocol.
18. Post-cardiac arrest.
19. Known active seizure disorder or a first seizure within the 6 hours immediately prior to administration of study drug.
20. Patient has only minor stroke symptoms (ie, 4 points on the National Institutes of Health Stroke Scale and normal speech and visual fields). or major symptoms that are rapidly improving by the time of randomization.

Cerebral Computed Tomographic Scan Exclusions

a. High-density lesion consistent with hemorrhage of any degree.
b. Evidence of significant mass effect with midline shift.
c. Subarachnoid hemorrhage.
d. Parenchymal hypodensity, loss of gray/white matter distinction, and/or effacement of cerebral sulci in 33% of the middle cerebral artery territory.

Methods

Sixty acute ischemic stroke patients males and females divided into 2 groups according to the time of onset of symptoms into group A within 3 hours and group B from 3-6 hours. Written consent was taken from patients or their relatives explaining the benefits and harm of alteplase infusion. All patients had their

vitals assessed (Pulse Rate, Blood Pressure, Respiratory Rate, Temperature, Oxygen Saturation, pupils) as well as date, time of onset of symptoms are recorded. Routine blood tests (Sugar, Hemoglobin, Total Leukocyte Count, Differential Count, Platelet Count, Creatinine, SGPT, Sodium, Potassium, Calcium, Prothrombin time, INR, aPTT, lipid profile) were done immediately for all the subjects. Electrocardiogram (ECG), Chest X Ray were done for all the subjects. We clinically assessed each subject, note NIHSS score of each of them at initial assessment. Then subjects are subjected to CT scan to exclude hemorrhage. Blood test (platelet count, PT, INR, aPTT) reports were collected before starting thrombolysis, confirmed to meet exclusion criteria. Cases with high blood pressure were treated with IV antihypertensive), titrated according to blood pressure. They were treated with IV isotonic fluids, statins, neuro-protective agents, insulin for diabetics. After controlling blood pressure, excluding exclusion criteria cases. We prepared alteplse by withdrawing 50 ml sterile water and insert it into the 50 mg alteplase vial for the concentration to be 1 mg/ml, the vial was left until foam subside. IV rtPA-alteplase was given in a separate IV line at a dose of 0.9 mg/kg body weight (maximum90 mg) with 10% of total dose over 1 minute and 90% of total dose as infusion over 1 hour). For the first 24 hours all patients were admitted in ICU care. We Followed up any signs suggestive of bleeding or neurological deterioration to stop infusion. Observe for angioedema (face, tongue, larynx) after alteplase administration and treat with hydrocortisone 100 mg iv/8 hours. We monitored blood pressure every 15 minutes for 2 hours then every 30 minutes for 6 hours then every 4 hours for 16 hours following treatment. NPO until dysphagia is properly assessed. Follow up CT Scan Brain is taken in all subjects after 24 hours of thrombolysis based on clinical status of each subject. Antiplatelets and anticoagulants (Heparin / LMWH) are started based on clinical status of each subject and follow up CT scan. The dose of antiplatelets and anticoagulants are fixed according to guideline. NIHSS score was assessed immediately and 24 hours after thrombolysis for all the subjects. Subjects were reassessed after 1 months with MRS (Modified Rankin Score) by phone.

Statistical Analysis:

Data entry, processing and statistical analysis was carried out using MedCalc ver. 18.2.1(MedCalc, Ostend, Belgium). Tests of significance (Mann-Whitney's, Wilcoxon's, Friedman's, Chi square, McNemar's tests, factorial ANOVA, logistic and multiple regression analysis, and ROC Curve analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

3. Results

Table (1) shows that, there is non-significant difference as regards age, BMI and sex of the patients, between the 2 groups ($p > 0.05$).

Table (2) shows that, there is non-significant difference as regards all risk factors, between the 2 groups ($p > 0.05$).

