

Comparison of the Outcome of Alteplase Administration after Acute Ischemic Stroke in Patients Over 80 Years and Under 80 Years Admitted

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Abstract

Introduction

Due to the presence of risk factors leading to bleeding in old age on one hand and the significant effect of alteplase in improving the symptoms of ischemic stroke on the other hand, also considering the high cost of rtPA injection, there are controversies regarding administration of rtPA in patients over 80 years of age. Therefore, in this study, we will compare the results of alteplase administration in patients over 80 years old and under 80 years old after AIS hospitalized in Allameh Bohlool Hospital, Gonabad, Iran.

Material & Method

The present study was a retrospective cross-sectional study. We collected information of all patients hospitalized due to stroke in Allameh Bahloul Gonabadi Hospital during the years 2016 to 2021. Patients treated with rtPA were divided into two groups under 80 years and over 80 years and the treatment results were compared.

Results

In the present study, the first group included 16 patients over 80 years old (86.00 ± 4.25) and 35 patients under 80 years old (65.62 ± 10.77). NIHSS at the time of arrival and at the time of discharge in the first group was 13.25 ± 4.41 and 3.84 ± 4.66 respectively, and in the second group it was 12.20 ± 5.44 and 4.37 ± 4.48 , respectively. Based on the NIHSS score, 10 people from the first group (62.5%) and 25 people from the second group (71.42%) improved (P value = 0.534). Finally, 3 people from the first group (18.3%) and 3 people from the second group (8.6%) died.

Conclusion

The present study showed that alteplase has good therapeutic results in patients over 80 years old as well as in patients under 80 years old. Alteplase for AIS should be evaluated on an individual benefit-risk basis.

Keywords: rtPA, AIS (rtPA), NIHSS, MRS.

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INTRODUCTION

Most ischemic strokes arise secondary to the blockage of blood vessels due to thromboembolism or atheromatous processes (1-3). Today, opening the vein lumen and reestablishing the blood flow of the brain tissue is the most effective treatment strategy. In this sense, clinicians often

administrate intravenous recombinant tissue plasminogen activator (rtPA) to dissolve the clot blocking the vessel (4-6). Of course, rtPA also has risks, for example, it penetrates into the brain after the effect of thrombolysis, and due to its high half-life and being a protease, it acts on the blood vessel building protein platelet-derived growth factor C (PDGF-C) and then acts on its receptor. And finally, it

disrupts the function of the blood-brain barrier (BBB) and causes vasogenic edema, causing rupture of cerebral vessels in that area (7). Recombinant tPA is an activator of plasminogen protein, which is made and secreted in the liver, but is not secreted or secreted less during heart attack, which slows down the healing process. The sooner it is administered, the better the result, and it is possible to inject within four and a half hours from the start of the stroke. The longer the injection is delayed from the start of the stroke, the higher the chance of cerebral hemorrhage after this treatment. This medicine is injected through the brachial vein or intra-arterially. If time is lost and the cause of the stroke is embolism or cerebral thrombosis, drugs such as aspirin or warfarin are prescribed to prevent blood clots by diluting the blood (9).

The NIHSS is a tool that can be used over time to determine whether the stroke is mild or severe, and whether patients are improving or debilitating, according to the severity of the stroke. The main use of the NIH in clinical medicine is to assess whether the degree of disability caused by a stroke is suitable for treatment with tPA or not (10). (0 = no stroke, 1-4 = small stroke, 5-15 = moderate stroke, 16-20 = moderate/severe stroke, 21-42 = severe stroke)

Alteplase is the most commonly used form of rtPA, which converts trapped plasminogen to plasmin. Plasmin breaks down both fibrin and fibrinogen. Alteplase is rapidly cleared from plasma through hepatic metabolism. Its initial half-life is 4 to 5 minutes and its final half-life is about 40 minutes. Allergic reactions due to alteplase occur less than streptokinase. If this drug is injected into a person immediately after a stroke, it causes the clots to disappear quickly and the tissues around it will not be destroyed due to malnutrition and the blood flow will return to normal (11).

In cases where the risk of bleeding is greater than the benefits of drug therapy, including intracranial hemorrhage, subarachnoid hemorrhage, active internal bleeding, recent intracranial or intraspinal surgery, serious head trauma within the last 3 months, uncontrolled severe hypertension, Alteplase is contraindicated (12).

Due to the presence of risk factors leading to bleeding in old age on one hand and the significant effect of alteplase in improving the symptoms of AIS on the other hand, also considering the high cost of rtPA injection, there are controversies regarding administration of rtPA in patients over 80 years of age. Therefore, in this study, we will compare the results of alteplase administration in patients over 80 years old and under 80 years old after acute ischemic stroke (AIS) hospitalized in Allameh Bahloul Hospital, Gonabad in 2019.

