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Research Article

Efficacy and Safety of Alteplase on Treatment of Acute Single Small Subcortical Infarction

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Abstract

Background: The 20% to 30% of SSSI patients were reported to have END in the acute phase which brought long-term adverse effects. The efficacy of alteplase treatment on SSSI is ambiguous.

Objective: To find the efficacy and safety of alteplase in prevention of END and on achieving favorable outcome at 3 months on SSSI patients as compared to patients who received standard medical care.

Method: The patients were retrospectively screened to find efficacy and safety alteplase, patients were dichotomized into alteplase and standard medical care groups. Propensity score matching was done, primary outcome was favorable functional outcome at 3 months defined by attaining score of ≤ 2 mRS, secondary outcome was prevention of occurrence of END defined by an increase of ≥ 2 points in total score or ≥ 1point on motor subunit in the NIHSS score within 72 hour of symptoms onset, safety features were sICH or death.

Results: Pre-match and post-match data showed that alteplase group showed higher proportion of good outcomes than medically treated group at 3 months follow-up [OR=0.36, 95% CI (0.13,0.92), p-0.040], [OR=0.35, 95% CI: 0.12, 0.90, P-0.035] respectively but did not reduce the incidence of END compared to medically treated group [OR=1.21, 95% CI: 0.58, 2.52, P-0.618], [OR=0.99, 95% CI: 0.43-2.26, P-0.974] respectively. There was one case of asymptomatic ICH in alteplase treated patients and no death.

Conclusion: Patients with SSSI in anterior circulation who were treated with alteplase achieved 3 months favorable outcomes than those who were treated with standard medical care; however treatment with alteplase may not prevent occurrence of END.

Keywords: Single small subcortical infarction; Early neurological deterioration; Small vessel disease; Modified rankin scale

Introduction

Single Small Subcortical Infarction (SSSI) is an isolated small infarction in the territory of perforating artery with a maximum diameter of less than 20 mm in axial Diffusion-Weighted Imaging (DWI), SSSI was traditionally considered to be a stroke subtype of relatively favorable prognosis, however about 20% to 30% of SSSI patients were reported to have Early Neurological Deterioration (END) in the acute phase which brought adverse effects on long-term outcome [1]. The END is a common event that occurs in 13% to 40% of acute strokes and approximately 33% to 51% of intracerebral hemorrhages and is associated with severe prognosis [2-8]. Alteplase has been recommended as the most important treatment for ischemic stroke worldwide; however, most of the previous studies excluded the patients with SSSI which were regarded as minor strokes. The effect of the alteplase on the outcome of SSSI, especially END and long-term outcome was ambiguous, alteplase therapy on SSSI which occurs as a result of occluded small perforating vessels in which the thrombosis in its pathophysiology is uncertain, and consequently, researchers have questioned whether these types of lacunar strokes would benefit from clot-dissolving pharmacological treatment of alteplase. Studies have conflicting results regarding treatment of ischemic strokes with some suggesting that similar benefit may be achieved regardless of ischemic stroke subtypes [9-13], others show benefit in either short or long outcomes [14-18] while other studies showed detrimental effects by causing asymptomatic or Symptomatic Intracerebral Hemorrhage (ICH/Sich) which may be associated with END and early death. A recent review of a variety of trials shows END in alteplase treated patients is 13% of all cases, of those 21% are caused by sICH [9,11,17,19,20]. So, in this study, we aimed at finding how does alteplase affect END and 3 months functional outcome in SSSI patients.

Methods

Subjects

The patients were retrospectively screened from a stroke registry of the neurology department of the 1st Affiliated Hospital of Zhengzhou University from January 2013 to December 2020. All patients with the presence of SSSI from anterior circulation presented with the following inclusion criteria: (1) Maximum diameter ≤ 20 mm in the penetrating arteries with a rounded, ovoid, or tubular shape on axial DWI /ADC map, (2) Patients with 18 years of age or above, (3) Patients treated within 4.5 hours of symptoms onset with alteplase or antithrombotic drugs.

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Patients were excluded if : (1) Images were of poor qualities, (2) Potential or confirmed source of cardio-aortic embolism or ipsilateral carotid artery stenosis ≥ 50%, (3) All key medical records in the entire course of treatment and follow up could not be retrieved, (4) Primary diagnosis or its confirmation did not involve MRI sequences, (5) They had a tumor or other known systemic diseases which could have compromised long term outcome of the patient, (6) Patients showed symptoms progression before MRI was done, (7) Pre admission mRS>1, (8) Relatives or legal surrogates declined consent (Figure 1). Because the study was retrospective observational, we maintained the anonymity of all data before being accessed. The study followed the principles of the declaration of Helsinki (WHO, 2001), and study approval was granted by the ethics committee of the First Affiliated Hospital of Zhengzhou University. Informed consent was acquired from all patients.

Outcomes

The primary outcome was favorable functional outcome at 3 months after stroke onset measured by attaining score of ≤ 2 points on the mRS, secondary outcome was prevention of occurrence of END defined as an increase of ≥ 2 points in total score or ≥ 1 point on motor subunit in the NIHSS score within 72 hour of symptoms onset and safety features were occurrence of sICH and early death within 72 hours of stroke onset.

