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The Effect of Intravenous Alteplase on Patients with Acute Ischemic Stroke: A Clinical Trial Study in a Specialty Hospital in Ilam

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A B S T R A C T

Introduction: Strokes rank among the leading causes of death and disability worldwide, with acute ischemic stroke (AIS) on the rise in Iran. Thrombolytic drugs constitute a primary treatment for ischemic stroke. However, due to limited studies in Iran, there exists hesitation among physicians regarding their administration. This study aims to assess the efficacy of these drugs on AIS patients.

Methods: In a clinical trial, 80 patients with ischemic stroke were divided into treatment and control groups. Both groups were assessed upon admission and 72 hours later using the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS) scores at discharge. The treatment group received Alteplase (0.9mg/kg), while the control group received standard care. Statistical analysis was performed using SPSS 20.

Results: The mean NIHSS ± SD scores at admission and 72 hours later in the treatment group were 10.0±3.51 and 4.55±8.75, respectively, compared to 8.53±3.52 and 7.88±9.21 in the control group, showing a significant difference in favor of the treatment group ($P < 0.001$). Similarly, the mean mRS± SD score in the treatment group was 1.68±1.79, significantly lower than the control group's 3.15±1.61 ($P < 0.001$).

Conclusion: Intravenous Alteplase administration proved effective in treating patients with ischemic stroke, significantly reducing neurological complications and disabilities compared to standard medical care.

Keywords: Cerebrovascular Disorders, Stroke, Tissue Plasminogen Activator, Alteplase, National Institutes of Health Stroke Scale

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Introduction

Among adult neurological diseases, strokes hold the top spot in terms of both prevalence and significance. Their importance lies in the staggering rates of death and disability they cause. Following heart disease, cancer, and accidents, strokes rank as the second leading cause of death in the United States (1). Approximately 85% of acute strokes are ischemic, while the remaining 15% are hemorrhagic (1). As the global average age rises, stroke incidence has surged from 4,309,356 cases annually in 1990 to 6,892,857 cases in 2013 (2). The 30-day mortality rate post-acute stroke stands at 10%, leaving the rest grappling with neurological impairments; hence, roughly 70% of these patients are unable to resume work, with 30% requiring assistance for mobility (2,3). Research conducted in Iran has uncovered a spike in acute stroke cases, with an incidence rate ranging from 128 to 149 per 100,000 individuals. Moreover, studies highlight that the average age of acute stroke onset in Iran is lower compared to the global average (4,5). Given the considerable socioeconomic burden resulting from stroke complications, it's imperative to explore avenues for mitigating their severity. A study conducted in the United States in 1994 delved into the direct and indirect costs associated with stroke complications, revealing annual figures of $20 billion and $46 billion, respectively (6,7). Among the primary treatments for acute ischemic stroke (AIS) are thrombolytic drugs (8), which have been employed in Iran for several years. However, the evidence regarding their efficacy in this context is limited, leading many physicians to administer them with hesitance and caution. While these drugs alleviate the complications of ischemic stroke, they also heighten the risk of intracranial hemorrhage (ICH). Furthermore, the efficacy of thrombolytic drugs has been a subject of debate in comparison to antiplatelet and anticoagulant therapies used for treating acute ischemic stroke. Consequently, this study endeavors to compare the impact of intravenous Alteplase with standard medical care among AIS patients.

Methods

Participants

Through a double-blinded clinical trial, 80 ischemic stroke patients were assessed at Shahid Mostafa Khomeini Hospital in Ilam, Iran, spanning from April 2016 to March 2019. Following the diagnosis of acute stroke, a neurologist conducted examinations on all patients, who underwent brain CT scans to rule out brain hemorrhage. Those identified with acute ischemic stroke were then enrolled and divided into treatment and control cohorts.

The inclusion criteria for this study encompassed a NIHSS (2) score ranging from 4 to 30, with patient referral within 4.5 hours after symptom onset for the treatment group, and within 4.5 to 24 hours for the control group. Exclusion criteria included: a history of stroke within the last 6 weeks, traumatic brain injury within the previous 3 months or trauma to other body parts within the last month, use of warfarin with an International normalized ratio (INR) >1.7, evidence of hemorrhage or brain edema in brain CT scan, a history of cerebral hemorrhage or intracranial tumor, coma, platelet count <100,000, pregnancy, age under 18 or over 80 years, and blood pressure >180/110.

