Factors affecting in-hospital delay of intravenous thrombolysis for acute ischemic stroke

A retrospective cohort study

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Abstract

This study was designed to investigate the factors affecting the in-hospital delay of intravenous thrombolysis (IVT) for acute ischemic stroke (AIS).

Two hundred and forty-eight consecutive AIS patients treated with intravenous administration of alteplase in Gansu Provincial Hospital from December 2014 to August 2018 were enrolled retrospectively in this study. According to door-to-needle (DTN) time, the patients were divided into either a delay group (DTN time > 60 minutes; n = 184) or a non-delay group (DTN time ≤ 60 minutes; n = 64). The baseline data, laboratory tests, onset-to-door (OTD) time, door-to-accepting time (DTA), door-to-imaging time (DTI), and decision-making time in both groups were recorded. Multivariate logistic analysis was performed to analyze the data.

There were significant differences in previous history of cerebral ischemic attack, emergency system admission, education degree of decision makers, annual income, admission National Institutes of Health Stroke Scale (NIHSS), OTD time, DTA time, decision-making time between the 2 groups (all $P < .05$). Other baseline data and clinical features showed no significant difference between 2 groups ($P > .05$). Multivariate logistic regression analysis revealed that the risk of in-hospital delay was lower for the higher NIHSS score (OR = 0.775, 95% CI: 0.644-0.933, $P = .007$), the longer OTD time (OR = 0.963, 95% CI: 0.937-0.991, $P = .010$), the shorter decision-making time (OR = 1.224, 95% CI: 1.004-1.492, $P = .045$).

This study suggested that NIHSS score, OTD time and decision-making time are the independent factors affecting the in-hospital delay of IVT for AIS.

Abbreviations: AIS = acute ischemic stroke, DTA = door-to-accepting time, DTI = door-to-imaging time, DTN = door-to-needle, IVT = intravenous thrombolysis, NIHSS = National Institutes of Health Stroke Scale, OTD = onset-to-door, rt-PA = recombinant tissue-type plasminogen activator.

Keywords: acute ischemic stroke, alteplase, in-hospital delay, intravenous thrombolysis

1. Introduction

Acute ischemic stroke (AIS) is the most common stroke type, accounting for 80% of the total numbers of stroke and the primary cause of adult disability.[1,2] Intravenous thrombolysis (IVT) is a proven effective therapy for patients suffering from AIS.[3] Studies showed that the time from onset to initiation of therapy is an important factor for good clinical outcome of IVT for AIS patients.[4,5] Recombinant tissue-type plasminogen

activator (rt-PA) has a strong thrombolytic effect. Time window (3–4.5 hours) is the only prerequisite for the thrombolysis with intravenous rt-PA.[6,7] The effectiveness of rt-PA treatment decreases as time from onset of AIS to use of rt-PA increases. It is the most effective to use rt-PA within 1.5 hours of onset of AIS and remains effective within 4.5 hours.[8] The American Heart Association (AHA)/American Stroke Association (ASA) guidelines recommend that DTN time should be ≤60 minutes.[9] Nevertheless, the goal of a door-to-IVT time within 60 minutes was achieved in only 40% of patients treated with IVT in America.[10] Chinese National Stroke Registry Study showed that the average door-to-needle (DTN) time of AIS patients was 116 minutes.[11] In China, less than 22% of all AIS patients arrived at hospital within 3 hours of onset of AIS, of which only 1.6% could be treated with IVT.[9] In-hospital delay contributed substantially to the barriers of the availability to IVT, which could even jeopardize the population benefit from extending the therapeutic time window of IVT.[12] The purpose of this study is to determine the factors affecting in-hospital delay and to share our experience to decrease in-hospital delay.

2. Materials and methods

2.1. Participants' enrollment and groups

Consecutive 248 AIS patients treated with rt-PA in Department of Cerebrovascular Disease Center of Gansu Provincial Hospital from January 2014 to August 2018 were included in this analysis.

According to DTN time, they were divided into either a delay group (DTN time > 60 minutes; n=184) or a non-delay group (DTN time ≤ 60 minutes; n=64). AIS patients or their family members should complete an in-person interview. The interview contained a detailed questionnaire regarding stroke risk factors and demographics. Emergency system admission, National Institutes of Health Stroke Scale (NIHSS), systolic blood pressure, serum glucose, occlusion site, CT manifestations and typing of responsible vessels, DTN, onset-to-door time (OTD), hospital arrival time, door-to-accepting time (DTA), door-to-imaging time (DTI), decision-making time were collected from the electronic medical record system.

2.2. Standard protocol approvals

This study was approved by the Ethical Committee of Gansu Provincial Hospital. Written informed consents were obtained from all included patients or their family members.

2.3. Performance of IVT

IVT using rt-PA (Boehringer Ingelheim) was performed as method described previously.[13] The doses of rt-PA were 0.5 to 0.9 mg/kg with the maximum dose of less than or equal to 90 mg. The administration rate was that 10% of rt-PA was injected within 1 minute and the remaining 90% was given intravenously within 1 hour. There was no contraindication for thrombolytic therapy. Admission NIHSS scores were evaluated and recorded by specialist senior physicians

2.4. Statistical analysis

All calculations were performed using SPSS 21.0 software, with 2 tailed $P < .05$ as statistically significant. Pearson chi-squared test was used for categorical variables and a Student's t test or Mann-Whitney U test for continuous variables. Multivariable linear regression analysis was used to identify factors of in-hospital delay.