Data collection

Patients' key demographic data, risk factors, baseline clinical characteristics recorded at the time of admission, important laboratory results, imaging results which correlate with SSSI as well as treatment history of other medical conditions and medications that were given during treatment or before treatment were recorded. Stroke severity scores were measured using the NIHSS. MRI and CT sequences were done before either treatment and follow-up CT or MRI was done after the first 24 hours post-admission or earlier if signs of neurological worsening were seen. Patients were followed up closely for the first 72 hours for any change of symptoms as per hospital protocol; all patients were assessed using NIHSS on admission. NIHSS scores were recorded after every 12 hours until 72 hours mark by two certified physicians who were blinded to the clinical information of the patients. Senior neurologists were consulted whenever there were controversies or unclear clinical assessments findings and consensus were reached before the final assignment of scores. Patients were followed up for an average of 3 months after discharge.

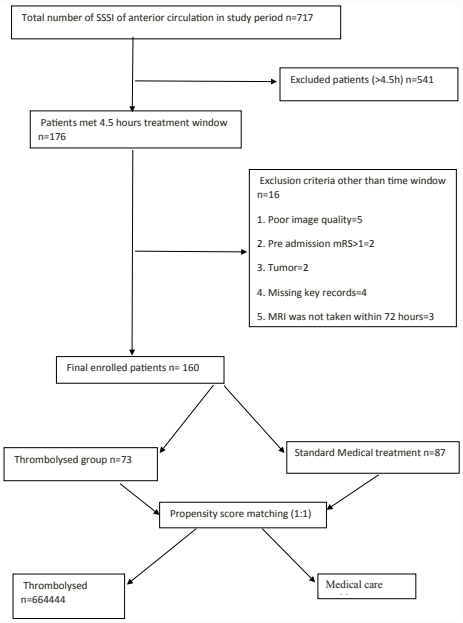

Figure 1: Flowchart of selection of eligible study subjects.

Definitions

Hypertension was defined as documentation of two or more blood pressure measures of 140/ 90 mmHg or higher or the use of antihypertensive drugs. Modified Rankin Scale is scale which assesses clinical disability of stroke patient, it has 6 points (1-6) according to clinical severity as follows: 6-Dead, 5- Severe disability; bedridden, incontinent and requiring constant nursing care and attention 4-Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 3- Moderate disability; requiring some help, but able to walk without assistance 2-Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 1-No significant disability despite symptoms; able to carry out all usual duties and activities 0-No symptoms at all. NIHSS scores are scores which provides a quantitative measure patient's stroke-related neurologic deficit and it ranges from 1-42 points.

Diabetes mellitus was defined as the use of glucose-lowering agents or measurements serum glucose levels of more than 11.1 mmol/L, at least twice on a 2-hours oral glucose tolerance test. Hyperlipidemia was defined as the use of cholesterol-lowering agents, Total Cholesterol (TC) level of 5.2 mmol/L or higher, or Triglyceride (TG) level of 1.7 mmol/L or higher. Smoker was defined as 1 or more cigarettes per day for 6 months or more. Alcoholism was defined as more than 2 bottles per day for men or more than 1 bottle per day for women.

Imaging assessment

All patients underwent MRI (Siemens 1.5/3.0 T MRI scanner, AG, Munich, Germany) scanning withT1-weighted imaging (T1WI), T2-weighted imaging (T2WI), Fluid-Attenuated Inversion Recovery (FLAIR), and Diffusion-Weighted Imaging (DWI) and MR-angiography sequences and with CT (Non-Contrast CT, CT-angiography) sequences for lesions assessment as per inclusion criteria. The SSSI was diagnosed by two neurologists (GY and BS) with more than 5 years of diagnostic experiences (Figure 2). If there were controversies in their diagnoses, another senior neurologist was consulted for the final decision.

Statistical analysis

Quantitative data were presented with means and standard deviation or median [IQR] and comparisons were made using the Student t-test or Mann-Whitney U test. The continuous data were expressed by frequency or percentage and compared using a chi-square test. Selection bias effects were minimized by performing propensity score matching analysis. Matching factors included all unbalanced variables ($P \leq 0.1$). One-to-one nearest-neighbor matching with a caliper of 0.1 was used to create two matched groups and probability value $P<0.05$ was considered statistically significant. Multivariate logistic regression analysis was performed using data with $p<0.1$ in univariate analysis. Outcomes were the unadjusted Odds Ratio (OR) for END and favorable outcome (mRS score, 0-2 point), using binary logistic regression analysis to assess the odds ratio and its 95% Confidence Interval (CI). Data were analyzed using

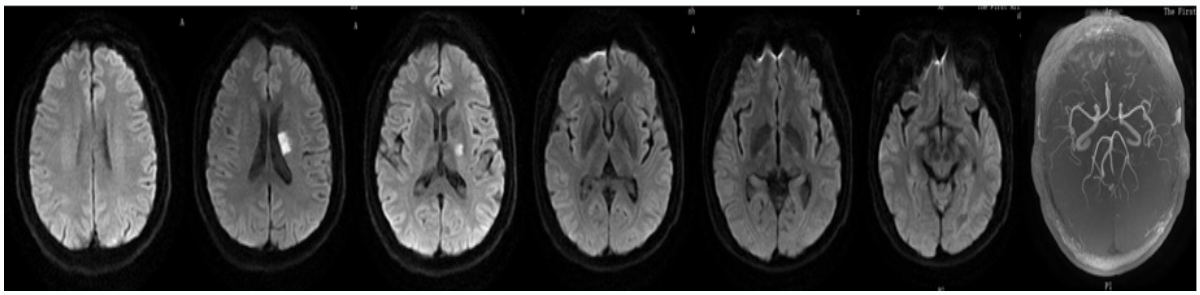

Figure 2: The lesions appearance in axial sections in the lenticulostriate artery region on the DWI sequence.

