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Running Title: Efficacy and safety of thrombolytic therapy in Mongolian young adults with acute ischemic stroke

Efficacy and Safety of Thrombolytic Therapy in Mongolian Young Adults with Acute Ischemic Stroke

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Objectives: The study aimed to assess the safety and efficacy of intravenous thrombolysis (IVT) in Mongolian young patients with acute ischemic stroke (AIS).

Methods: Data of 30 AIS patients aged <50 years who were treated with IVT between 2013 and 2023 at the Stroke Department of Third Central Hospital were retrospectively analyzed. For outcome comparison, 60 controls with AIS not treated with IVT and 60 older controls (>50 years) treated with IVT matched age, gender and baseline NIHSS score were selected. Functional outcome at three (3) months defined as "Favorable" and "Unfavorable" (modified Rankin Scale score 0-1 vs 2-6). Symptomatic intracerebral hemorrhage (sICH) was defined according to the SITS-MOSTStudy.

Results: "Favorable" outcome at 3 months was significantly higher in young IVT-treated patients (53.3% vs 30.0%, $p < 0.05$) compared with their matched young and older controls treated with IVT (53.3% vs 26.7%, $p = 0.019$). The sICHoccurred in 3% of young IVT-treated patients and in 5% of older controls but this difference was nonsignificant. Mortality rate was 21.7% ($p = 0.245$) among older controls, whereas in young IVT-treated and matched young controls 10% during the 3months follow-up.

Conclusions: IVT is safe and beneficial for Mongolian young adults with AIS.

Keywords: Ischemic stroke, Treatment Outcome, Tissue Plasminogen Activator, Safety, Young Adult

Introduction

Ischemic stroke in young individuals can have a devastating impact, causing a significant loss of productive years and profoundly affecting the lives of the affected individuals, their families, and society at large. Although the incidence of ischemic stroke increases with age, an estimated 10%-20% of these events occur in young adults aged 18 to 50 years [1]. In contrast to the incidence of stroke in the elderly, the incidence of ischemic stroke among young adults is increasing worldwide [2-4,28] and regardless of less vascular risk factors, young patients in low- and middle-income countries more often died within 3 months of diagnosis as compared with those from high-income countries [5]. Between 1990 and 2019, a notable increase in age-standardized incidence, mortality, and DALYs (Disability-Adjusted Life Years) rates was observed on a global scale. These increases were particularly pronounced in regions with low and low-middle sociodemographic indices, such as North Africa, the Middle East, and Southeast Asia. Notably, these regions witnessed a significant surge in the occurrence of ischemic stroke among young adults [28]. Moreover, data of statistical reports on morbidity and mortality in Mongolia show that young adults account for approximately 20%-26% of all stroke patients as opposed to 10%-13% in Western countries [6].

Ischemic stroke is a preventable and treatable disease, frequently caused by cerebral artery thrombosis or thromboembolic occlusion [6]. Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA), as the primary thrombolytic agent given within 4.5 hours of onset of acute ischemic stroke (AIS) improves outcome and it is widely accepted as a first-line treatment and recommended by many guidelines worldwide[7,8,12]. A number of sources have reported that IVT is more effective in younger patients with AIS than in older patients [9-11,29,30]. According to the safety implementation of IVT(SITS-MOST) study, patients under 50 years of age have less complications of intracerebral hemorrhage and better functional recovery than older patients [10].

In 2013, the Stroke Department of the Third Central Hospital in Mongolia implemented the initial administration of thrombolytic therapy, which subsequently became integrated into the standard treatment protocol and obtained official licensure.

Although previous studies have examined the etiology, risk factors, clinical features, and prognosis of ischemic stroke in young adults [6], there is a lack of information regarding the efficacy and effectiveness of intravenous thrombolysis (IVT) using rt-PA (alteplase) specifically in Mongolian young patients with ischemic stroke. Therefore, this study aimed to compare outcomes in AIS patients after IVT at young (<50 years), old (50 <years) age groups and matched young controls untreated with IVT as well. The study sought to improve clinical management for ischemic stroke in young adults which is critical for addressing these epidemiologic trends.