Table (3) shows that, there is; highly significant shorter time of onset of symptoms, in A group; compared to B group ($p < 0.01$). On the other hand, there is non-significant difference as regards baseline NIHSS and mRS scores, between the 2 groups ($p > 0.05$).

Table (4) shows that, there is non-significant difference as regards all baseline laboratory variables, between the 2 groups ($p > 0.05$).

Table (5) shows that, there is non-significant difference as regards baseline ECG and CT abnormalities, between the 2 groups ($p > 0.05$).

Table (6) shows that, there is, highly significant decrease in 24-hours post-infusion NIHSS and mRS scores, in A group ($p < 0.01$). Table (6) shows that, there is, non-significant difference in post-infusion and CT abnormalities, in A group ($p > 0.05$).

Table (7) shows that, there is, highly significant decrease in post-infusion NIHSS score in B group ($p < 0.01$). Table (7) shows that, there is, highly significant increase in post-infusion CT abnormalities, in B group ($p < 0.01$). Table (7) shows that, there is, non-significant difference in post-infusion mRS score, in B group ($p > 0.05$).

Table (8) showed significant decrease in NIHSS score in A group; compared to B group; during the post-infusion measurements ($p = 0.026$).

Table (9) shows that, there is; significant decrease in mortality in A group; compared to B group ($p = 0.02$).

Table (9) shows that, there is non-significant difference as regards parenchymal hemorrhages, between the 2 groups ($p > 0.05$).

Table (10) shows that, the increase in baseline NIHSS score, aPTT and CT abnormalities; had an independent effect on increasing post-infusion 24-h NIHSS score ($p < 0.05$).

Table (11) shows that, the increase in baseline mRS score, platelets, and FDP; had an independent effect on increasing post-infusion 30-days mRS score ($p < 0.05$). Also, delayed 3-6 Alteplase usage; had an independent effect on increasing post-infusion 30-days mRS score ($p < 0.01$). While, the decrease in baseline hemoglobin; had an independent effect on increasing post-infusion 30-days mRS score ($p < 0.05$).

Table (12) shows that, the increase in baseline mRS score and TLC; had an independent effect on increasing the probability of disability occurrence ($p < 0.05$). Also, the delayed 3-6 Alteplase usage, had an independent effect on increasing the probability of disability occurrence ($p < 0.01$).

Table (13) shows that, the increase in age and time of onset of symptoms; had an independent effect on increasing the probability of mortality occurrence ($p < 0.05$).

Table (14) shows that, the decrease in baseline mRS score and TLC; had an independent effect on increasing the probability of neurological improvement occurrence ($p < 0.05$ respectively). Table (14) shows that, the increase in baseline hemoglobin; had an independent effect on increasing the probability of neurological improvement occurrence ($p < 0.05$). Table (14) shows that, the increase in early 0-3 Alteplase usage; had an independent effect on increasing the probability of neurological improvement occurrence ($p = 0.01$).

Table (1): Comparison between the 2 groups as regards basic clinical data:

Variable		A group (30)	B group (30)	P value
Age (years)		62 (57 – 66)	60 (55 – 65)	= 0.254
BMI		22.5 (20 – 25)	20 (20 – 24)	= 0.137
Gender	Female Male	12 (40%) 18 (60%)	8 (26.7%) 22 (73.3%)	= 0.277

Data are expressed as median (IQR): inter-quartile ratio, and number (%).

Table (2): Comparison between the 2 groups as regards risk factors:

Variable	A group (30)	B group (30)	P value
+ve Smoking	12 (40%)	17 (56.7%)	= 0.2002
+ve HTN	18 (60%)	16 (53.3%)	= 0.605
+ve DM	18 (60%)	17 (56.7%)	= 0.795
+ve AF	6 (20%)	2 (6.7%)	= 0.132
+ve History of stroke	0 (0%)	2 (6.7%)	= 0.153

Data are expressed as number (%).