MATERIAL AND METHOD

Type of study: Cross-sectional study.

Inclusion criteria

1. Presence of clinical and imaging evidence in favor of ischemic stroke
2. Onset of symptoms within less than 4.5 hours from diagnosis
3. Treatment with rtPA
4. Patient's consent

Exclusion criteria

1. Evidence of hemorrhagic stroke

Summary of methods

The current study was a retrospective cross-sectional investigation. After obtaining the code of ethics to collect the required information, the files of all patients hospitalized due to stroke in Allameh Bohlool Gonabad Hospital from 2016-2021 were reviewed. In this study, patients were contacted to follow up on long-term disabilities caused by AIS (after 6 months) and the rest of the information was collected from the patients' records. Patients treated with rtPA, who met the inclusion criteria, were divided into two groups according to age, under 80 years old and over 80 years old, and demographic characteristics (age and gender), blood pressure and blood sugar at the time of entering the hospital, onset to door (the duration of the onset of symptoms until entering the hospital), door to needle (the duration of entering the hospital until the start of rtPA), patients' risk factors, patients' weight, prescribed rtPA dose, drug complications, NIHSS at the time of admission and during Discharge, MRS at the time of discharge, three months later and six months later were examined and compared in two groups.

Finally, the obtained data were statistically analyzed using SPSS version 26 statistical analysis software. Independent t test was used for quantitative variables such as the level of requested tests, and Pearson test and Spearman coefficient were used to determine the relationship between data. Significance level was considered $P < 0.05$.

Ethical considerations

After the approval of the Regional Ethics Committee of Gonabad University of Medical Sciences (IR.GMU.REC.1400.143), the current study will be evaluated based on the information included in the file, the study criteria during hospitalization and during the follow-up of the patients. Also, the principle of usefulness and non-harmfulness will be observed in this study, and all the participants will be informed about the purpose of the study and how it will be carried out, stating that all their information will be kept confidential and their personal information will not be mentioned anywhere. And after obtaining consent to participate in the study, they will enter the study. Also, the received information will be analyzed in

a coded form, and finally, in the present study, no additional diagnostic and therapeutic interventions will be performed on the patients.

RESULTS

In the present study, the first group included 16 patients over 80 years old (86.00±4.25) and 35 patients under 80 years old (65.62±10.77). In the first group there were 10 men (62.5%) and 6 women (37.5%), and in the second group 21 men (60%) and 14 women (40%). The average systolic and diastolic pressure at the time of arrival to the hospital in the first group was 154.00 + 35.05 and in the second group 65.62 ± 10.77. Blood sugar on arrival in the first group was 129.69 ± 28.75 and in the second group it was 148.60 ± 26.15. The amount of rtPA prescribed was 0.9 mg/kg, which was 56.68 ± 11.71 in the first group and 62.37 ± 10.85 in the second group.

Prevalence of risk factors in the first group was as follows: hypertension (11, 68.8%), diabetes (1, 6.2%), hyperlipidemia (1, 6.2%), history of stroke (1, 6.2%) and history of drug abuse (0%). Prevalence of risk factors in the second group was as follows: hypertension (22, 62.9%), diabetes (8, 22.9%), hyperlipidemia (4, 11.4%), history of stroke (1, 2.9%) and history of drug abuse (1, 2.9%).

NIHSS at the time of arrival and at the time of discharge in the first group was 13.25 ± 4.41 and 3.84 ± 4.66 respectively, and in the second group it was 12.20 ± 5.44 and 4.37 ± 4.48, respectively (table 1). Based on the NIHSS score, 10 people from the first group (62.5%) and 25 people from the second group improved (71.42%) (P value = 0.534).

Table 1: Comparison of rtpa effect in two groups Based on the NIHSS score

group	Initial NIHSS score	Discharge NIHSS score	Recovered people	P value
first group (over 80)	13.25 ± 4.41	3.84 ± 4.66	6 (37.5%)	0.534
second group (under 80)	12.20 ± 5.44	4.37 ± 4.48	10 (71.42%)	

Finally, 3 people from the first group (18.3%) and 3 people from the second group (8.6%) died. Full functional independence based on MRS scores at 0, 3, and 6 months after receiving rtpa was seen in 5 (31/2%), 9 (69/2%) and 9 (69/2%) people in the first group, respectively, and in 14 (40%), 22 (68.8%) and 24 (75%) people, respectively, in the second group. (p value = 0.532, 0.538 and 0.156) (table 2).