Material and Methods

Data collection

A retrospective observational case-control study was conducted on data from the Stroke Department of Third Central Hospital, Ulaanbaatar, Mongolia. All medical records of consecutive patients aged <50 years treated with IVT (Alteplase, Boehringer Ingelheim, Germany) for AIS from 2013 to January 2023 were received. AIS was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours or with evidence of acute brain ischemia on neuroimaging when symptoms lasted less than 24 hours. Intravenous rt-PA (alteplase) was administered at a dose of 0.9 mg per kilogram (maximum, 90 mg), with 10% given as an initial bolus within 1 minute and the remaining 90% as a constant infusion over a period of 60 minutes [12]. The inclusion/exclusion criteria were based on the 2013 AHA/ASA Guidelines for the early management of patients with acute ischemic stroke (within 4.5 hours) [12].

All patients or patient's care providers gave written informed consent before thrombolytic management therapy, and all patients were followed up for 3 months. All patients had a baseline CT scan and a second scan performed within 24-36 hours after rt-PA infusion to detect any intracerebral hemorrhage. Data of young matched controls (1:2) aged 20 to 49 with AIS treated at the Stroke Department from 2013 to January 2023 and older matched controls to the IVT-treated patients by age, gender, and National Institute of Health Stroke Scale (NIHSS) score were also reviewed. We conducted a matching process for control subjects with the alteplase-treated patients based on age, gender, and National Institute of Health Stroke Scale (NIHSS) score. We initially chose the first matching control

patient for each case and then thoroughly reviewed their medical records. Furthermore, we aimed to compare the outcomes and the incidence of hemorrhagic events in comparison to older control subjects (1:2) aged between 50 to 79 years, who had AIS and were treated with alteplase. These older control subjects were similarly selected from our thrombolysis register and matched based on gender and admission NIHSS score. All patients received standard stroke care and secondary prevention following generally accepted recommendations [17].

Demographic data and clinical characteristics

Demographic characteristics, risk factors, stroke onset to treatment time (OTT), door-to-needle time (DNT), and complete general and neurological examinations were reviewed including the Glasgow Coma Scale (GCS) to assess the consciousness level and the National Institute of Health Stroke Scale (NIHSS) [16] to assess the stroke severity. Various subtypes of ischemic stroke as per the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were determined [15]. The outcome was measured using the modified Rankin Scale (mRS) at 3-month. The mRS is a global measure of disability on a seven-level scale, with scores ranging from 0 (no symptoms) to 6 (death) [13]. A favorable outcome was defined as a mRS score of 0-1whilee unfavorable outcome was defined as a mRS score of 2-6. Symptomatic intracerebral hemorrhage (sICH) was defined according to SITS-MOST criteria's local or remote parenchymal hemorrhage type 2 on the 22- to 36-hour posttreatment imaging combined with a neurological deterioration of >4 points on NIHSS from baseline or from the lowest NIHSS value between baseline and 24 hours or leading to death [10]. Asymptomatic ICH involved hemorrhage on follow-up CT without associated clinical deterioration. Dense cerebral artery sign, age, glucose level on admission, onset-to-treatment time, NIHSS on admission (DRAGON) score were recorded [27]. Magnetic resonance imaging (MRI) and angiography (MRA) of the brain was done in suspected brain stem lesions, early ischemic stroke, and when follow-up CT brain is free (Figure 3). Cardiac evaluation including ECG and echocardiography was available.

Statistical Analysis

All data were collected and statistically analyzed using IBM SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA). According to the type of data, quantitative variables were expressed as the mean ± SD and median range. The qualitative data were expressed as a number or percentage. Difference and association of qualitative variables were statistically tested for significance using the chi-square test, Fisher exact test, and differences between the quantitative independent groups were tested using the t test or Friedman test of significance. Univariate and multivariate logistic regression were used to calculate the odds ratio (OR) with 95% confidence intervals (CI) and for the outcomes in the young age group. All statistical tests were two-sided, and p-values of <0.05 were considered statistically significant.

Ethical statement

The permission to conduct the research was obtained from the Ethical Review Committee of
MNUMS (#2023/3-04), and the researchers maintained the confidentiality of the participants.

Results

Comparison of IVT efficacy in the young patients with AIS

The baseline data including the common risk factors were non significantly different for the IVT young patients (n=30) and non-IVT (n=60) controls (Table 1). Etiology by TOAST classification was similar. As predicted, there was a prolonged period of time from the onset of stroke symptoms to the arrival at the hospital (onset to door time) observed in age-matched control subjects (99.20±24.56vs109.90±15.25, p=0.013).