Table (3): Comparison between the 2 groups as regards baseline neurological data:

Variable	A group (30)	B group (30)	P value
Time of onset of symptoms	2 (1 – 2)	4 (4 – 4)	< 0.0001**
NIHSS score	10 (9 – 13)	12 (8 – 15)	= 0.0861
mRS score	3 (2 – 3)	3 (1 – 3)	= 0.4976

Data are expressed as median (IQR).
** Highly significant

Table (4): Comparison between the 2 groups as regards baseline laboratory data:

Variable	A group (30)	B group (30)	P value
Hb (g/dL)	11.7 (12.3 – 13)	13 (12 – 13.3)	= 0.098
Platelets (10^3/µL)	192 (160 – 200)	170 (160 – 190)	= 0.073
TLC (10^3/µL)	8.6 (7 – 9.2)	8.6 (7.5 – 8.9)	= 0.532
INR	1 (1 – 1.1)	1 (1 – 1.1)	= 1.000
PT (seconds)	12 (11 – 12)	12 (12 – 13)	= 0.071
aPTT (seconds)	29.5 (27 – 30)	30 (29 – 32)	= 0.074
Fibrinogen	200 (150 – 250)	170 (160 – 200)	= 0.659
FDP	8.5 (8 – 10)	8 (8 – 10)	= 0.757

Data are expressed as median (IQR).

Table (5): Comparison between the 2 groups as regards baseline radiological data:

Variable	A group (30)	B group (30)	P value
+ve ECG abnormality	5 (16.7%)	2 (6.7%)	= 0.231

+ve CT abnormality (Hemorrhage or infarction)	0 (0%)	2 (6.7%)	= 0.153

Data are expressed as number (%).

Table (6): Comparison between pre and post-infusion neurological and radiological assessments in group A:

Variables	Baseline	Immediate post-infusion	24-hours post-infusion	P value
NIHSS score	10 (9 – 13)	10 (8 – 13)	4.5 (0 – 6)	<0.0001**
mRS score	3 (2 – 3)	---	0 (0 – 1)	<0.0001**
+ve CT abnormality (Hemorrhage or infarction)	0 (0%)	---	1 (3.3%)	= 1.000

Data are expressed as median (IQR), and number (%). ** Highly significant

Table (7): Comparison between pre and post-infusion neurological and radiological assessments in group B:

Variables	Baseline	Immediate post-infusion	24-hours post-infusion	P value
NIHSS score	12 (8 – 15)	12 (8 – 15)	6.5 (0 – 15)	= 0.00004**
mRS score	3 (1 – 3)	---	1.5 (0 – 4)	= 0.521
CT abnormality (Hemorrhage or infarction)	2 (6.7%)	---	15 (50%)	= 0.0002**

Data are expressed as median (IQR), and number (%). ** Highly significant

Table (8): Comparison between the 2 groups as regards pre and post-infusion neurological assessments:

Variables	Repeated 2 measures ANOVA (2-F: between the 2 groups)	
	F ratio	P value
NIHSS score	5.52	0.026*
mRS score	00	00

ANOVA: analysis of variance, 2-F: 2-factor study. F ratio: represents the difference between the means of serial measurements in the 2 groups. * Significant

Table (9): Comparison between the 2 groups as regards disability and neurological improvement outcomes:

Variable		A group (30)	B group (30)	P value
Parenchymal hemorrhages	+ve	6 (20%)	8 (26.7%)	= 0.544
Mortality rate	+ve	0 (0%)	5 (16.7%)	= 0.02*

Data are expressed as number (%).
* Significant

Table (10): Multiple regression model for the Factors affecting post-infusion (24-h) NIHSS score:

Predictor Factor	β	SE	P
(Constant)	-19.1899		
NIHSS score (baseline)	0.7281	0.1672	0.0001**
aPTT	0.5620	0.2596	0.034*
CT (baseline)	10.5787	4.0146	0.01*

--- excluded from the model if (p value > 0.1) --- **β:** Regression coefficient, SE: Standard error.
* Significant; ** Highly significant

Table (11): Multiple regression model for the Factors affecting post-infusion (30-days) mRS score:

Predictor Factor	β	SE	P
(Constant)	-4.5379		
mRS score (baseline)	0.5950	0.1313	<0.0001**
Hb	-0.4188	0.1802	0.023*

Platelets	0.01106	0.00443	0.015*
FDP	0.5269	0.1622	0.002**
Group= (delayed 3-6 Alteplase usage)	**2.1324**	**0.3424**	**<0.0001****

--- excluded from the model if (p value > 0.1) --- **β:** Regression coefficient, SE: Standard error.
* Significant; ** Highly significant

Table (12): Logistic regression model for the Factors affecting disability occurrence:

Predictor Factor	Coefficient	Std. Error	P value
(Constant)	-27.01437		
mRS score (baseline)	1.84708	0.60918	0.0024**
TLC	2.79639	0.86603	0.0012**
Group= (delayed 3-6 Alteplase usage)	**5.98012**	**1.76356**	**0.0007****

--- excluded from the model if (p value > 0.1). * Significant; ** Highly significant

Table (13): Logistic regression model for the Factors affecting mortality occurrence:

Predictor Factor	Coefficient	Std. Error	P value
(Constant)	-2334673.2		
Age	18466.7	0. 2074	0.032*
Time of onset of symptoms	1778956.8	0.9935	0.043*

--- excluded from the model if (p value > 0.1). ** Highly significant

Table (14): Logistic regression model for the Factors affecting neurological improvement occurrence:

Predictor Factor	Coefficient	Std. Error	P value
(Constant)	27.76991		
mRS score (baseline)	-2.95724	1.14338	0.0097**
Hb	1.90905	0.84630	0.024*
TLC	-5.52252	2.35168	0.018*
Group= (early 0-3 Alteplase usage)	**11.43521**	**4.47185**	**0.01****

--- excluded from the model if (p value > 0.1). * Significant; ** Highly significant

Table (15): Roc-curve of early Alteplase infusion (0-3h), to predict neurological improvement occurrence:

Variable	AUC	SE	Sensitivity (%)	Specificity (%)	P value
Alteplase infusion (0-3h)	0.683	0.0699	86.67	50	0.0087**

ROC (Receiver operating characteristic), AUC= Area under curve, SE= Standard Error.
** Highly significant

By using ROC-curve analysis, early Alteplase infusion (0-3h), predicted patients with neurological improvement, with failed accuracy, sensitivity= 86% and specificity= 50% ($p < 0.05$).

4. Discussion

Our study was a prospective open-label controlled clinical trial was conducted on 60 patients with acute ischemic stroke (AIS); to compare safety and effectiveness of Alteplase given 3-6 hours versus 0-3hours after acute ischemic stroke.

A total of 60 AIS patients, recruited from the department of neurology, Cairo Governorate Hospitals. The duration of the study ranged between 01/10/2017 to 1/6/2018.

- Our primary objective was to evaluate the effectiveness of intravenous alteplase defined as a decrease of 4 points in the 24-hour NIHSS score compared to baseline or the resolution of neurological deficit within 24 hours and its safety by incidence of parenchymal hemorrhages and mortality.

Our secondary objectives were to evaluate Independence assessed by the modified Rankin Scale (mRS), as 'independence' (score from 0 to 1) or 'dependence' (score from 2 to 6).

Regarding demographic data, we found that; the mean age of all patients was (58.41 ± 11.2) years, and the mean BMI was (22.2 ± 3.37). Regarding gender of the patients, the majority (66.7%) of patients were males; while (33.3%) were females. These results came in agreement with **Lees et al., 2010**, who studied time to treatment with intravenous alteplase and outcome in stroke, and reported that, the average

age of patients was 66 years and 60% of them were males **(Lees et al., 2010).**

Regarding risk factors, (48.3%) of patients were smokers, (56.7%) had HTN, (58.3%) had DM, (13.3%) had AF, and only (3.3%) had history of stroke.