All participants underwent an assessment based on the National Institutes of Health Stroke Scale (NIHSS) upon admission. Subsequently, patients indicating the use of Alteplase were assigned to the treatment group, while others were assigned to the control group and received standard care. Throughout hospitalization and at the time of discharge, patients in the treatment group and those in the control group displaying symptoms suggestive of intracranial hemorrhage (ICH) (manifesting as an increase of more than 4 NIHSS scores during hospitalization) underwent brain CT scans to detect the occurrence of ICH. At 72 hours post-admission, all patients from both groups were re-evaluated using NIHSS criteria, and upon discharge, they were assessed using modified Rankin Scale (mRS) criteria.

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Patients were discharged from the hospital subsequent to undergoing a stroke workup, receiving initial treatment, experiencing symptom amelioration, and having life-threatening complications resolved. Upon discharge, patients were excluded from our study, and their treatment continued with antiplatelet agents, with rehabilitation processes being facilitated in other medical centers.

The National Institutes of Health Stroke Scale (NIHSS) serves as an objective measure to quantify the impairment caused by a stroke. Consisting of 11 items, each item scores a specific ability on a scale from 0 to 4. A score of 0 typically indicates normal function, while higher scores indicate varying levels of impairment. These scores are then summed to calculate the patient's total NIHSS score, ranging from 0 to 42.

On the other hand, the modified Rankin Scale (mRS) assesses the degree of disability or dependence in daily activities among individuals who have experienced a stroke or other neurological disabilities. Spanning from 0 to 6, the scale reflects a spectrum from perfect health without symptoms to death.

Due to the stringent inclusion and exclusion criteria, patients were carefully selected for this study, which posed challenges in matching all potential confounders that could influence outcomes, such as smoking, alcohol consumption, underlying diseases, and occupation. Nevertheless, efforts were made to control for age and the initial NIHSS score by selecting similar patients in the control group to those in the treatment group.

Treatment protocols

In the treatment group, patients were administered Alteplase at a single dose of 0.9mg/kg (with a maximum dose of 90mg). Ten percent of this dose was initially administered as a bolus over 1 minute, followed by the remainder infused over 60 minutes. Additionally, after 24 hours, these patients received subcutaneous injections of 5000 units of Heparin twice daily and 80mg of Aspirin daily until hospital discharge.

On the other hand, patients in the control group were given an initial dose of 325 mg of Aspirin, followed by a daily dosage of 80mg. They also received subcutaneous injections of 5000 units of Heparin twice daily until discharge from the hospital.

This study was conducted with the ethical approval obtained from the Ethics Committee of Ilam University of Medical Sciences (ir.medilam.rec.1396.111).

Statistical analysis

The results were presented as mean ± standard deviation. Data analysis was conducted using paired t-tests, independent t-tests, chi-square tests, and Pearson correlation, as appropriate, utilizing the Statistical Package for the Social Sciences 20.0® (SPSS Inc., Chicago, IL, USA). A p-value of less than or equal to 0.05 was deemed statistically significant.

Results

In this study, 80 acute ischemic stroke patients were evaluated and allocated into two groups. Within the treatment group, 24 (60%) patients were male, while in the control group, 22 (55%) patients were male. There were no significant differences in gender distribution between the treatment and control groups ($P = 0.65$). The mean age ± standard deviation (SD) for the treatment and control groups were 64.5 ± 9.9 and 66.6 ± 7.6 years, respectively ($P = 0.29$) (Table 1).

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Table 1. Patient Characteristics, Clinical Variables, and Outcome of Acute Ischemic Stroke Patients in Treatment and Control Groups.