Table 1. Comparison of the baseline data of IVT and non-IVT groups <50 year's old AIS patients

Variables	IVT (+) (n=30)	IVT (-) (n=60)	P-value
Age, years; mean ± SD	42.97± 5.35	41.05 ± 5.63	0.126
Male, n (%)	16 (33.3%)	32 (66.6%)	1.000
NIHSS score at admission	13.70± 4.78	13.9 ± 4.49	0.976
GCS at admission	12.60± 2.04	13.20± 3.00	0.327
Hypertension, n (%)	20 (66.7%)	36 (60%)	0.647
Ischemic heart disease	7 (13.3%)	19 (31.7%)	0.468
Diabetes mellitus, n (%)	3 (10%)	9 (15%)	0.794
Dyslipidemia, n (%)	6 (20%)	24 (40%)	0.063
Migraine	4 (13.3%)	9 (15%)	0.876
Atrial fibrillation, n (%)	3 (10%)	2 (3.3%)	0.328
Smoking, n (%)	14 (46.7%)	27 (45%)	1.000
Alcohol intake, n(%)	9 (30%)	20 (33.3%)	0.814
Blood glucose, mmol/L	6.75 (5.6-7.7)	6.94 (6.3-9.0)	0.844
SBP, mmHg	140.65±26.96	157.33± 25.28	0.051
DBP, mmHg	89.68 ±22.07	102.06± 18.80	0.070
Onset to door time	99.20±24.56	109.90±15.25	0.013*
OTT	199.36± 48.80	-	
Circulation			
Anterior	28 (93.3%)	55 (91.6%)	0.986
Posterior	2 (6.7%)	5 (8.3%)	0.973
Stroke subtypes, n (%)			
LAA	6 (20%)	12 (20%)	1.000
Cardiogenic embolism	9 (30%)	11 (18.3%)	0.282
Small vessel disease	9 (30%)	11 (18.3%)	0.282
Other determined etiology	3 (10%)	13 (21.7%)	0.245
Undetermined etiology	3 (10%)	13 (21.7%)	0.245
Mortality	3 (10%)	6 (10%)	1.000

IHD, ischemic heart disease; OTT, Onset to treatment time; DNT, Door to needle time; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; NIHSS, National Institute of Health Stroke Study;NIHSS on admission; LAA, Large Artery Atherosclerosis; sICH, Symptomatic Intracerebral hemorrhage

As shown in Figure 1A, a significant difference was observed for the 3months and favorable outcome rates between young patients treated with IVT and matched controls (53.3% vs 30.0%, $p < 0.05$). However, the mortality rate was not considerably different. Therefore, compared to the non-IVT controls, the IVT-treated young patients showed improved efficacy, enhanced short-term prognosis, and no increased death rate.