SPSS 26.0 software (IBM, Armonk, NY, USA).

Results

Baseline characteristics

A total of 717 patients were diagnosed with anterior circulation SSSI from January 2013 to December 202. Of those 717 patients, 176 arrived within 4.5 hours from symptoms onset however, only 160 met the inclusion criteria as per Figure 1. Of 160 patients, 73 (45.63%) patients were treated with alteplase and 87 (54.37%) patients received standard medical treatment. Male and female patients were 112 (70%) and 48 (30%) respectively. Unmatched and matched sets of demographic and clinical characteristics were presented in Table 1. Glycosylated hemoglobin (HbA1c) percentages levels on unmatched cohort were 5.87 ± 1.29 on Alteplase group *vs.* 6.38 ± 1.34 on medical treated group with p-value of 0.014 while on matched cohort it was 5.94 ± 1.31 on alteplase-treated group *vs.* 6.14 ± 1.15 medical treated group with p-value of 0.353 hence there are significant higher percentage of glycosylated hemoglobin in medically treated patients in original cohort. Baseline NIHSS (IQR) on unmatched cohort was 4 (2.6) on alteplase treated group *vs.* 3 (1.4) on medically treated group with p-value of <0.001 while in matched cohort it was 4 (2.5) on alteplase treated group *vs.* 3 (2.5) on medically treated group with p-value of 0.092, this showed patients treated with alteplase in original cohort had significant higher baseline NIHSS score (Table 1). Other parameters with no significant findings were summarized in Table 1.

Unmatched baseline characteristics

In risk factors assessment, hypertension on END outcomes showed to be 35 (85.4%) in the END group *vs.* 76 (63.9%) of non-END group with a p-value of 0.017 while at 3 months outcomes showed 27 (87.1%) in the unfavorable group *vs.* 84 (65.1%) in a favorable group with a p-value of 0.030, these results show that hypertension is statistically significant risk for in both END and unfavorable outcome at 3 months in original cohort. History of stroke on END outcome was seen in 13 (31.7%) of the END group *vs.* 38 (31.9%) of non-END group with a p-value of 1.000 while on 3 months outcome was seen in 15 (48.4%) unfavorable group *vs.* 36 (27.9%) of the favorable group with a p-value of 0.047, these results show that stroke history is statistical significance risk for unfavorable at 3 months in original cohort (Table 2). Other variables which showed no significant influence on either END or 3 months outcomes on this unmatched cohort have been shown in Table 2.

Effect of treatment on outcomes in unmatched

A total of 129 [80.63%] patients had favorable functional outcomes at 3 months, of which 64 (87.7%) were in thrombolysed group and 65 (74.4%) in unthrombolysed group (Table 3). A total of 41 (25.63%) patients suffered END, 20 (27.4%) in the thrombolysed group, and 21 (24.1%) from unthrombolysed (Table 3). When multivariate logistic regression analysis was run on an unmatched cohort, we found END outcome had an adjusted odds ratio (OR)(95% CI) of 1.21 (0.58,2.52) with a p-value of 0.618 and mRS scores of ≤ 2 at 3 months had an adjusted OR (95% CI) of 0.36 (0.13,0.92) with a p-value of 0.040, therefore, there was a statistically significant association between treatment with alteplase and favorable functional outcome at 3 months (Table 3).

No death or symptomatic intracranial hemorrhage was seen on patients who had END or at 3 months on either of the treatment modalities taken (Table 3).

Also, in multiple regression analysis, we found that hypertension had an adjusted OR (95% CI) of 3.14 (1.28, 8.89), p-value-0.019 on END study outcome, these results show that hypertension is statistically significant independent predictor of END.

Matched baseline characteristics on END and at 3 months outcomes

Baseline demographic and clinical characteristics of the matched cohort showed. Hypertension on END outcomes was in 28 (87.5%) of the END group *vs.* 65 (65.0%) of non-END group with a p-value of 0.027 while at 3 months outcome was seen in 21 [87.5%] of those with an unfavorable group *vs.* 72 (66.7%) in a favorable group with a p-value of 0.076, this shows that hypertension is a statistically significant risk for development of END. Diabetes mellitus on END outcomes was in 9 (28.1%) of the END group *vs.* 22 (22.0%) of non-END group with a p-value of 0.637 while at 3 months outcome was seen in 10 (47.7%) of the unfavorable group *vs.* 21 (19.4%) of the favorable group with a p-value of 0.040, these results show statistically significant that diabetes mellitus is a risk for developing unfavorable functional outcome at 3 months. Glycosylated hemoglobin (HbA1c) percentages levels on END outcomes were 6.05 ± 0.97 in END group *vs.* 6.04 ± 1.31 in non-END group with p-value of 0.972 while it was 6.59 ± 1.46 in unfavorable group *vs.* 5.92 ± 1.15 in favorable group with p-value of 0.044 at 3 months outcomes, this showed that higher percentage of glycosylate hemoglobin is a statistically significance risk of having unfavorable outcomes at 3 months (Table 4). Other variables with statistically insignificant influence on outcome are listed in Table 4.