In accordance with our results, **Lees et al., 2010**reported that, (57%) had HTN, (19%) had AF, but only (18%) had DM, and a higher history of stroke was reported (15%), compared to our results **(Lees et al., 2010).**

Comparative studies between the 2 groups revealed the following:

Regarding baseline data, we found that, there is non-significant difference as regards age, BMI and sex of the patients, between the 2 groups ($p > 0.05$). These results came in agreement with **Ahmed et al. (2013)**, who did an observational study about the results of intravenous thrombolysis within 4.5 to 6 hours and updated results within 3 to 4.5 hours of onset of acute ischemic stroke recorded in the safe implementation of treatment in stroke international stroke thrombolysis register (SITS-ISTR) **(Ahmed et al., 2013).**

The study found that, there is non-significant difference as regards all risk factors, between the 2 groups ($p > 0.05$) this can be explained by strict application of eligibility criteria. These results came in agreement with **Zhang et al. (2011)**, who reported that, there were no significant differences in age, blood pressure, blood glucose, AF and history of stroke between the groups **(Zhang et al., 2011).**

The study revealed that, there is; highly significant shorter time of onset of symptoms, in group A; compared to group B ($p < 0.01$). These results came in agreement with **Ahmed et al. (2013)**, who reported that, time from stroke onset to treatment as a continuous variable was significantly associated with higher rates of intracranial hemorrhage and poor 3-month outcomeafter adjustment for age and National Institutes of Health Stroke Scale score **(Ahmed et al., 2013).**

Paired comparative studies regarding (A group) revealed the following:

This study revealed that, there is, highly significant decrease in 24-hours post-infusion NIHSS and mRS scores, in A group ($p < 0.01$). This prove effectiveness of alteplase in AIS.

These results came in agreement with **Campbell et al., 2019**, who conducted a systematic review and meta-analysis of individual patient data, and reported, early neurological NIHSS improvement in Alteplase group (28%) versus placebo group (16%) with (P value < 0.0001) **(Campbell et al., 2019).**

Campbell et al. (2019), also reported functional independence (mRS score 0–2) at 3 months was achieved in 76 (36%) of 211 patients in the Alteplase group and 58 (29%) of 199 patients in the placebo group had achieved excellent functional outcome at 3 months (adjusted odds ratio [OR] 1.86, 95% CI 1.15–2.99, p= 0.011) **(Campbell et al., 2019).**

Paired comparative studies regarding (B group) revealed the following:

We found that, there is, highly significant decrease in post-infusion NIHSS score in B group ($p < 0.01$).

We also found that, there is, highly significant increase in post-infusion CT abnormalities, in B group ($p < 0.01$).

We also found that, there is, non-significant difference in post-infusion mRS score, in B group ($p > 0.05$).

These results came in agreement with **Zhang et al. (2011)**, who studied thrombolysis with alteplase 4.5–6 hours after acute ischemic stroke, and reported that, IV thrombolysis in patients with AIS may still be considered up to 6 h after ischemic stroke, but it also provides a less satisfactory result than 0-3 hours alteplase thrombolysis **(Zhang et al., 2011).** This proved that a longer duration of time from stroke onset to treatment, was significantly associated with higher SICH rates and poor3-month outcomes. This emphasizes the value of early treatment, which is well established in randomized controlled trials.

Comparison between the 2 groups as regards pre and post-infusion neurological assessments revealed the following;

We found, significant decrease in NIHSS score in A group; compared to B group; during the post-infusion measurements ($p = 0.026$). These results came in agreement with **Ogata et al. (2013)**, who reported that, the reperfusion rate was increased (62.7% vs 31.7%; P=0.003), and NIHSS score markedly decreased especially after 3-6 h Alteplase infusion **(Ogata et al., 2013).**

In disagreement with our study, **Zhang et al. (2011)** studied 100 patients and, 24-h NIHSS improvement was achieved in 25.9% in A group and 23.8% in B group, with non-significance difference ($p > 0.05$) the possible reason could be selecting patients with similar baseline data **(Zhang et al., 2011).**

Our results disagreed with **Clark et al.,** that reported that, 32% of the placebo and 34% of rt-PA patients had an excellent recovery at 90 days (P =.65). There were no differences on any of the secondary functional outcome measures **(Clark et al., 1999).**

We also found, non-significant decrease in mRS score in A group; compared to B group; during the post-infusion measurements ($p > 0.05$).