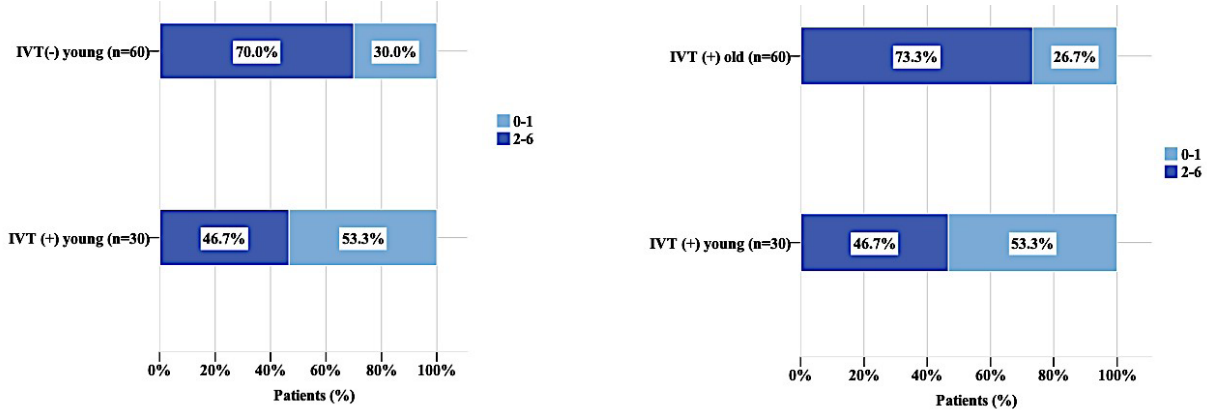

Figure1. Patient's outcome at 3 months based on mRS score. Favorable=modified Rankin Scale (mRS) score of 0-1, Unfavorable= modified Rankin Scale (mRS) score of 2-6. **A.** Proportions of cases (n=30) and age, matched control subjects (n=60), **B.** Proportions of cases (n=30), and older control subjects (n=60) by dichotomized outcomes at 3 months (mRS).

Comparison of the safety of IVT in young and older patients

Comparison of patient demographic data and baseline characteristics between the two groups is shown in Table 2. Ischemic heart disease was significantly lower in young adults compared to older adults (23.3% vs 48.3%, p<0.05). The traditional risk factors for stroke, such as hypertension (30.8% vs 69.2.0%) and atrial fibrillation (10% vs 20%) were significantly less common in young adults compared to older adults. Alcohol consumption was slightly more prevalent among the young adults, although there was non significant difference compared to the older adults. Baseline serum glucose and SBP (systolic blood pressure) were lower in young adults, with no difference between the two groups inbaseline diastolic blood and hyperdense artery signs. A higher proportion of young adults had DNT ≤60 minutes (10% vs 3.3%), although there was non-significant difference in mean DNT and OTT between the two groups.

The prevalence of other determined etiology (10% vs 0, p<0.05) was higher among the young adults, but the prevalence of large-artery atherosclerotic stroke (35.3% vs 64.7%) and cardiogenic embolism (25.6% vs 74.4%) was higher in the older adults. No significant difference was observed in small vessel disease and undetermined etiology between the two groups.The proportions of patients with sICH (3.3% vs 5%) and 3months mortality (10% vs 21.7%) were lower for the young adults compared to older adults, but not significantly (Table 2).

Table 2. Comparison of the baseline data of young and old patients who had received IVT

Variables	Patients<50 Years old (n=30)	Patients 50< Years old (n=60)	P-value
Age, years; mean ± SD	42.97± 5.35	63.52±7.67	0.000*
Male, n (%)	16 (53.3%)	32 (53.3%)	1.000
Hypertension, n (%)	30 (30.8%)	45 (69.2%)	0.458
Diabetes mellitus, n (%)	3 (10%)	9 (15%)	0.744
Dyslipidemia, n (%)	6 (20%)	14 (23.3%)	0.794
Atrial fibrillation, n (%)	3 (10%)	12 (20%)	0.369
IHD, (%)	7 (23.3%)	29 (48.3%)	0.025*
Smoking, n (%)	14 (46.7%)	28 (46.7%)	1.000
Alcohol n(%)	9 (30%)	11 (18.3%)	0.282
Blood glucose, mmol/L	6.75± 3.51	7.25± 2.76	0.489
SBP, mmHg	140.65± 26.56	147.29± 26.11	0.271
DBP, mmHg	89.69± 22.07	90.59± 18.62	0.842
Hyperdense artery signs a, n (%)	14 (46.7%)	25 (41.7%)	0.660
NIHSS score	13.70± 4.78	14.01± 4.86	0.876
OTT, (onset to treatment time) min	199.36± 48.80	202.12± 45.27	0.792
DNT, min	114.50± 37.75	117.52± 39.77	0.731
DNT<60 min	3 (10%)	2 (3.3%)	0.328
DRAGON score	4.86±1.79	4.87±2.01	0.965
Stroke subtypes, n (%)			
LAA	6 (35.3%)	11 (64.7%)	1.000
Cardiogenic embolism	11 (25.6%)	32 (74.4%)	0.180
Small vessel disease	8 (26.7%)	12 (20%)	0.592
Other determined etiology	3 (10%)	0	0.035*
Undetermined etiology	2 (6.7%)	5 (8.3%)	1.000
Mortality	3 (10%)	13 (21.7%)	0.245
sICH	1 (3.3%)	3 (5%)	1.000

*p-value < 0.05, **p-value < 0.001, IHD, ischemic heart disease; OTT, Onset to treatment time; DNT, Door to needle time; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; NIHSS, National Institute of Health Stroke Study; NIHSS on admission; LAA, Large Artery Atherosclerosis; sICH, Symptomatic Intracerebral hemorrhage

Clinical outcome defined by mRS at 3 months is shown in Figure 1B. There was significant difference in the proportion of patients with favorable outcome between the young adults and older adults (53.3% vs 26.7%, p=0.019).

