Low versus standard dose intravenous alteplase in the treatment of acute ischemic stroke in Egyptian patients

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ABSTRACT

الأهداف: لتقييم نتيجة جرعة منخفضة من التيباز وسلامتها بالمقارنة مع نظام الجرعة القياسية لعلاج السكتة الدماغية الحادة في المرضى المصريين.

المنهجية: أجريت دراسة رصدية استطلاعية غير عشوائية منفردة عمياء خلال الفترة من نوفمبر 2017م إلى ديسمبر 2018م. قسمنا 80 مريضًا مصريًا من مرضى السكتة الدماغية الإقفارية الحادة، مؤهلون للحصول على التيبلاز عن طريق الوريد، إلى مجموعتين (40 مريضًا في كل مجموعة). ظهر تخثر للمرضى بجرعة 0.6 مجم/كجم في المجموعة الأولى و 0.9 مجم/كجم في المجموعة الثانية. قارنا كلا المجموعتين فيما يتعلق بالسلامة والنتيجة. تم التعبير عن السلامة من خلال معدل النزف داخل الجمجمة المصحوب بأعراض (SICH) والوفيات خلال فترة 3 أشهر، والتعبير عن النتيجة من خلال النتائج الإيجابية عند ثلاثة أشهر (مقياس رانكين المعدل[mRS] من 0 إلى 2).

النتائج: في المجموعة الأولى 69.2% (العدد=27) حققوا نتائج إيجابية في 90 يومًا مقارنة بـ 64.1% (العدد=25) في المجموعة الثانية (p=0.631). كان معدل الوفيات لمدة 90 يومًا 5% (العدد=2) في المجموعة الأولى مقابل 2.5% (العدد=1) في المجموعة الثانية (p=0.556). لُوحظ أعراض نزيف داخل الجمجمة في 3 مرضى في المجموعة الثانية وصفر في المجموعة الأولى (p=0.077).

الخلاصة: جرعة منخفضة من التيبلاز يمكن أن تكون بديلاً عمليًا للسكان المصريين المصابين بالسكتة الدماغية الحادة خاصة في فترة تتراوح من 3 إلى 4.5 ساعات.

Objectives: To assess low dose altepase outcome and safety in comparison with a standard-dose regimen for acute ischemic stroke treatment in Egyptian patients.

Materials: An observational prospective cohort non-randomized single blinded study was carried out during the period from November 2017 to December 2018. Eighty Egyptian acute ischemic stroke patients, all eligible for intravenous alteplase, were subdivided into 2 groups (40 patients in each group). Patients were thrombolysed at a dose of 0.6 mg/kg in the first group and 0.9 mg/kg in the second group. Both groups were compared in regard to safety and outcome. Safety was expressed by the rate of symptomatic intracranial hemorrhage (SICH) and 3 months mortality, while outcome was expressed by favorable outcomes at three months (modified Rankin Scale [mRS] of 0 to 2).

Results: In the first group, 69.2% (n=27) achieved favorable outcomes at 90 days compared with 64.1% (n=25) in the second group (p=0.631). Ninety-day mortality was 5% (n=2) in the first group versus 2.5% (n=1) in the second group (p=0.556). Symptomatic intracranial hemorrhage was noted in 3 patients in the second group and zero patients in the first group (p=0.077).

Conclusion: Low-dose alteplase could be a practical alternative for Egyptian populations with acute ischemic stroke especially in 3 to 4.5 hours window.

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Cerebrovascular stroke is the second death and the seventh disability leading cause worldwide.[1] Tissue-type plasminogen activator (tPA) alteplase was the first medication approved by the Food and Drug Administration (FDA) for the acute ischemic stroke (AIS) treatment on June 1996, within 3 hours of stroke onset with a recommended dose of 0.9 mg/kg (maximum 90mg).[2] In 2008, the safety of using alteplase within 3 to 4.5 hours of stroke onset was approved by the Safe