Variable		Treatment group n=40	Control group n=40	P Value
Demographics	Age (Mean ± SD)	64.5±9.9	66.6±7.6	0.292
	Sex (M)	24 (60%)	22 (55%)	0.656
Outcome	mRS score (Mean ± SD)	1.7±1.8	3.15±1.6	<0.001
	mRS score 0-1 (%)	25 (62.5)	5 (12.5)	<0.001
	mRS score 2-3 (%)	10 (25)	23 (57.5)	<0.001
	mRS score 4-5 (%)	0 (0)	5 (12.5)	<0.001
Complications	ICH (%)	2 (5)	0 (0)	0.160
	Death (%)	5 (12.5)	7 (17.5)	0.537

SD: Standard Deviation; M: Male; mRS: modified Rankin Scale; ICH: Intracranial Hemorrhage

The mean ± SD of NIHSS scores at admission for the treatment and control groups were 10.0 ± 3.5 and 8.5 ± 3.5, respectively, with no statistically significant difference observed (P = 0.06). Subsequently, the mean ± SD of NIHSS scores 72 hours post-admission for the treatment and control groups were 4.6 ± 8.5 and 7.9 ± 9.2, respectively. The mean difference in NIHSS scores between admission and 72 hours later for the treatment and control groups were 5.6 ± 7.4 and 0.7 ± 6.2, respectively, with a significant difference observed in the treatment group (P < 0.001) but not in the control group (P = 0.51) (Table 2).

Table 2. Comparison of NIHSS Scores at Admission and 72 Hours Later in Acute Ischemic Stroke Patients in Treatment and Control Groups.

Variables	Treatment Group	Control group	P Value
Baseline NIHSS (Mean ± SD)	10.0±3.5	8.5±3.5	0.064
72 h later NIHSS (Mean ± SD)	4.6±8.5	7.9±9.2	0.102
↓ Mean Diff. (Mean ± SD)	5.45±7.39	0.65±6.19	<0.001
P Value	<0.001	0.511	

NIHSS: National Institutes of Health Stroke Scale; h: Hours; Diff: Difference; SD: Standard deviation

The mean ± SD of mRS scores at discharge for patients in the treatment and control groups were 1.7 ± 1.8 and 3.2 ± 1.6, respectively, indicating a significant difference (P < 0.001) (Table 1). Notably,

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the most frequent mRS score observed in the treatment group was 1, with none of the patients exhibiting scores 3, 4, or 5, suggesting the absence of severe disability among the treatment group upon discharge. Conversely, in the control group, the most prevalent mRS score at discharge was 3 (indicative of moderate disability), with some patients scoring 4 and 5 (indicating severe disability).

Regarding adverse events, two patients (5%) in the treatment group experienced intracranial hemorrhage (ICH) following treatment with Alteplase, while none in the control group experienced this complication. However, this difference was not statistically significant (P = 0.16) (Table 1). Additionally, there were five deaths among patients in the treatment group (12.5%) and seven deaths in the control group (17.5%) throughout the study period, with no significant difference observed (P = 0.54) (Table 1).

Discussion

Although numerous studies have explored the efficacy of t-PA drugs in treating AIS worldwide, a comprehensive assessment of their effectiveness in Iran is lacking. The FDA approved the use of these drugs for AIS treatment in 1996, and in Iran, the national protocol for prescribing them was established in 2012 (10,11). Despite this, many neurologists in Iran harbor doubts about prescribing these drugs and lack confidence in this treatment modality, likely due to the scarcity of studies on their efficacy and complications within the Iranian context.

The findings of this study revealed that the mean NIHSS scores at admission and 72 hours post-admission were 10.0 and 4.6, respectively, in the treatment group, and 8.5 and 7.9, respectively, in the control group. The difference was significant for the treatment group but not for the control group. In a study conducted by Vuletic and colleagues (2008), the average NIHSS score of AIS patients who received Alteplase at admission and discharge was 12.6 and 5.8, respectively (12).

In another study conducted by Vukasinovic et al. from 2006 to 2009 among patients with AIS who received Alteplase, the average NIHSS score at admission and discharge was 16 and 4.2, respectively (13). Similarly, in a study by Andrade et al. from 2005 to 2009 among AIS patients who received Alteplase, the mean baseline NIHSS score and score 24 hours after receiving Alteplase were 14 and 8, respectively (14). The results of the present study align with these findings, demonstrating that the administration of intravenous Alteplase significantly reduced the NIHSS score of AIS patients. It appears that the use of this medication among AIS patients yields better outcomes compared to standard care alone.