Proportions of each subgroup of mRS at 3 months is shown in Figure 2. Dependence (mRS, ≥4 points) in the IVT-group was also markedly lower than that in the control groups.

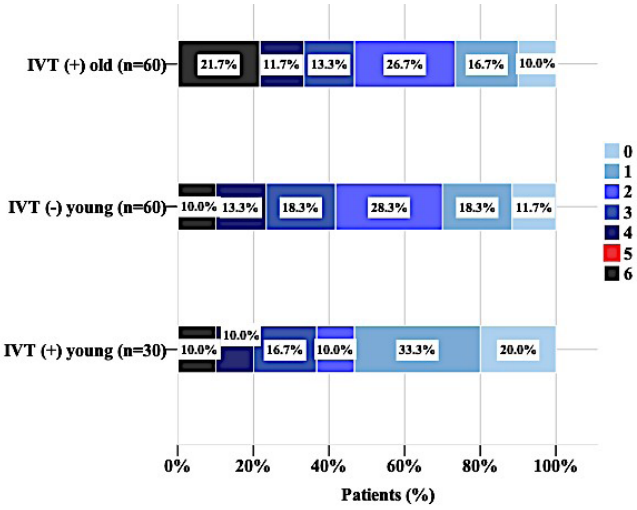

Figure 2. The distribution of scores on the modified Rankin scale (mRS) at 3 months after stroke was in favor of intravenous thrombolysis. The mRS scores ranged from 0 to 6, in which higher scores indicated more severe disability.

Unfavorable outcome was more frequent among those with hypertension, with high NIHSS score at admission (Table 3). There was nonsignificant trend toward better outcome among patients with undetermined etiology as well as other stroke subtypes.

Table 3. Risk factors for outcomes in patients aged <50 years treated with IVT

Variables	mRS 0-1 (n=16)	mRS 2-6 (n=14)	P-value
Age, years; mean ± SD	42.01±5.71	42.50±5.20	0.070
Male, n (%)	8 (50%)	8 (57.1%)	0.730
Hypertension, n (%)	7 (43.8%)	13 (92.9%)	0.007*
Diabetes mellitus, n (%)	0	3 (21.4%)	0.090
Dyslipidemia, n (%)	4 (25%)	2 (14.3%)	0.657
Atrial fibrillation, n (%)	2 (15.4%)	1 (7.1%)	1.000
IHD	4 (25%)	3 (21.4%)	1.000
Smoking, n (%)	7 (43.8%)	7 (50%)	1.000
Alcohol n (%)	4 (25%)	5 (35.7%)	0.694
Blood glucose, mmol/L	5.61± 1.24	7.89 ± 4.61	0.085
SBP, mmHg	136.33±18.24	145.29±33.42	0.374
DBP, mmHg	86.07±16.32	93.58±27.04	0.370
Hyperdense artery signs a, n (%)	5 (35.7%)	9 (56.3%)	0.299
NIHSS score	11.69±3.19	16.0±5.44	0.011*
OTT, min	186.32±54.21	213.71±38.83	0.134
DNT, min	11.13±37.08	118.36±39.55	0.609
DNT<60 min	1 (6.3%)	2 (14.3%)	0.586
DRAGON score	4.13±1.63	5.71±1.66	0.013*
Stroke subtypes, n (%)			
LAA	1 (6.3%)	5 (35.7%)	0.072
Cardiogenic embolism	5 (31.3%)	4 (28.6%)	1.000
Small vessel disease	7 (43.8%)	2 (14.3%)	0.118
Other determined etiology	2 (12.5%)	1 (7.1%)	1.000
Undetermined etiology	1 (6.3%)	2 (14.3%)	0.586
Mortality	0	3 (21.4%)	0.090
sICH	0	1 (7.1%)	0.467

*p-value < 0.05, OR-Odds ratio, CI-Confidence interval, IHD, ischemic heart disease; OTT, Onset to treatment time; DNT, Door to needle time; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; NIHSS, National Institute of Health Stroke Study; DRAGON, Dense cerebral artery sign, age, glucose level on admission, onset-to-treatment time, NIHSS on admission; LAA, Large Artery Atherosclerosis; sICH, Symptomatic Intracerebral hemorrhage

The variables with p-values < 0.1 in the univariate analysis underwent binary logistic multivariate analysis and the results demonstrated that the DRAGON score (OR 2.404, 95% CI, 1.001–5.772, p < 0.05) after IVT was independently associated with unfavorable outcomes at 3 months in AIS young patients (Table 4).