In agreement with our study, **Zhang et al. (2011)** studied 100 patients and, after 90 days, 47.6% of the patients in the A group reached independence in

comparison to 44.8% patients in the B group, with non-significance difference (p = 0.840) **(Zhang et al., 2011).**

In disagreement with our study, **Emberson et al. (2014)** conducted a large meta-analysis of individual patient data from randomized trials and found that, treatment within 3.0 h resulted in a good outcome for 259 (32.9%) of 787 patients who received alteplase versus 176 (23.1%) of 762 who received control (OR 1.75, 95% CI 1.35–2.27); delay of greater than3.0 h, up to 4.5 h, resulted in good outcome for 485 (35.3%) of 1375 versus 432 (30.1%) of 1437 (OR 1.26,95% CI 1.05–1.51); and delay of more than 4.5 h resulted in good outcome for 401 (32.6%) of 1229 versus 357 (30.6%) of 1166 (OR 1.15, 95% CI 0.95–1.40) this could be explained by larger sample size and older age **(Emberson et al., 2014).**

Lees et al. (2010) studied the time to treatment with intravenous alteplase and outcome in stroke, and reported that, odds of a favorable 3-month outcome increased as onset to start of treatment (OTT) decreased (p=0.0269) and no benefit of alteplase treatment was seen after around 4.5 h. Adjusted odds of a favorable 3-month outcome were 2.55 (95% CI 1.44–4.52) for 0–1.5 h, 1.64 (1.12–2.40) for 1.5–3 h, 1.34 (1.06–1.68) for 3 – 4.5 h, and 1.22 (0.92–1.61) for 4.5–6 h in favor of the alteplase group this explained by risk of ICH out weight benefits **(Lees et al., 2010).**

Comparison between the 2 groups as regards disability and neurological improvement outcomes revealed the following;

The study revealed that, there is significant decrease in mortality in A group; compared to B group (p = 0.02). These results came in agreement with **Lees et al. (2010)**, who reported that, adjusted odds of mortality increased with OTT (p=0.0444) and were 0.78 (0.41–1.48) for 0–1.5 h, 1.13 (0.70–1.82) for 1.5–3 h, 1.22 (0.87–1.71) for 3–4.5 h, and 1.49 (1.00–2.21) for 4.5–6 h this prove that time is brain **(Lees et al., 2010).**

Our study disagree with **Zhang et al. (2011)** who reported that, the incidence of mortality was 7.1 and 17.2% for the 2 groups, respectively, with non-significance difference (p = 0.228) could be due to racial differences and the patients were younger and blood pressure was lower in the 4.5-6 hours group **(Zhang et al., 2011).**

Our study disagreed with **Campbell et al. (2019)** who reported that, 29 (14%) of 213 patients in the alteplase group and 18 (9%) of 201 patients in the placebo group died (adjusted OR 1.55, 0.81–2.96, p=0.66), with non-significant difference between the 2 groups, But the outcome was significantly better among the patients with alteplase group compared to that of with the placebo group. This could be explained by stroke severity evidenced by high baseline NIHSS **(Campbell et al., 2019).**

Emberson et al. (2014) conducted a large meta-analysis of individual patient data from randomized trials and found that, mortality at 90 days was 608 (17.9%) in the alteplase group versus 556 (16.5%) in the control group (hazard ratio 1.11, 95% CI 0.99–1.25, p=0.07) despite early increases in fatal intracranial haemorrhage, alteplase significantly improves the overall likelihood of a good stroke outcome at 3–6 months.