Effects of treatment on outcomes in matched cohort

On propensity score-matched cohort showed that alteplase treated patients, 16 [50%] suffered END *vs.* 50 [50%] who had no END with a p-value of 1.000 while at 3 months outcome 7 [29.2%] had unfavorable *vs.* 59 [54.6%] had favorable functional outcome with a p-value of 0.042 a result which shows alteplase treated had statistically significant favorable functional outcome at 3 months (Table 4).

Table 1: The demographics and clinical characteristics.

Variables	Unmatched Cohort			Matched Cohort		
	Alteplase (n=73)	Medical (n=87)	P-value	Alteplase (n=66)	Medical (n=66)	P-value
Demography						
Age(years), mean ± SD,	56.9 ± 12.6	57.7 ± 14.2	0.71	57.3 ± 13.1	56.7 ± 12.9	0.8
Male, n=(%)	50 (68.5%)	62 (71.3%)	0.835	44 (66.7%)	46 (69.7%)	0.852
Risk factors						
Hypertension, n (%)	49 (67.1%)	62 (71.3%)	0.076	45 (68.2%)	48 (72.7%)	0.703
Hyperlipidemia n (%)	30 (41.1%)	30 (34.5%)	0.486	28 (42.4%)	25 (56.8%)	1
TC (mmol/L)	4.45 ± 0.99	4.29 ± 0.89	0.295	4.43 ± 1.01	4.33 ± 0.83	0.536
TG (mmol/L)	1.58 ± 1.00	1.71 ± 1.47	0.499	1.56 ± 0.97	1.96 ± 1.56	0.08
HDL (mmol/L)	1.15 ± 0.31	1.10 ± 0.23	0.227	1.15 ± 0.30	1.09 ±0.23	0.231
LDL (mmol/L)	2.84 ± 0.88	2.69 ± 0.80	0.258	2.84 ± 0.89	2.74 ± 0.78	0.524
Stroke history, n (%)	23 (31.5%)	28 (32.2%)	1	21 (31.8%)	24 (36.4%)	0.713
Alcoholism n (%)	18 (24.7%)	31 (35.6%)	0.184	18 (27.3%)	26 (39.4%)	0.196
Clinical Evaluation						
Baseline blood glucose (IQR), mmol/L	6.19 ± 2.08	6.02 ± 2.03	0.626	6.02 ± 2.03	6.16 ± 1.81	0.731
HbA1C(%) mean ± SD	5.87 ± 1.29	6.38 ± 1.34	0.014	5.94 ± 1.31	6.14 ± 1.15	0.353
Baseline NIHSS, (IQR)	4 (2,6)	3 (1,4)	<0.001	4 (2,5)	3 (2,5)	0.092
SBP, mean ± SD, mmHg	152 ± 21.0	150 ± 21.9	0.335	152 ± 21.3	152 ± 21.7	0.904
DBP, mean ± SD, mmHg	91.8 ± 14.9	89.9 ± 13.1	0.377	91.5 ±15.4	91.6 ±13.8	0.944
OTT (h), (IQR)	3 (2,4)	3 (3,4)	0.136	3 (2,4)	3 (3,4)	0.2

OTT: Onset to Treatment Time; IQR: Interquartile Range; CHD: Coronary Heart Disease; SD: Standard Deviation; NIHSS: National Institute of Health Stroke Scale; TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; HbA1C: Hemoglobin A1C; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Table 2: Unmatched study outcomes.