Implementation of Treatments in Stroke International Stroke Thrombolysis Registry (SITS -ISTR)[3] and the European Cooperative Acute Stroke Study (ECASS III).[4] However, thrombolytic therapy use has not been widely adopted, especially in developing countries. The restricted time window (3 to 4.5 hours), intracerebral hemorrhage (ICH) risk and the drug high cost are major obstacles preventing its broad application.[5] Coagulation and fibrinolysis responses differ among different races, which increase symptomatic intracerebral hemorrhage (SICH) risk with standard-dose alteplase[6] in Asian populations, many Asian neurologists considered alteplase low dose to be a better alternative for ischemic stroke treatment. Many studies had been conducted in order to prove the efficacy and safety of Alteplase low dose.[7-9] One of these studies was the Japan Alteplase Clinical Trial (J-ACT) conducted by Yamaguchi et al[10] According to this study, using a 0.6 mg/kg dose of intravenous recombinant tissue plasminogen activator (rtPA) in Japanese patients was safe and effective. Despite the relatively stroke high rate among Egyptian populations, 963/100,000 inhabitants, only less than 1% of stroke patients receive intravenous thrombolysis. A major reason for this is the drug cost.[11,12] Low-dose regimens (0.6 mg/kg) use will lower the economic burden of thrombolytic therapy in the community and will greatly promote the implementation of this therapy in Egypt. Our study aim was to assess the outcome and safety of alteplase low dose in comparison to the standard-dose regimen in AIS treatment in Egypt.

Methods. This study was an observational prospective cohort non-randomized single blinded study done during the period from November 2017 to December 2018. Eighty ischemic stroke patients within four and a half hours from symptom onset were recruited from both El-Mataria Teaching Hospital and Menoufia University Hospital. This study was approvad by the Research and Ethics Committee of the Faculty of Medicine, Menoufia University. All patients were considered eligible for intravenous thrombolysis according to the American Heart Association (AHA) and American Stroke Association (ASA) guidelines with inclusion criteria which are: age ≥18 years old, time window ≤4.5 hours, patients presented with moderate to severe symptoms and demonstrate early improvement before starting alteplase, patients with seizures at time of onset if evidence suggests that residual impairment is secondary to stroke and not a postictal phenomenon, patients with blood pressure ≤185/ 110 or those who presented with high blood pressure and responded successfully to intravenous antihypertensive and patients with early ischemic changes (other than obvious hypodensity) as demonstrated on initial non-contrast CT brain.[13] Informed written consent forms for alteplase were signed by patients or first-degree relatives. All patients were subjected to complete history taking, including assessment of vascular risk factors, previous treatment, time window, pre-stroke modified Rankin Scale (mRS), and initial stroke severity measured as a National Institutes of Health Stroke Study (NIHSS) score. Non-contrast computed tomography (CT) brain scans were done in all patients upon presentation, and these scans were analyzed for the presence of intracranial hemorrhage or any findings preventing thrombolysis. Alberta Stroke Program Early CT (ASPECT) scores were used to assess early signs of ischemia.[14] Trial of ORG 10172 in acute stroke treatment (TOAST)[15] and Oxfordshire community stroke project (OCSP)[16] classifications to clarify stroke subtypes. The patients were assigned to treatment groups non-randomly. The first group was given a single dose of intravenous alteplase as a low dose of 0.6 mg/kg (not exceeding 60 mg), with 10% given as a bolus followed by a continuous infusion of the remainder over one hour. We give the low dose to patients who are more risky to haemorragic transformation as old age, when we suspect large infarction and those with time window more than 3h and less than 4.5 h. The second group was given a standard dose of 0.9 mg/kg (not exceeding 90 mg), with 10% given as a bolus followed by a continuous infusion of the remainder over one hour. Alteplase infusion and monitoring for complications over the next 24 hours were done following AHA/ASA guidelines.[13] Follow-up non-contrast CT brain scans 24 hours post treatment were assessed for ICH. The NIHSS was assessed 24 hours after treatment and at day seven of admission or at discharge. In-hospital mortality was recorded. All patients were followed-up with 90 days from admission by telephone calls or face-to-face interviews to assess mRS and mortality.

Primary objectives. 1) Assessment safety of low-dose and standard-dose alteplase by assessing the incidence of symptomatic intracranial hemorrhage (SICH) within 24 hours of starting treatment and assessing mortality (in-hospital mortality and 90-day mortality). We defined SICH according to the ECASS study definition (any hemorrhage plus a neurological deterioration of ≥ 4 points from the NIHSS baseline or from the lowest

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NIHSS value after baseline for seven days, or leading to death).[4]

2) Assessment of outcome of low-dose and standard-dose alteplase by assessing the proportion of patients with favorable outcomes (mRS scores of 0 to 2) and unfavorable outcome (mRS scores of 3 to 6) at 90 days.

Secondary objectives. An assessment was made regarding predictors of favorable outcomes (mRS scores of 0 to 2).