Table 4. Binary logistic multivariate analysis of risk factors of functional outcome at 3 months after IVT in young patients with AIS

Variables	OR	95% CI	p-value
Age, years	1.050	0.780-1.414	0.748
Hypertension	0.118	0.003-4.740	0.257
Baseline NIHSS	1.105	0.845-1.445	0.465
DRAGON score	2.404	1.001-5.772	0.048*
LAA	0.305	0.010-8.982	0.491
Blood glucose, mmol/L	1.971	0.508-7.653	0.327
Diabetes mellitus	0.000	-	0.999

*p-value < 0.05, OR-Odds ratio, CI-Confidence interval, NIHSS, National Institute of Health Stroke Study; DRAGON, Dense cerebral artery sign, age, glucose level on admission, onset-to-treatment time, NIHSS on admission, LAA, Large Artery Atherosclerosis

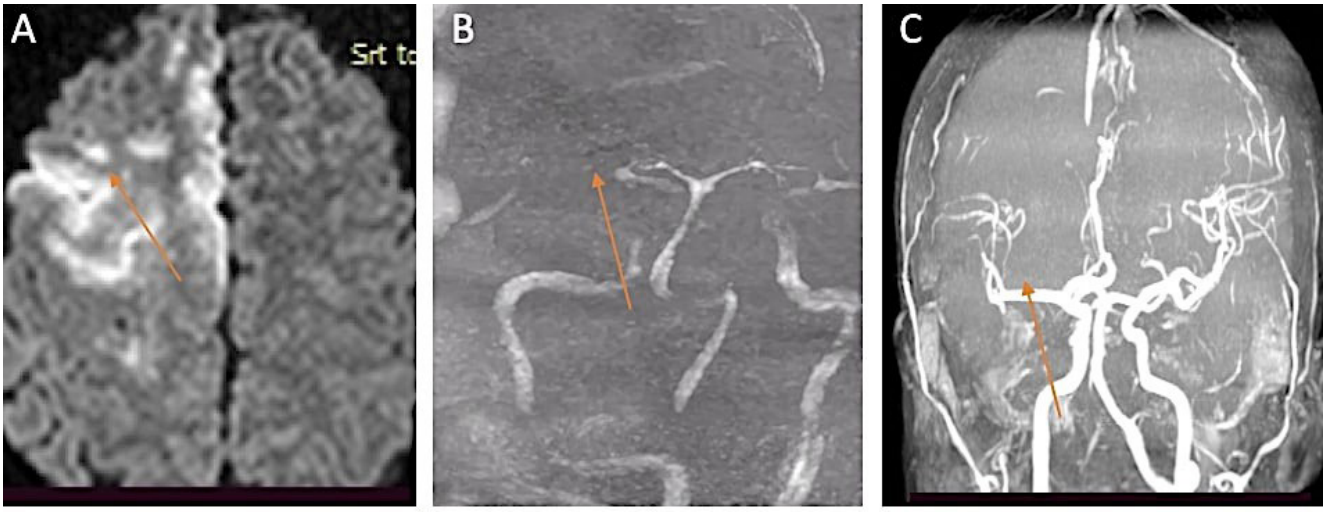

Figure 3. Images of young AIS patient: Brain magnetic resonance imaging diffusion-weighted imaging shows bright signal in the left middle cerebral artery territory (A) (red arrow); magnetic resonance angiography at admission shows non visualization of M1 (B) (red arrow); magnetic resonance angiography at 48 h post thrombolysis shows recanalization (C) (red arrow).