Variables Unmatched Cohort	Unmatched Cohort					
	END outcome			3 Months outcome		
	END group	Non-END	P-value	Unfavorable	Favorable	P-value
Demography						
Age (years) mean ± SD,	60.1 ± 13.8	56.4 ± 13.2	0.14	61.5 ± 15.6	56.3 ± 12.7	0.098
Male, n= (%)	32 (78.0%)	80 (67.2%)	0.269	22 (71.0%)	90 (69.8%)	1
Risk factors						
Hypertension, n (%)	35 (85.4%	76 (63.9%)	0.017	27 (87.1%)	84 (65.1%)	0.03
Hyperlipidemia, n (%)	12 (29.3%)	48 (40.3%	0.282	14 (45.2%)	46 (35.7%)	0.439
TC (mmol/L)	4.59 ± 0.88	4.28 ± 0.95	0.066	4.45 ± 0.92	4.34 ± 0.95	0.581
TG (mmol/L)	1.58 ± 1.22	1.58 ± 1.22	0.678	1.90 ± 1.59	1.59 ± 1.19	0.313
HDL (mmol/L)	1.16 ± 0.28	1.11 ± 0.26	0.401	1.11 ± 0.28	1.13 ± 0.26	0.754
LDL (mmol/L)	2.86± 0.71	2.72 ± 0.88	0.292	2.84 ± 0.82	2.74 ± 0.84	0.516
Diabetes, n (%)	14 (34.1%)	31 (26.1%)	0.428	13 ± 41.9%	32 ± 24.8%)	0.093
Smoking, n (%)	14 (34.1%)	40 (33.6%)	1	10 (32.3%)	44 (34.1%)	1
Stroke history, n (%)	13 (31.7%	38 (31.9%)	1	15 (48.4%)	36 (27.9%	0.047
Alcoholism n (%)	10 (24.4%)	39 (32.8%)	0.419	8 (25.8%)	41 (31.8%)	0.666
CHD, n (%)	4 (9.76%)	13 (10.9%)	1	3 (9.68%)	14 (10.9%)	1
Clinical Evaluation						
Baseline blood glucose(mean), mmol/L	6.48 ± 2.06	5.97 ± 2.03	0.172	6.14 ± 1.97	5.98 ± 2.03	0.72
HbA1C (%), mean ± SD	6.21 ±1.23	6.12 ± 1.38	0.696	6.48 ± 1.36)	6.07 ± 1.32	0.132
Baseline NIHSS(IQR)	4(2,8)	3 (2,5)	0.437	4 (2,9)	3 (2,5)	0.058
SBP, mean ± SD, mmHg	154 ± 21.1	150 ± 21.6	0.232	150 ± 24.4	151 ± 20.8	0.803
DBP, mean ± SD, mmHg	92.6 ± 12.9	90.2 ± 14.3	0.31	88.0 ± 12.1	91.4 ± 14.3	0.186
OTT (h), median (IQR)	3 (2.55,3.5)	3 (2,4)	0.107	3 (3,4)	3 (2.3,6)	0.562
Treatment						
Alteplase	20 (48.8%)	53 (44.5%)	0.773	9 (29.0%)	64 (49.6%)	0.062
Antiplatelets	17(41.5%)	52(43.7%)	0.803	12(38.7%)	57(44.2%)	0.58
Anticoagulation	11 (26.8%)	23 (19.3%)	0.429	6 (19.4%)	28 (21.7%)	0.966
Statins	40 (97.6%)	114 (95.8%)	1	28 (90.3%)	126 (97.7%)	0.087
Antihypertensive	11 (26.8%)	23 (19.3%)	0.429	22 (71.0%)	64 (49.6%)	0.052

OTT: Onset to Treatment Time; IQR: Interquartile Range; CHD: Coronary Heart Disease; SD: Standard Deviation; NIHSS: National Institute of Health Stroke Scale; TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; HbA1C: Hemoglobin A1c; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

In univariate logistic analysis we found diabetes mellitus on 3 months outcome to have OR (95% CI) of 2.96 (1.14, 7.58), with p- value of 0.024 a significant finding. Moreover, percentage of glycosylated hemoglobin (HbA1c) on 3 months outcome had OR (95% CI) of 1.45 (1.05, 2.07), with p-value of 0.028 a significant finding that Diabetes and HbA1c could independently predict unfavorable outcomes at 3 months.

In multivariate logistic regression analysis on matched cohort found END outcome had an OR (95% CI) of 0.99 (0.43, 2.26), p-value of 0.974 while mRS scores of ≤ 2 at 3 months had adjusted OR (with

Table 3: Unmatched multivariate logistic regression analysis study outcomes.

Outcomes	Medical treatment	Alteplase	Regression Analysis	
Unmatched cohort	**N=87**	**N= 73**	**Adjusted OR (95% CI)**	**P-value**
Primary outcomes				
mRS ≤ 2 at 3 months, *n* (%)	65 (74.4%)	64 (87.7%)	0.36 (0.13,0.92),	0.04
Secondary outcome				
END, *n* (%)	21(24.1%)	20(27.4%)	1.21 (0.58,2.52)	0.618
Safety outcomes				
sICH n (%)	-	-	-	-
Death n (%)	-	-	-	-

mRS: modified Ranking Scale; sICH: symptomatic Intracranial Hemorrhage; END: Early Neurological Deterioration

Table 4: Matched study outcomes.