Statistical methods. Results were collected, tabulated, and statistically analyzed by IBM personal computer and the Statistical Package for the Social Sciences (SPSS) version 22 (Armonk, NY: IBM Corp, 2013). Data were presented as descriptive statistics including percentage (%), mean (x), standard deviation (SD), and range. Statistical tests used included the Chi-square test ($\chi 2$), the Student's t-test, the Mann-Whitney test, the Wilcoxon Signed Rank test, and binary

Table 1 - Demographic and baseline characteristics of patients treated with IV tissue-type plasminogen activator (tPA) in low dose and standard dose groups.

Items	Low dose (n=40)	Standard dose (n=40)	Total (n=80)	χ^2	*P*-value
Age Mean± SD	60.58±14.16	61.03±8.49	60.80±11.60	t=0.17	0.864
Gender					
Males	22 (55.0)	30 (75.0)	52 (65.0)	χ^2 =3.52	0.061
Females	18 (45.0)	10 (25.0)	28 (35.0)		
Current smokers	16 (40.0)	21 (52.5)	37 (46.3)	1.26	0.262
Hypertension	26 (65.0)	26 (65.0)	52 (65.0)	--	--
Diabetes mellitus	19 (47.5)	12 (30.0)	31 (38.8)	2.58	0.108
Dyslipidemia	14 (35.0)	15 (37.5)	29 (36.2)	0.49	0.485
Previous stroke	5 (12.5)	4 (10.0)	9 (11.3)	0.13	0.723
AF	12 (30.0)	6 (15.0)	18 (22.5)	2.58	0.108
IHD	12 (30.0)	13 (32.5)	25 (31.3)	0.06	0.809
NIHSS on admission (Mean± SD)	12.58±4.37	14.03±4.17	13.30±4.31	t=1.52	0.133
Time to treatment (hours)					
0-3	4 (10.0)	39 (97.5)	43 (53.8)	χ^2=61.60	<0.001*
3-4.5	36 (90.0)	1 (2.5)	4 (5.0)		
Previous treatment					
Antiplatelet drugs	12 (30.0)	3 (7.5)	15 (18.8)	3.22	0.023*
Warfarin anticoagulant	4 (10.0)	2 (5.0)	6 (7.5)	0.72	0.396
Prestroke mRS	34 (85.0)	35 (87.5)	69 (86.0)	0.88	0.644
Score 0	2 (5.0)	3 (7.5)	5 (6.0)		
Score 1	4 (10.0)	2 (5.0)	6 (7.5)		
Score 2					
Early signs of ischemia	6 (15.0)	4 (10.0)	10 (12.5)	0.46	0.499
ASPECT score (Mean±SD)	6.83±3.09	5.55±2.59	6.19±2.90	U=2.00	0.049*
TOAST classification	12 (30.0)	7 (17.5)	19 (23.8)	1.73	0.189
Cardio embolic	18 (45.0)	14 (35.0)	32 (40.0)	0.83	0.361
Lacunar	14 (35.0)	9 (22.5)	23 (28.8)	1.53	0.217
Large artery	0	1 (2.5)	1 (1.3)	1.01	0.314
Other determined	1 (2.5)	4 (10.0)	5 (6.3)	1.92	0.166
Undetermined					
Oxfordshire classification	14 (35.0)	15 (37.5)	29 (36.3)	0.05	0.816
LACI	13 (32.5)	16 (40.0)	29 (36.3)	0.49	0.485
PACI	8 (20.0)	0	8 (10.0)	8.89	0.003*
POCI	5 (12.5)	9 (22.5)	14 (17.5)	1.39	0.239
TACI					

Values are presented as number and percentage (%).
AF - atrial fibrillation, IHD: ischemic heart disease, NIHSS: National Institute of Health Stroke Scale, mRS - modified rankin scale, ASPECT - Alberta Stroke Program Early CT Score, U - Mann-Whitney test, TOAST - Trial of ORG 10172 in Acute Stroke Treatment, LACI - lacunar infarction, PACI - partial anterior circulation infarction, TACI - total anterior circulation infarction, POCI - posterior circulation infarction

Table 2 - Comparison between low dose and standard dose Alteplase treated acute ischemic stroke patients regarding hemorrhagic transformation after treatment.