In this study, the mean mRS scores at discharge for the treatment and control groups were 1.7 and 3.2, respectively, indicating a significant difference. Notably, eight patients (20%) in the treatment group achieved an mRS score of 0 (indicating no disability) upon discharge. Additionally, 62.5% of patients in the treatment group and only 12.5% in the control group attained a favorable mRS score (0-1) at discharge, underscoring the superior outcome associated with Alteplase administration.

In a study by Khurana et al. from 2011 to 2015, 39.8% of AIS patients who received rt-PA achieved a favorable mRS score (0-1) in the quarterly survey (15). Similarly, in a study by Hacke and colleagues (1988), 40.3% of AIS patients who received Alteplase and 36.6% of those who received a placebo attained a favorable mRS score (0-1) in the quarterly survey (16). Furthermore, in a study spanning from 2003 to 2014 by Rodrigues et al., 47.5% of AIS patients who received Alteplase achieved favorable mRS scores (0-1) in the quarterly survey (17). Conversely, in a study by Ghiasian and colleagues on AIS patients who received standard care, the mean mRS score at discharge was 2.5 (18).

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In the present study, the mean mRS score of the treatment group at discharge was lower than the figures reported in previous studies, potentially attributable to differences in inclusion criteria or methodological approaches. For instance, Khurana's study included patients over 80 years old, whereas our study excluded patients in this age group. Similarly, in Hacke's study, patients received Alteplase within a 6-hour window from symptom onset, whereas in our study, the time frame for treatment initiation was limited to 4.5 hours post-onset. Additionally, Rodrigues's study included patients over 80 years old and reported a higher mean NIHSS score of 14.3 at admission, whereas our study's treatment group had a lower mean NIHSS score of 10.0 at admission. These variations in inclusion criteria and treatment protocols likely contributed to the improved mRS scores observed in our study compared to others.

In our study, all patients in both the treatment and control groups who exhibited an increase of more than 4 NIHSS scores during hospitalization underwent Brain CT Scan to detect potential intracranial hemorrhage (ICH). None of the control group patients displayed bleeding, whereas ICH occurred in two patients (5%) of the treatment group. ICH is recognized as the most severe and dangerous complication associated with the administration of t-PA drugs, with an estimated incidence among AIS patients ranging from 2% to 7% (19).

In a study conducted in Turkey by Kutluk et al., the occurrence of ICH following rt-PA administration in AIS patients was reported to be 4.9% (20). Similarly, Vukasinovic's study indicated that 4% of AIS patients who received t-PA experienced ICH following treatment (13). These findings align closely with the results observed in our study, underscoring the consistency of ICH incidence across various research investigations.

In our study, the incidence of death during hospitalization was 12.5% in the treatment group and 17.5% in the control group, with no statistically significant difference observed between the two groups. Comparatively, in a study conducted by Liu et al. from 2008 to 2011, the overall mortality rate attributed to ischemic stroke was reported as 18.1% (21). Additionally, in Hacke et al.'s study on AIS patients treated with Alteplase, the death rate was 10.5% (16). Similarly, Vukasinovic and colleagues reported a mortality rate of 16.8% among AIS patients receiving Alteplase (13). Furthermore, in Groppa et al.'s study, 13% of AIS patients treated with Alteplase died during hospitalization (22).

The mortality rate observed in our study closely aligns with the rates reported in these aforementioned studies, demonstrating consistency across different research investigations.

Conclusion

Based on the findings of this study, intravenous administration of Alteplase emerges as an effective treatment for AIS. This medication notably alleviates neurological symptoms and mitigates disabilities resulting from ischemic strokes. The results suggest that the application of Alteplase among AIS patients yields superior outcomes compared to standard care alone.

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Conflict of interest

There is no conflict of interest among the authors involved in this study.

Authors' contributions

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AK and MM: Data analysis and interpretation, drafting, and approval of the final version for publication. RA and AM: Critical interpretation of content, approval of the final version for publication. All authors have reviewed and approved the final version of this study.

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