Variables	Matched Cohort					
	END outcome			**3 Months outcome**		
	END group	**Non-END**	**P-value**	**Unfavorable**	**Favorable**	**P-value**
Demography						
Age(years), mean ± SD,	58.6 ± 13.4	56.5 ± 12.9	0.438	60.2 ± 13.8	56.3 ± 12.7	0.206
Male, n= (%)	23 (71.9%)	67 (67.0%)	0.766	16 (66.7%)	74 (68.5%)	1
Risk factors						
Hypertension, n (%)	28 (87.5%)	65 (65.0%)	0.027	21 (87.5%)	72 (66.7%)	0.076
Hyperlipidemia, n (%)	9 (28.1%)	46 (46.0%)	0.114	14 (58.3%)	41 (38.0%)	0.109
TC (mmol/L)	4.43 ± 1.01	4.33 ± 0.83	0.536	4.56 ± 0.91	4.34 ± 0.92	0.312
TG (mmol/L	1.56 ± 0.97	1.96 ± 1.56)	0.08	2.16 ± 1.71)	1.67 ± 1.19	0.188
HDL (mmol/L	1.15 ± 0.30	1.09 ± 0.23	0.231	1.0 ± 9 0.31	1.12 ± 0.26	0.642
LDL (mmol/L	2.84 ± 0.89	2.74 ± 0.78	0.524	2.92 ± 0.78)	2.76 ± 0.85	0.377
Diabetes, n (%)	9 (28.1%)	22 (22.0%)	0.637	10 (41.7%)	21 (19.4%)	0.04
Smoking, n (%)	11 (34.4%)	38 (38.0%)	0.873	10 (41.7%)	39 (36.1%)	0.783
Stroke history, n (%)	10 (31.2%)	35 (35.0%)	0.861	12 (50.0%)	33 (30.6%)	0.114
Alcoholism n (%)	9 (28.1%)	35 (35.0%)	0.615	8 (33.3%)	36 (33.3%)	1
CHD, n (%)	1 (3.12%)	12 (12.0%)	0.187	1 (4.17%)	12 (11.1%)	0.461
Clinical Evaluation						
Baseline blood glucose (mmol/L)	6.16 ± 1.66	5.97 ± 1.97	0.493	6.47 ± 2.17	5.99 ± 1.84	0.349
HbA1C (%) mean ±SD	6.05 ± 0.97	6.04 ± 1.31	0.972	6.59 ± 1.46	5.92 ± 1.15	0.044
Baseline NIHSS(IQR)	4(2,5)	3 (2,5)	0.572	4(2,8)	3(2,4.75)	0.177
SBP, mean ± SD, mmHg	157.90 ± 20.3	151. ± 21.6	0.111	151 ± 23.2	153 ± 21.1	0.725
DBP, mean ± SD, mmHg	91.1 ± 15.0	93.2 ± 13.4	0.45	89.0 ± 12.5	92.1 ± 15.0	0.289
OTT (h), median (IQR)	3(2.7,3.374)	3 (2,4)	0.508	3.25(2.625,4)	3 (2,4)	0.233
Treatment						
Alteplase	16 (50.0%)	50 (50.0%)	1	7 (29.2%)	59 (54.6%)	0.042
Antiplatelets	14(43.8%)	41(41%)	0.784	11(45.8%)	44(40.7%)	0.657
Anticoagulation	8 (25.0%)	21 (21.0%)	0.818	4 (16.7%)	25 (23.1%)	0.674
Statins	31 (96.9%)	95 (95.0%)	1	21 (87.5%)	105 (97.2%)	0.073
Antihypertensive	19 (59.4%)	53 (53.0%)	0.67	17 (70.8%)	55 (50.9%)	0.122

OTT: Onset to Treatment Time, IQR: Interquartile Range; CHD: Coronary Heart Disease; SD: Standard Deviation; NIHSS: National Institute of Health Stroke Scale; TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; HbA1C: Hemoglobin A1c; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Table 5: Matched logistic regression analysis study outcomes.

Outcomes	Medical treatment	Alteplase	Regression Analysis	
Matched cohort	**N=66**	**N=66**	**Adjusted OR (95% CI)**	**P-value**
Primary outcomes				
mRS ≤ 2 at 3 months, n (%)	49(74.2%)	59(89.4%)	0.35(0.12, 0.90)	0.035
Secondary outcome				
END, n (%)	16(24.2%)	16(24.2%)	0.99(0.43, 2.26)	0.974
Safety outcomes				
sICH n (%)	-	-	-	-
Death n (%)	-	-	-	-

mRS: modified Ranking Scale; sICH; symptomatic Intracranial Hemorrhage; END: Early Neurological Deterioration

95% CI) of 0.35 (0.12, 0.90), p-value of 0.035 a result which shows alteplase treated patients to have a statistically significant favorable functional outcome at 3 months (Table 5).

A total of 108 [81.8%] of all patients in matched cohort had favorable outcomes, of which 59 (88.4%) were from thrombolysed group and 49 (74.2%) from medically treated group. A Total of 32 (24.24%) of matched cohort suffered END, of which a pair of 16 (24.2%) patients in both alteplase and medical treated groups suffered END.

Multiple regression analysis also found that hypertension with an OR [95% CI] of 3.98 (1.41, 14.32) p-value-0.017 a statistically significant result which shows that hypertension is an independent predictor of END.

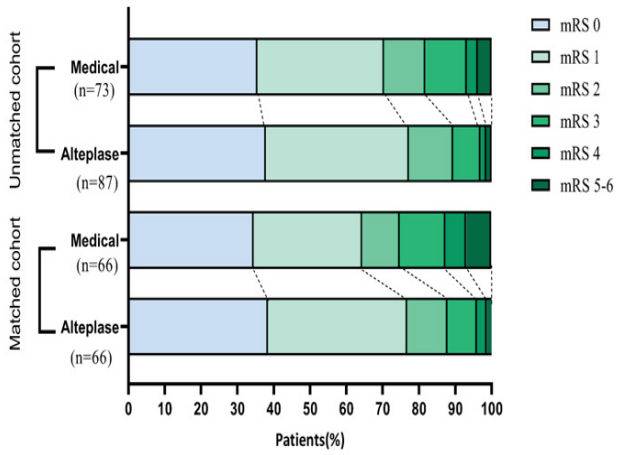

Figure 3: The distribution of scores on the modified Rankin scale (mRS) at 3 months after stroke which shows favorable outcome with alteplase therapy in both cohorts.