Items	Low dose (n=40)	Standard dose (n=40)	Total (n=80)	χ^2	*P*-value
Hemorrhagic transformation	1 (2.5)	5 (12.5)	6 (7.5)	2.88	0.090
Symptomatic ICH	0	3 (7.5)	3 (3.8)	3.12	0.077
Asymptomatic ICH	1 (2.5)	2 (5.0)	3 (3.8)	0.35	0.556
Parenchymal hemorrhage 1	1 (2.5)	2 (5.0)	3 (3.8)	0.35	0.556
Parenchymal hemorrhage 2	0	3 (7.5)	3 (3.8)	3.12	0.077

Values are presented as number and percentage (%). ICH - intracranial hemorrhage

Table 3 - Comparison between low dose and standard dose Alteplase treated acute ischemic stroke patients regarding their outcome of treatment assessed by modified rankin scale (mRS) at 3 months and prevalence of deaths.

Items	Low dose (n=40)	Standard dose (n=40)	Total (n=80)	χ^2	*P*-value
Outcome					
Favorable	27 (67.5)	25 (62.5)	52 (65.0)	0.23	0.631
Death					
In hospital	1 (2.5)	1 (2.5)	2 (2.5)	--	---
Within 3 months	2 (0.5)	1 (2.5)	3 (3.8)	0.35	0.556
Overall deaths	3 (7.5)	2 (5.0)	5 (6.3)	0.21	0.644

Values are presented as number and percentage (%). Favorable outcome: mRS from 0-2

Table 4 - Binary logistic regression analysis for predictors of favorable outcome at 3 months.

Variables	B	P-value	OR	95% CI	
				Lower	Upper
Age	-0.041	0.347	0.960	0.881	1.046
Gender (male)	1.209	0.307	3.352	0.329	34.195
DM	1.032	0.288	2.806	0.418	18.845
HTN	-1.098	0.143	0.333	0.077	1.449
Smoking	0.037	0.972	1.038	0.130	8.312
Dyslipidemia	-1.364	0.094	0.256	0.052	1.260
Previous stroke	0.535	0.804	1.707	0.025	115.316
AF	20.969	1.000	127.287	0.000	-
IHD	-0.081	0.929	0.923	0.157	5.429
Single antiplatelets	2.592	0.082	13.360	0.718	248.528
Double antiplatelets	0.503	0.783	1.654	0.046	59.316
Anticoagulant	-0.953	0.549	0.386	0.017	8.686
Time window 3 hours	2.271	0.089	9.684	0.707	132.667
tPA (0.9)	-0.912	0.504	0.402	0.028	5.824
NIHSS (≤13)	-2.338	0.018	0.097	0.014	0.673
Sign ischemia (1)	1.821	0.129	6.179	0.587	65.051
Old stroke	-1.867	0.334	0.155	0.004	6.800
TOAST (cardioembolic)	-18.096	1.000	0.000	0.000	-
TOAST (lacunar)	24.512	0.999	44183383884.966	0.000	-
TOAST (large artery)	3.084	0.151	21.849	0.326	1463.972
TOAST(other determined)	-19.249	1.000	0.000	0.000	-
Oxford (LACI)	-21.197	0.999	0.000	0.000	-
Oxford (PACI)	1.897	0.179	6.666	0.419	106.126
Oxford (POCI)	-19.361	0.999	0.000	0.000	-
Symptom Hg	-20.131	0.999	0.000	0.000	-

B - beta coefficient, OR - odd's ratio, CI - confidence interval, ICH - intracranial hemorrhage, DM - diabetes mellitus, HTN - hypertension, AF - atrial fibrillation, IHD - ischemic heart disease, NIHSS - National Institute of health stroke scale, TOAST - Trial of ORG 10172 in Acute Stroke Treatment, LACI - lacunar infarction, PACI - partial anterior circulation infarction, POCI - posterior circulation infarction, tPA - Tissue-type plasminogen activator

logistic regression. A *p*-value of <0.05 was considered statistically significant.

Results. Half of the study population (40 patients) received a standard dose of alteplase (0.9 mg/kg) and another 40 patients received a low dose (0.6 mg/kg). Basal characteristics of both groups are shown in (**Table 1**). The mean age of the study population was 60.80±11.60 years, with male predominance in both groups. There was no significant difference between the low and standard-dose groups regarding vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, ischemic heart disease, or history of previous cerebrovascular stroke). Hypertension was the most prevalent risk factor in both groups (65% in each). There was no significant difference regarding patients number taking warfarin anticoagulant in both groups (*p*=0.396). The initial stroke severity (assessed by National Institute of health stroke scale [NIHSS][17]) did not significantly differ between both groups, with a moderate stroke severity prevalent in both the low and standard-dose groups (12.58±4.37 versus 14.03±4.17 respectively, *p*=0.133).