Discussions

The current study investigated the initial characteristics and outcomes of young adult patients who received intravenous tissue plasminogen activator (tr-PA) treatment for stroke, in comparison to their control counterparts who did not receive alteplase. The control group was carefully matched to the treatment group based on age, gender, and baseline stroke severity. Several studies have consistently reported favorable functional outcomes and lower mortality rates among young adult stroke patients [6,11,14,18]. In our findings more than half of those treated with IVT had reached favorable functional outcome at 3 months follow-up compare to their young controls not treated with IVT(53.3% vs 30.0%, p < 0.05)and death rates were 10%. In study SITS-MOST patients aged 18–45 years treated within 3 hours, mortality rates were 5.5% and 54%-76% scored 0-1 and 0-2 on the 3months mRS [10]. Our findings closely mirror previous research, except for the mortality rate. Notably, our study revealed a significant

difference in the proportion of young adult patients achieving a favorable outcome, as measured by a score of 0-1 on the modified Rankin Scale (mRS) at 3 months, when compared to older control subjects treated with intravenous thrombolysis (53.3% vs. 26.7%, p=0.019). Additionally, a post hoc analysis of the SITS-ISTR trial demonstrated that 72.1% of young adults achieved a favorable outcome, with 52% experiencing no or minimal disability, compared to 54.5% and 38.6%, respectively, among older adults [19].

The findings of a retrospective observational study, conducted using a comprehensive stroke registry in south west Germany, revealed the effectiveness of IVT in young adults. The study reported a favorable outcome, defined as a modified Rankin Scale (mRS) score of 0-1 or not worse than pre-stroke, in 50% of patients aged 18-50 years who received IVT. In comparison, the favorable outcome rate was 36% among patients aged 51-80 years. These results highlight the positive impact of IVT on the functional outcomes of young adult stroke patients [20]. Putaala et al. found that proportions of dichotomized 3-month outcome scores did not differ significantly between cases and older alteplase-treated control subjects (40% and 48%, p=0.343) [18].The differences between our results and others were likely because patients from previous studies were enrolled from single or multiple centers, while our data were from a hospital-based stroke documents with consecutively-enrolled patients.

The occurrence of sICH according to according to SITS-MOST criteria [10] was lower in young adults compared with older adults, although there was non significant difference between the two groups. Intracerebral hemorrhage is known to be an infrequent complication of IVT for the treatment of acute stroke [21,22]. Data from a randomized, placebo-controlled trial in patients with ischemic stroke treated within 3 hours of symptom onset showed that approximately 30% of patients with post-thrombolytic intracerebral hemorrhage according to NINDS criteria [23] had favorable outcomes (mRS 0-3) at 1 year. Moreover, other studies that compared clinical scores using multiple sICH definitions found no meaningful differences between sICH definitions [23-25]. Above all, these findings indicated that the risk of sICH should not be a major concern when treating young stroke patients.

The DRAGON score predicts functional outcome in the hyperacute phase of IVT treatment of ischemic stroke patients [27]. The score consists of 6 parameters with a maximum score of 10 that includes: dense cerebral artery sign or early infarct signs on admission CT head scan, age, glucose level on admission, OTT, NIHSS on admission. In our study, patients with DRAGON score of more than 5 had poor outcome.

Finally, in our analysis, the 3-month mortality rate was lower in patients aged 18-50 years than in older patients (10% vs 21.7%), but there was non significant difference between the two groups. Putaala et al. evaluated 48 patients aged 16 to 49 years with hemispheric ischemic stroke treated with IVT, and none of the young patients died at 3 months [18]. Mortality in our young adults was nearly half that of older patients, which was similar to the SITS-ISTR study results (young vs older: 4.9% vs 14.4%)[26].

The limitation of our study was that the study was conducted in a retrospective observational manner, and the number of young stroke patients was relatively small especially regarding sICH, which may restrict our ability to evaluate multiple factors.

Future larger studies and clinical trails are needed to confirm our findings. Finally, the evaluation of the 3months efficacy of IVT is far from enough and in we should continue the follow-up of these treated patients, to identify the long-term efficacy of IVT in these young patients.

Conclusion

In conclusion, our analysis indicated that IVT with recombinant tissue plasminogen activator (alteplase) is safe and beneficial for Mongolian young adults with acute ischemic stroke. Although larger studies are needed to confirm our findings given our limited sample size, acute ischemic stroke treatment with IVT in young patients should be performed at least as actively as for older patients.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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