Discussion

The current study showed patients with SSSI who were treated with alteplase are more likely to achieve 3 months favorable functional outcomes than those who were treated with standard medical care; however treatment with alteplase may not prevent END to patients with SSSI. Our study results found that alteplase have higher positive effects on achieving favorable functional outcomes at 3 months in both matched and unmatched data as shown on figure 3. As per our dataset, this study is more likely involved large proportion of SSSI cases from branches of MCA which suffer more dSSSI a pattern which studies have shown to be more associated with SVD [21]. The following theories could explain effectiveness of alteplase on treatment of SSSI at 3 months outcome as compared to other medical treatments. As it has been shown that SSSI cases of our study are more of dSSSI pattern which is associated with SVD, pathophysiological changes which lead to SVD has been shown to involve lipohyalinosis or fibrinoid degeneration which is known to be induced by chronic hypertension, lipohyalinosis induced vessels have been shown to thicken with focal dilation and impaired autoregulation [22,23] which may be predisposed to clot formation. Clot formation resulted from irregular shape of lumen of these small vessels may be easily lysed by alteplase which is known to work efficiently in fresh formed thrombi, this is desired therapeutical effect needed in acute stroke. Based on above possible explanation, as compared to antithrombotic which work mainly by preventing platelets activation, aggregation and clot stabilization in their mechanisms of action may not be so effective to already formed clots in these small vessels as it has been revealed by arriving late to medical facility and hence possibility of persistent clots in deep vessels which could have poor long term neurological outcomes. Moreover, patients with lacunar infarction have been found to present with endothelial dysfunction manifested by increased circulating levels of Intercellular Adhesive Molecules-1(ICAM1), Thrombomodulin (TM) and Tissue Factor Pathway Inhibitor (TFPI) [24], these components of hemostasis are essential for controlling clot formation. It has been shown endothelial failure of small vessels may result to uncontrolled clot formation due malfunction of TM and TFPI of failed endothelial, therefore, with alteplase therapy formed clots may be lysed and prevention of further neuronal damage.

The current study shows favorable outcomes at 3 months results are consistent with several studies, Peak et al. [15] who investigated the effects of intravenous alteplase on Small Vessel Occlusion (SVO) by grouping those who received alteplase and placebo. 193 were given alteplase and 2289 were given placebo, alteplase group showed significant increased odds of excellent outcome mRS 0-1 by 1.56-fold at 3 months and only 3 (1.6%) patients suffered sICH with no death within 3 months in alteplase group while 1 (0.04%) suffered sICH with 16 (0.7%) death in placebo group. Mustanoja et al. [25] in their study of outcomes by stroke etiology in patients receiving alteplase showed that 101 (11%) of lacunar stroke had a better prognosis at 3 months compared with other stroke subtypes in terms of mortality and functional outcome. Also, they had low baseline NIHSS (7{4.5-10}), no case of sICH and low ICH (2.2%). However, they differ from ours by not having control group for comparison. Eggers et al. [14] from the Austrian Stroke Unit Registry found that at 3-month follow-up, alteplase was significantly associated with a better functional outcome in LacS (P<0.001) and non-LacS patients (P<0.001), an equal benefit of alteplase, their study compared lacunar *vs.* non-lacunar infarctions and their result may be more significant because sample size was much larger.

To explore safety of alteplase treatment on lacunar strokes Griebe et al. [17] made a comparison between 468 patients treated with standard medical care and 69 patients who were given alteplase. They found that both groups achieved similar functional outcomes at 3 months with no case sICH, however, hemorrhagic transformation occurred more in alteplase group (11.6% *vs.* 1.9%, p-0.001) and thrombolysed group had higher baseline NIHSS scores (5 *vs.* 3, p-0.001). Their sample size and 3 months outcomes differ from ours but other findings look similar. The study of 76 acute lacunar stroke patients by Hwang et al. [9] to examine the rate of achieving good functional outcomes found no positive statistically significant effects of alteplase on favorable functional outcome at 3 months on lacunar patients, However, they found slight trend toward favorable function outcomes at 3 months, however their proportion of favorable outcomes (31% *vs.* 23%) was low compared to ours (89.4% *vs.* 74.2%) and their results were statistically insignificant, they also had 2 cases of ICH. Yang et al. [26] in their study of 57 (67.9%) patients who were given alteplase found no significant effects of alteplase therapy in patients with penetrating arterial infarction as compared to non-alteplase at 3 months functional outcomes. The studies mentioned above involved infarctions from anterior and posterior circulation which differentiated them from ours, we also confined to only SSSI of anterior circulation.

The ineffectiveness of alteplase to prevent END in our study may be explained by the fact that there are possibilities of platelets rich thrombi to be resistance to alteplase because of presence of plasminogen activator inhibitor-1 in those thrombi and variation of platelet aggregation and platelet surface receptor expression induced by alteplase therapy in early stages of ischemic events [27,28]. Anatomical locations in which anterior circulation SSSI occurs also could be a contributing factor since are more likely to result into patients with more pure motor lacunar syndromes. Most structures that may manifest with these syndromes are supplied from lenticulostriatal arteries are in close proximity to the corticospinal tracts and these have been shown to cause early motor deterioration which is normally progressive in its early course even after thrombolysis [26,29]. Previous studies also found that treatment with alteplase in patients with infarction as result of occlusion of penetrating arteries have shown to be associated with END [30].