Thirty-six patients (90%) in the low-dose group received alteplase between 3 and 4.5 hours of stroke onset, while 97.5% (n=39) of the standard-dose group received alteplase within 3 hours of stroke onset (*p*<0.001). Pre-stroke modified Rankin Scale (mRS) scores ranged from 0 to 2, with most patients of both groups having pre-stroke mRS scores of 0 (86%).

Regarding stroke subtypes, there was a significantly higher percentage of patients with posterior circulation infarction (POCI) in the low-dose group (20%), while no cases of POCI were present in the standard-dose group (*p*=0.003).

There was a significantly higher mean value for the Alberta Stroke Program Early CT (ASPECT) scores in the low-dose group than in the standard-dose group (6.83±3.09 versus 5.55±2.59, *p*=0.049).

Regarding outcome, favorable outcomes (mRS scores of 0 to 2) at 3 months were recorded in 67.5% of the low-dose group versus 62.5% of the standard-dose group (*p*=0.631).

Alteplase dose was not a significant predictor of favorable outcome (OR=0.402, *p*=0.504, 95% CI 0.028-5.824). The only significant predictor of a favorable outcome at 3 months was a NIHSS score ≤13. For each one-degree decrease in NIHSS, there was a 2.338 degree increase in favorable outcomes (OR=0.097, *p*=0.018, 95% CI (0.014-0.673)).

Regarding safety, no cases of SICH were found in the low-dose group. In comparison, 3 cases (7.5%) were found in the standard-dose group (*p*=0.077). The overall rate of hemorrhagic transformation was 2.5% in the low-dose group versus 12.5% in the standard-dose group. Three cases were parenchymal hemorrhage type 1 (lesion occupying <30% with no mass effect) and 3 cases were parenchymal hemorrhage type 2 (lesion occupying > 30% with definite mass effect) (**Table 2**).

Mortality at 3 months was 5% in the low-dose group versus 2.5% in the standard-dose group (*p*=0.556). Only 2 patients died in the hospital (one from each group) (**Table 3**).

Discussion. Low-dose alteplase use in treating acute ischemic stroke is not common in Egypt. This study demonstrated the results of thrombolysis with a low dose in a sample of the Egyptian population. The time from stroke onset to thrombolysis was strikingly different between the low and standard-dose groups. In the low-dose group, 90% of patients were thrombolysed between 3 and 4.5 hours of stroke onset, while 97.5% of the standard-dose group patients were thrombolysed within 3 hours of stroke onset. The extended time window (3 to 4 and a half hours) in the low-dose group was a strong rationale for using low-dose alteplase, as the increased time could increase hemorrhagic transformation risk. This was evidenced by Wahlgren et al[3] and Hacke et al,[4] who recorded the standard dose efficacy in the extended window (3 and 4.5 hours) but found SICH higher risk in comparison to a 3-hour window (2.2%-2.4% versus 1.7%).

In most of the studies comparing low and standard alteplase doses, favorable outcome was considered with a modified Rankin Scale score of 0 to 1 and a score of 0 to 2 represented functional independence. In the current study, a favorable outcome was considered with a score of 0 to 2 at 3 months. Our justification was that with scores of 0 to 2, the patient achieves a state of functional independence, which is considered a good outcome.

In the current study, 67.5% of patients in the low-dose group had favorable outcomes at 3 months in comparison to 62.5% of the standard-dose group patients, with no significant difference between both groups. This finding is consistent with the results of Kim et al,[17] who found that 45.5% (n=450) of patients who received low-dose alteplase achieved mRS scores of 0 to 2 at 3 months in comparison to 49% (n=1,076) of the standard-dose group. In addition, Chao et al,[19] who studied different doses of alteplase for acute stroke in Chinese patients (0.6, 0.7, 0.8, and 0.9 mg/kg), demonstrated that patients with mRS scores of 0 to 2 at 3 months included 53% (n=146) of the low-dose (0.6

mg/kg) group and 47% (n=367) of the standard-dose group (0.9 mg kg).