The proportional benefit increases with earlier treatment and remains statistically significant up to at least 4·5 h after initial stroke symptoms, irrespective of age or stroke severity **(Emberson et al., 2014).**

We also found that, there is non-significant difference as regards parenchymal hemorrhages, between the 2 groups (p > 0.05). These results came in agreement with **Alexandrov et al. (2019)**, who studied safety and efficacy of thrombolysis for acute ischaemic stroke, and reported that, 51 (16%) of 317 patients in the intervention group and 44 (13%) of 329 patients in the control group died (unadjusted OR 1.24, 95% CI 0.8–1.92; p= 0.37) and 83 (26%) and 79 (24%), respectively, had serious adverse events (1.12, 0.79–1.6; p= 0.53) with non-significance difference between the 2 groups **(Alexandrov et al., 2019).**

Alper et al. (2015) found that, the risk of fatal intracranial hemorrhage at seven days was increased (adjusted odds ratio 5.63, 95% CI 2.49 to 12.76, estimated number needed to harm=44). These rounds up to a 2% absolute increase in mortality at seven days could be due to high baseline NIHSS and stroke type **(Alper et al., 2015).**

Lees et al. (2010) reported that, large parenchymal hemorrhage was seen in 96 (5.2%) of 1850 patients assigned to alteplase and 18 (1%) of 1820 controls, with no clear relation to OTT (p=0.4140) contrary to our study in which we selected younger age and low NIHSS **(Lees et al., 2010).**

Ahmed et al. (2013) reported that, the treatment remains safe and effective for patients treated within 3 to 4.5 hours compared with patients treated within 3 hours, but it might be due to non equivalence of the cohorts, particularly the 4.5- to 6-hour cohort relative to the other 2 cohorts There is a risk of potential patient selection bias for treatment beyond the 4.5-hour time window (eg, for patients who are younger or have a less severe stroke). The sample size for the 4.5- to 6-hour cohort is rather small and represents only 1%of the total **(Ahmed et al., 2013).**

Campbell et al. (2019) reported that, symptomatic intracerebral hemorrhage was more common in the alteplase group than the placebo group (ten [5%] of 213 patients vs one [<1%] of 201 patients in the placebo group; adjusted OR 9.7, 95% CI 1.23–

76.55, p=0.031) this in line with NINDS trial which predict risk of ICH by 6%. **(Campbell et al., 2019).**

In disagreement with our study, **Emberson et al. (2014)** conducted a large meta-analysis of individual patient data from randomized trials and found that, Alteplase significantly increased the odds of symptomatic intracranial hemorrhage (type 2 parenchymal hemorrhage definition 231 [6.8%] of 3391 vs 44 [1.3%] of 3365, OR 5.55, 95% CI 4.01–7.70, p<0.0001; SITS-MOST definition 124 [3.7%] vs 19 [0.6%], OR 6.67, 95% CI 4.11–10.84, p<0.0001) and of fatal intracranial hemorrhage within 7 days (91 [2.7%] vs 13 [0.4%]; OR 7.14, 95% CI 3.98–12.79, p<0.0001). The relative increase in fatal intracranial hemorrhage from alteplase was similar irrespective of treatment delay, age, or stroke severity, but the absolute excess risk attributable to alteplase was bigger among patients who had more severe strokes **(Emberson et al., 2014).**

Regression analysis of predictors of un-favorable outcomes shows that;

We found that, the increase in baseline NIHSS score, aPTT and CT abnormalities; had an independent effect on increasing post-infusion 24-h NIHSS score ($p < 0.05$).

We also found that, the increase in baseline mRS score, platelets, and FDP; had an independent effect on increasing post-infusion 30-days mRS score ($p < 0.05$). Also, delayed 3-6 Alteplase usage; had an independent effect on increasing post-infusion 30-days mRS score ($p < 0.01$). While, the decrease in baseline hemoglobin; had an independent effect on increasing post-infusion 30-days mRS score ($p < 0.05$).