Ineffectiveness of alteplase in END prevention in our study could have not happened because of higher proportional of hypertension in these group patients which was found to be independent predictor of END in both original and matched cohort, therefore we suspect that being hypertensive may affect alteplase efficacy on early outcome phases of ischemic stroke a consistent finding from other studies [6,31].

END findings in our study were similar to those of Hwang et al. [9] which they found no statistically significant effects of alteplase on preventing END on lacunar patients, in their study patients treated with alteplase had a higher proportion of END than those treated with medical care (24% *vs.* 21%) and their results were statistically insignificant. Fuentes et al. [11] also found no neurological improvement in the first 24 hours after alteplase treatment in all stroke subtypes including lacunar infarction. On the other hand, several studies have shown early good outcomes, Yang et al. [26] found 67% of patients with acute perforating artery infarction who were given alteplase showed improvement by reduction of NIHSS score within 24 hours of symptoms onset than those who did not receive it. Also, in a study by Eggers et al. [14] showed clinical improvement by reduction of 3 NIHSS scores in thrombolysed patients compared to 2 NIHSS score reduction in control within 72 hours, p-value 0.001 (15). Griebe et al. [17] also showed frequent clinical improvement by reduction of 4 ≥ points on the NIHSS in thrombolyzed patients than in standard medical care (31.9 *vs.* 7.7%, p-0.001).To find the treatment benefit of alteplase on lacunar infarction Zivanovic et al. [18] compared 46 lacunar patient who were given alteplase with 45 patients who did not receive and found that excellent outcome at discharge was significantly more frequently in thrombolysed than non-thrombolysed (41.3% *vs.* 15.6% p-0.01) and no hemorrhagic transformation occurred, their study shares some similarities with ours, however they had smaller sample than ours. Wu et al. [32] studied the effects of alteplase on Branch Atheromatous Disease (BAD) and found alteplase to prevent early neurological deterioration significantly compared to the control group in both unmatched and matched by 15.7% *vs.* 32.1% and 11.9% *vs.* 31% respectively, however other studies showed alteplase did not have effect END occurrence in BAD [1,33,34].

We speculated that alteplase in BAD might have shown favorable outcomes in preventing END in their study because mostly it involves atherothrombosis of the larger parent artery which has the tendency to show good response with alteplase treatment as it has been theorized that atherosclerotic larger parent arteries have a high risk of forming atherothrombosis which may contain more pharmacologically lysable contents prone to alteplase, therefore more likely to achieve earlier favorable outcome. However, from available knowledge of two different pathological patterns of SSSI i.e dSSSI and pSSSI, several studies have shown that patients with SSSI have significant higher proportion of pSSSI [34,35], Duan et al. [34] in their study showed that pSSSI to be an independent significant predictor of END. Although in our study we did not find the proportional of pSSSI, based on the above trend of a large proportional of pSSSI in SSSI studies we suspect the proportional of pSSSI in our study to be also high and from Jeong et al. [1] study which found that the atherosclerotic pattern of pSSSI to be associated significantly with many ENDs then we might suspect that alteplase might not prevent END in these small vessels as it has been shown in our study because of the presence significant larger proportional pSSSI patients which might have affected overall short term outcome, however we cannot rule out the possibilities of the results to be different if larger sample could have been used.

The current study also found history of stroke to be significant predictor of poor functional outcomes at 3 months a similar finding with those of Strbian et al. [36]. There was no symptomatic intracranial hemorrhage however there was one asymptomatic case of intracranial hemorrhage in the thrombolysed group a consistent finding with other studies [17,37,38] and no death was seen. This might be explained by the facts that our study cases had low mean baseline NIHSS score (≤ 5) at admission in both thrombolysed and medical treatment which may be a low risk of ICH. Despite tendency of alteplase to potentiate hemorrhages, it has shown to be safe for treatment of SSSI. To the best of our clinical knowledge and current study findings, intravenous alteplase seems to be effective and safe in patients with SSSI and might be applied if there are no absolute contraindications. However, alteplase should not be entirely relied on its effect on the prevention of END in SSSI patients, more medical treatment such as heparin, tirofiban, and others may be considered in case of the occurrence of END.

The study had several research limitations which included; the small sample size which may affect the general conclusion, single centered nature of our study may exclude other factors which may influence our outcome, we studied only anterior circulation which may have different features from as compared to other parts hence general conclusion based on only this single area may not be precise, retrospective nature of our study may have missed some of the crucial findings in some cases.

Conclusion

Use of alteplase for treatment of anterior circulation SSSI improves 3 months outcome than standard medical care. Additionally, alteplase has been shown no effect on END, intravenous alteplase seems to be effective and safe in patients with SSSI and might be applied if there are no absolute contraindications, however it should not be entirely relied on its effect on the prevention of END in SSSI patients, more medical treatment such as heparin, tirofiban, and others may be considered in case of the occurrence of END. As the controversies on different etiologies of SSSI and mechanisms and side effects of alteplase therapy persists, further studies with large sample sizes, involving multi centers, molecular biological studies of penetrating vessels should be undertaken to explore its efficacy.

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