In the current study, a binary logistic regression analysis for predictors of favorable outcomes at 3 months revealed that an NIHSS score of ≤13 was the only significant predictor of a favorable outcome at 3 months, and that for each one-degree decrease in NIHSS scores, there was a 2.338-degree increase in favorable outcomes (OR=0.097, *p*=0.018, 95% CI: 0.014 to 0.673) (**Table** 4). This result goes with Chao et al[19] who stated that an NIHSS score ≤8 was an independent predictor of a good outcome after intravenous alteplase (OR=0.37, *p*=0.0001, 95% CI). The different values of NIHSS scores could be explained by the different scores of favorable outcomes considered - an mRS score of 0 to 1 in Chao et al[19] study versus a score of 0 to 2 in the current study.

This analysis revealed that the dose of alteplase was a non-significant predictor of stroke outcome at 3 months (OR=0.402, *p*=0.504, 95% CI: 0.028 to 5.824). No patients developed SICH in the low-dose group, in comparison to 3 cases developed (7.5%) in the standard-dose group. This result agrees with Anderson et al,[20] in which fewer major SICH occurred in the low-dose group than in the standard-dose group (1% versus 2.1%). The difference in patients percentage that developed SICH in this study versus the study of Anderson et al[20] might be the result of SITS-MOST criteria use for SICH in the latter study. In addition, Chao et al[19] showed that there was no difference between their 2 treatment groups regarding SICH according to the ECASS definition (5% in both).

Nguyen et al,[21] in their comparative study between low-dose and standard-dose alteplase in Vietnam, also documented no difference in the occurrence of SICH (per the ECASS definition) in their standard-dose group compared with their low-dose group (5% versus 2%).

Kim et al[18] also reported that no statistically significant differences in the incidence of SICH between their standard-dose and low-dose groups (6% versus 8%).

There were no significant differences between low-dose and standard-dose groups regarding mortality at 3 months: there were 2 cases in the low dose group versus one case in the standard-dose group (5% versus 2.5%, *p*=0.556). Most of the studies that compared low and standard rt-PA doses have been compatible with our present study result showing no significant difference between the 2 doses regarding the 3 months mortality. Kim et al,[18] found that there was no significant difference between the low dose and standard dose (13% versus 14%). Chao et al[19] documented a 3 months mortality of 8% in both 0.6 and 0.9 mg/kg groups. Sharma et al,[22] in Singapore documented that there was no significant difference in the 3 months mortality between low and standard doses (10% versus 13%). Anderson et al[20] also showed that mortality at 90 days did not differ significantly between the 2 groups (8.5% and 10.3%).

Yang et al[23] studied a comparison between the 2 groups where the mortality in the 0.6 mg/kg dose group had a non-significantly higher incidence than that of the standard-dose group (4.3% versus 1.6% in the 0.9 mg/kg dose group, *p*=0.792). The mortality in the 0.6 mg/kg dose group was higher than that in the 0.9 mg/kg dose group (4.3% versus 1.6%, respectively; *p*>0.05)

Nguyen et al[21] was the only study to show a significant difference in the mortality rate at 3 months, mortality rates of 2% in the low-dose group and 12% in the standard-dose group.

Study limitations. First, the sample size was small because of the following factors: public awareness of stroke symptoms and the relevant time window is still deficient in our region, so many stroke patients arrive at the hospital after the thrombolytic window. In addition, thrombolytic therapy was recently introduced to our center in 2017 at a high cost (which is still not covered by health insurance), so many patients cannot afford it. Some other studies recruited small numbers of patients, like Nguyen et al[21] who included 48 in the low-dose group versus 73 standard-dose patients; Sharma et al,[22] who included 48 low-dose patients versus 32 patients receiving the standard dose; and Zhou et al[24] who included 23 patients receiving a low dose). Second, the alteplase dose selection was not randomized. Also, both groups were not balanced regarding to ASPECTS score and POCI. Finally, the stroke team that conducted the outcome assessments was not blinded to the treatments, raising the possibility of observer bias.

In conclusion, the present study showed that there was no statistically significant difference between low and standard alteplase doses regarding either safety or outcome. Taking into consideration the economic burden of the treatment, low-dose alteplase (0.6 mg/kg) could be a practical alternative for Egyptian populations with acute ischemic stroke especially in 3-4.5 hours window. This study compares between different doses of alteplase in acute ischemic stroke treatment in a big country like Egypt where utilization of reperfusion therapies for stroke remains <1% Zakaria et al[25] Therefore, additional confirmation with randomized controlled trials in Egyptian patients is necessary.

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