3. Results

3.1. Comparison of demographic characteristics between 2 groups

As shown in Table 1, there were 184 cases in delay group and 64 cases in non-delay group respectively. The mean ages were 64.17 years in delay group and 64.63 years in non-delay group respectively 54.3% and 50.0% of cases were male patients respectively. There were significant differences in transient ischemic attack, emergency system admission, the education of decision maker, annual income between the 2 groups (all $P < .05$). Other demographic characteristics such as gender, age and medical history showed no significant differences in 2 groups ($P > .05$).

3.2. Comparison of clinical features and time intervals between 2 groups

The results revealed that delay group had lower scores of NIHSS ($P < .01$) than non-delay group. DTA ($P = .01$) and decision-making time ($P = .03$) were significantly longer, but OTD ($P < .01$) were significantly shorter (Table 2) in delay group than that in non-delay group. Other clinical features such as SBP,

Table 1

Comparison of demographic characteristics between 2 groups.

Items	Delay group (n=184)	Non-delay group (n=64)	P
Gender			.548
Male	100 (54.3)	32 (50.0)	
Female	84 (45.7)	32 (50.0)	
Age (yr)	64.17±5.45	64.63±4.46	.767
Weight (kg)	65.50±10.81	63.19±9.66	.355
Medical history			
Hypertension	96 (52.2)	16 (25.0)	.015
Diabetes	64 (34.8)	28 (43.8)	.393
Transient ischemic attack	28 (15.2)	28 (43.8)	.000
Hyperlipemia	84 (45.7)	32 (50.0)	.720
Atrial fibrillation	44 (23.9)	20 (31.2)	.381
Emergency system admission	72 (39.1)	44 (68.8)	.018
Education of decision maker			.022
Graduate degree and above	132 (71.8)	36 (56.3)	
Graduate degree below	52 (28.3)	28 (3.8)	
Annual income of patients			.000
≥RMB 120,000	60 (32.6)	40 (62.5)	
<RMB 120,000	124 (67.4)	24 (37.5)	

DBP, blood glucose, typing of responsible vessels, CT manifestations, hospital arrival time and DTI time showed no significant differences in 2 groups ($P > .05$).

3.3. Multivariate linear regression analysis to identify independent variables that affect in-hospital delay

As shown in Table 3, seven variables (sex, age, weight, NIHSS, hospital arrival time, emergency system admission, OTD time, decision-making time) were included in the multivariate linear regression models, respectively to analyze the risk factors affecting the in-hospital delay. The results revealed that the in-

Table 2

Comparison of clinical features and time intervals between 2 groups.

Items	Delay group (n=184)	Non-delay group (n=64)	P
NIHSS	10.67±5.88	16.58±12.66	<.001
SBP (mmHg)	137.38±14.27	137.38±14.278	.322
DBP (mmHg)	78.07±9.10	76.75±8.18	.615
Blood glucose (mmol/L)	7.87±2.51	8.01±2.52	.855
Typing of responsible vessels			.14
Arteria carotisinterna	76 (41.3)	12 (18.8)	
Middle cerebral artery	48 (26.1)	32 (50.0)	
Arteria basilaris	60 (32.6)	20 (31.2)	
CT manifestations			.248
New infarcts	44 (23.9)	20 (31.2)	
No infarcts	140 (76.1)	44 (68.8)	
Hospital arrival time			.007
8:00 to18:00	116 (63.0)	52 (81.2)	
18:00 to 8:00 (+1 day)	68 (37.0)	12 (18.8)	
OTD (min)	70.98±27.79	108.31±41.00	<.001
DTA (min)	16 (12–30)	12 (10–15)	.015
DTI (min)	18.87±4.23	16.44±3.40	.235
Decision-making time (min)	5 (0–12.5)	1.5 (0–5)	.036

DBP = diastolic blood pressure, DTA = door-to-accepting time, DTI = door-to-imaging time, NIHSS = National Institutes of Health Stroke Scale, OTD = onset-to-door time, SBP = systolic blood pressure.

Multivariate linear regression analysis to identify independent variables that affect in-hospital delay.

Variables	Standardized coefficient	95% CI	*P*
Gender	1.482	0.198–11.079	.701
Age	1.011	0.943–1.085	.742
Weight	0.993	0.894–1.103	.909
NIHSS	0.775	0.644–0.933	.007
Hospital arrival time	0.237	0.030–1.847	.169
Emergency system admission	0.529	0.088–3.189	.488
Onset-to-door time	0.963	0.937–0.991	.010
Decision-making time	1.224	1.004–1.492	.045

hospital delay was closely related to NIHSS score (OR = 0.775, 95% CI: 0.644-0.933, P =.007), OTD time (OR = 0.963, 95% CI: 0.937-0.991, P =.010) and decision-making time (OR = 1.224, 95% CI: 1.004-1.492, P =.045). These results suggested that NIHSS and OTD and decision-making time were the independent risk factors of in-hospital delay of IVT for AIS patients.