These results came in agreement with **Alexandrov et al. (2019)**, who studied safety and efficacy of thrombolysis for acute ischaemic strokes, and reported that, between August, 2013, and April, 2015, 335 patients were randomly allocated to the intervention group and 341 patients to the control group. Compared with the control group, the adjusted cOR for an improvement in modified Rankin Scale score at 90 days in the intervention group was 1.05 (95% CI 0.77–1.45; p= 0.74) **(Alexandrov et al., 2019).**

The study revealed that, the increase in baseline mRS score had an independent effect on increasing the probability of disability occurrence ($p < 0.05$). Also, the delayed 3-6 Alteplase usage, had an independent effect on increasing the probability of disability occurrence ($p < 0.01$).

The increase in age and time of onset of symptoms; had an independent effect on increasing the probability of mortality occurrence ($p < 0.05$).

The previous results came in agreement with **De Brun et al. (2018)**, who studied factors that influence clinicians' decisions to offer intravenous alteplase in acute ischemic stroke patients with uncertain treatment indication, and reported that, seven patient factors were individually predictive of increased likelihood of immediately offering IV alteplase: stroke onset time 2 h 30 min [50 min]; pre-stroke dependency mRS 3 [mRS 4]; systolic blood pressure 185 mm/Hg [140 mm/Hg]; stroke severity scores of NIHSS 5 without aphasia, NIHSS 14 and NIHSS 23 [NIHSS 2 without aphasia]; age 85 [68]; Afro-Caribbean [white] **(De Brun et al., 2018).**

Also, **Gill et al. (2016)** reported that, occurrence of the parenchymal hematoma 2 (PH2) subtype was independently associated with reduced improvement or worsening in the NIHSS score, with an average effect size of 7 points (95% confidence interval −10 to −4, p <.001) **(Gill et al., 2016).**

Regression analysis of predictors of favorable outcomes shows that;

We found that, the decrease in baseline mRS score had an independent effect on increasing the probability of neurological improvement occurrence ($p < 0.05$ respectively).

We also found that, the increase in early 0-3 Alteplase usage; had an independent effect on increasing the probability of neurological improvement occurrence ($p = 0.01$). These results came in agreement with **Alper et al. (2015)**, who reported that, it has already been established that thrombolysis with iv alteplase (rt-PA) is both effective and safe when administered to particular types of patient within 3 h of stroke onset, and that treatment benefit diminishes with increasing treatment delay **(Alper et al., 2015).**

By using ROC-curve analysis, early Alteplase infusion (0-3h), predicted patients with neurological improvement, with poor accuracy, sensitivity= 86% and specificity= 50% ($p < 0.05$).

These results came in agreement with **Liu et al. (2019)**, who studied efficacy at different time points; Group A (2 h), Group B (2-12 h), Group C (12-24 h), and Group D (control), after intravenous thrombolytic therapy with alteplase in patients with acute ischemic stroke, and reported that, the efficacy in Group A was better than that in Group C (P =.006) and Group D (P =.001), but there was no significant difference in the efficacy between Groups A and B (P =.268), and there was no significant difference in the incidence of adverse events among the four groups **(Liu et al., 2019).**

Our study limitations were: Relatively small sample size because other studies showed considerable differences between the 2 group in outcome, which may have limited our ability to detect statistically significant differences between the 2 groups. Sample profile: most hospital in Egypt choose

patients with low NIHSS because of the limited resources. Difficulties in tracking patients after discharge. Lack of proper treatment facilities. Data Collection Process in Egypt is hard for a researcher since we lack computerized filing system.

Conclusion

Our data suggested that, Alteplase infusion therapy within the first 3 hours of stroke onset, convey a great benefit regarding improvement of NIHSS and mRS scores, along with decreased mortality and intracranial hemorrhage rates, as compared with 3-6 hours Alteplase infusion. The 3-6 hours group can benefit from IV thrombolytic by proper selection of patients.

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