Table 2: Comparison of complete functional independence based on MRS scores at 0, 3 and 6 months after receiving rtpa in two groups

	first group (over 80)	second group (under 80)	P value
MRS0	5 (31/2%)	14 (40%)	0.532
MRS3	9 (69/2%)	22 (68.8%)	0.538
MRS6	9 (69/2%)	24 (75%)	0.156

DISCUSSION

In this study based on the NIHSS score, 10 people from the first group (62.5%) and 25 people from the second group improved (71.42%). also 3 people from the first group (18.3%) and 3 people from the second group (8.6%) After receiving rtpa died. In 2022, Ahmetović et al. retrospectively followed 102 stroke patients aged ≥ 80, 50% of whom had undergone endovascular thrombectomy (ET), with the remaining half receiving only symptomatic treatment (ST). They found that patients who had received ET were more likely to perform their daily activities without assistance than those who had only received ST. Moreover, ET was found to be associated with lesser post-stroke mortality than ST (33% vs. 41%) (9). The same year, McDonough et al. surveyed the efficacy of ET in 1,764 patients with stroke, 4.4% of whom were aged ≥85, reporting a markedly lower rate of mortality among older patients undergoing ET compared to the control group of the same age (31.0% vs. 54.3%) (10).

According to the treatment guidelines in Iran, the only medicine used in the present study was the rtpa. Yogendrakumar et al., in 2022, evaluated the therapeutic effects of Tenecteplase (TNK), a tPA, in 137 older stroke patients (age > 80) with large vessel occlusion. Their findings indicated that administration of TNK (0.25 mg/kg) was associated with better 90-day modified Rankin Scale (mRS) scores than alteplase, with an overall lesser rate of mortality. However, such beneficial effects, in relation to alteplase, were not observed with higher doses of TNK (0.40 mg/kg) (11). Later that year, Chen et al. explored the efficacy of alteplase on 378 patients with ischemic stroke, reporting beneficial effects in all age subgroups (12).

In 2021, Khazaal et al. investigated the outcomes of dual antiplatelet therapy (tPA + thrombectomy) compared with single antiplatelet therapy (thrombectomy) on 377 stroke patients, reporting lesser frequency of symptomatic ICH compared to those receiving single therapy (13). The same year, Krajčicková et al. analyzed the outcomes of single ET and dual ET/IVT (intravenous thrombolytic therapy) in 138 patients aged ≥ 80, suggesting that IVT was a negative predictor of 3-month good clinical outcome (14). A small-scale study in 2021 by Baena Álvarez et al. on 4 female patients (age > 100) with AIS reported that 3 patients were functionally independent within 90 days from receiving

alteplase (15). Xiong *et al.* reported a discharge rate of 91.1% in 6,752 patients (age > 80) with mild stroke who had been treated with intravenous rtPA, with only 18.5% experiencing unfavorable outcomes (16). In this study Full functional independence based on MRS scores at 0, 3, and 6 months after receiving rtpa was seen in 5 (31/2%), 9 (69/2%) and 9 (69/2%) people in the first group, respectively, and in 14 (40%), 22 (68.8%) and 24 (75%) people, respectively, in the second group. Thommessen *et al.* compared TNK against alteplase in a population of 273 Norwegian patients with stroke (age > 80), reporting a rate of 3-month excellent functional outcome in 43.1% vs. 39.9% for patients receiving TNK and alteplase, respectively. Three-month mortality rate was measured to be 14.3% for the TNK group and 15.3% for alteplase group (17). In 2020, Sari Aslani *et al.* surveyed 217 stroke patients with a mean age 66 undergoing thrombolytic treatment, reporting a mortality and discharge rate of 21.7% and 78.3%, respectively (18).

CONCLUSION

The present study showed that alteplase has good therapeutic results in patients over 80 years old as well as in patients under 80 years old. Alteplase for AIS should be evaluated on an individual benefit-risk basis. To compare the effectiveness of alteplase in people over 80 years old and under 80 years old after AIS, few studies have been done so far and reliable and sufficient evidence is not available. Among the advantages of this research, it can be mentioned that now a number of Iranian specialists consider rtPA injection inappropriate in elderly people due to the presence of risk factors, but in new researches, evidences of the effectiveness of alteplase administration have been observed in middle-aged people. This study can help us in identifying the best treatment. Also, with a better understanding of the pathophysiology of the disease, we can hope for therapeutic measures in the field of preventing disability caused by stroke. Considering the significant prevalence of stroke and the heavy burden of this disease on the health and economy of the society, it is appropriate that with more research in this field and a better understanding of the effects of the disease, prevention, diagnosis and treatment methods for this disease at the public level.

LIMITATION

This was a single-center study with population-specific results, which may not be extrapolated to other communities. Also, some variables may be affected by confounding factors and demographic conditions. Therefore, it is recommended to conduct similar studies in several centers and check more parameters.

AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection and acquisition were performed. All authors read and approved the final manuscript.

Compliance with ethical standards:

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