4. Discussion

At present, the most effective treatment for AIS patients is IVT with rt-PA.[14–16] However, this therapy has the disadvantages of a strict time window, a large number of contraindications and high cost, resulting in not using widely in China. According to the National Stroke Record Database of China, only 1.6% of AIS patients undergo IVT in China. Patients with thrombolytic DTN ≤ 60 minutes are approximately 26.6% to 47.0% all over the world.[9] Prompt administration of rt-PA for AIS patients has been shown to improve patients' outcomes. To optimize the benefits of IVT, all efforts should be directed towards reducing or even eliminating treatment delays. In the present study, we investigated the factors associated with in-hospital delay in Gansu Provincial Hospital, revealing that NIHSS and OTD and decision-making time were the independent risk factors of in-hospital delay.

NIHSS is a relatively universal and concise stroke assessment scale in the world, mainly evaluating the neurological deficits in the treatment of AIS.[3] The level of NIHSS score can reflect the clinical situation of the patient more intuitively.[17,18] This study shows that patients with higher admission NIHSS scores have a lower risk of in-hospital delays, which might be explained by that fact that severe clinical symptoms easily attracted the family members and emergency medicine specialist and specialist physicians. Namely, the patients who have higher NIHSS score underwent quick inspections after they arrived at hospital and the green channel in hospital for AIS closely connected all stroke units, which reduced hospital transit time and the risk of in-hospital delays. The OTD was independent risk factor of in-hospital delay, which might be attributed to the facts that the longer time of the symptom progression makes the DTN time shorter. Our results are consistent with the reports in other study.[19] The inverse relationship between OTD time and DTN time is known as the '3-hour effect'. The DTN time of patients admitted to the hospital at the early time window are longer than that of cases admitted for nearly 3 hours of onset of stroke.[20,21] In our series, the '3-hour effect' significantly interfered with DTA time, which may be associated with the

emergency level perceived by clinicians. Clinicians are more concerned about critical patients. Patients with shorter time of symptom progression have more time for IVT and were treated with less urgency. It is well known that the effect of IVT is significantly reduced with the increase in the time from the onset of AIS to the acceptance of IVT. Receiving early IVT suggested the better prognosis of patients. In order to ensure the therapeutic effect, patients within the time window also should receive IVT as soon as possible. For eliminating the 3-hour effect, previous studies proposed some actions including constant review of DTN times by the stroke care team, exchange of feedback among doctors responsible for in-hospital care of acute stroke patients, and better adherence to treatment guidelines.[21]

Decision-making process for IVT could be a factor affecting in-hospital delay. Our study supported that the process of decision-making for IVT contributed to a prominent in-hospital delay. At present, AIS patients should be firstly examined by emergency physician followed by being informed to specialists. Once the definite diagnosis is made, medical professionals should communicate with patients or their family members stating the risk of IVT, letting them to sign the consents which are absolutely necessary. In China, AIS patients or their family members have much more concerns about IVT risks and expensive cost of rt-PA, leading to the longer time to make a decision, subsequently increasing DTN time. The international standard of DTN time is 60 minutes, while the average DTN of Chinese AIS patients are 116 minutes. This difference might be largely due to the longer decision-making time in China. In USA, United Kingdom, and some European countries, IVT for AIS patients is mostly routine and signing a consent form is not necessary.[19] The relationship between doctors and patients in China is complex. Candidates older than 60 years undergoing IVT in China usually have more than 1 son or daughter, making it even harder to designate an appropriate decision-maker. The public education regarding the AIS in China is not as good as that in Western countries, resulting in the facts that the presentation of risk and benefit is often biased by the physicians who are under threat of frequent violence from the patients or their family members. In order to confirm that patients or their family members understand the risks and take all responsibilities of the potential unexpected outcomes, signing a consent form is of absolute necessities. To eliminating the influence, clinical professionals should be trained to have the talking skill; therefore, the DTN time is accordingly reduced.

The in-hospital delay in China is mainly due to the lack of coordination between all stroke units from previous study.[22] In order to reduce the DNT time and increase the rate of thrombolytic therapy, some measures were taken in China and remarkable results were achieved,[23,24] making the delay less serious. For the first time, our study supported that in-hospital delay is mainly due to longer time of physician's assessment of the patient's condition, as well as the poorer communication between physicians and patients.

Our study has several limitations. First, one single-center experience may not depict the full picture of the whole country. Second, we did not divide the degrees of severity of delay situation. Finally, our experience on reducing in-hospital delay might be only successfully applied in specific local conditions (e.g., Lanzhou). However, given to the huge homogeneity in the process of IVT, efforts to reduce in-hospital delay are more likely to work in a similar way.

5. Conclusion

In summary, this study suggested that NIHSS score, OTD time, and decision-making time are the independent factors affecting the in-hospital delay of thrombolysis for AIS.

Author contributions

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