Int J Clin Exp Med 2020;13(10):7896-7902
www.ijcem.com /ISSN:1940-5901/IJCEM0117119

Original Article

Observation on the clinical effects of alteplase thrombolysis combined with arterial stent thrombectomy for acute stroke

Haihong Zhang[1], Wenchen Li[2]

Departments of [1]Emergency, [2]Neurology, Dongyang Hospital Affiliated to Wenzhou Medical University, Dongyang, Zhejiang Province, China

Received June 28, 2020; Accepted July 19, 2020; Epub October 15, 2020; Published October 30, 2020

Abstract: Objective: To study the clinical effects of alteplase thrombolysis combined with solitaire AB stents thrombectomy for acute stroke. Methods: Patients with acute stroke treated in Dongyang Hospital Affiliated with Wenzhou Medical University from January 2017 to March 2020, were randomly divided into the thrombolysis group (n=60) and the combined treatmen group (n=60). The thrombolysis group was treated with alteplase thrombolysis only, while the combined treatment group was treated with alteplase thrombolysis + solitaire AB stents thrombectomy. Before treatment, at 1 day, and 1 week after treatment, glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), S100β, C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) were detected; besides the, National Institutes of Health Stroke Scale (NIHSS) score and modified ranki scale (mRS) score were also observed. Results: Compared with before treatment, both groups had lower levels of GFAP, NSE, S100β, CRP, TNF-α and lower NIHSS and mRS scores at 1 day, which were even lower at 1 week after treatment (P<0.05). Compared with the thrombolysis group, there were lower levels of GFAP, NSE, S100β, CRP, TNF-α and lower NIHSS and mRS scores in the combined treatment group at 1 day and 1 week after treatment (P<0.05). The recanalization rate in the combined treatment group was higher than that in the thrombolysis group (P<0.05). Conclusion: Alteplase thrombolysis combined with solitaire AB stents thrombectomy for acute stroke has obvious clinical efficacy, improves patient's nerve function, promotes recanalization, reduces adverse events and improves the treatment safety.

Keywords: Alteplase, arterial stent thrombectomy, acute stroke, vascular recanalization, safety

Introduction

Acute stroke is a common and serious cardiovascular disease related to atherosclerosis. With the blood circulation affected, brain tissue necrosis and neurological dysfunction occur due to prolonged hypoxia and ischemia in the brain. Patients are prone to limb paralysis, and consciousness disturbances; often facing a high risk of disability [1, 2]. At present, clinical treatment, such as thrombolysis and anti-platelet therapy, mainly promote the flow of the blood supply in the occluded blood vessels within a short time. Stent thrombectomy has achieved certain therapeutic effects in the treatment of acute ischemic stroke [3, 4].

Alteplase, a glycoprotein with a high affinity for fibrin, can promote the conversion of plasminogen to plasmin. Combined with fibrin, it promotes thrombolysis and vessels regeneration, thereby improving blood supply recovery and reducing damage and necrosis in brain tissues [5, 6]. A study pointed out that alteplase caused no damage to the coagulation system and saved patients from bleeding tendency [7]. Currently, solitaire stent mechanical thrombectomy is a widely-used treatment for intravenous thrombolysis bridging endovascular occlusions. Its main advantages lie in it being a simple operation and it has a high recanalization rate, which can be increased in patients with cerebral infarction [8]. There are few clinical studies on alteplase thrombolysis combined with arterial stent thrombectomy. This paper aims to observe the clinical effects of alteplase thrombolysis combined with solitaire AB stents thrombectomy for acute stroke, and provide a new

research direction for clinical treatment of acute stroke.

Materials and methods

Clinical information

A total of 120 patients (70 males and 50 females) with acute stroke admitted to Dongyang Hospital Affiliated with Wenzhou Medical University from January 2017 to March 2020 were selected, and randomly divided into the thrombolysis group (n=60) and the combined group (n=60). They were 40-78 years old (average age: 59.6±10.3 years old), and the course of disease lasted for 1-6 h (mean course: 3.5±0.6 h). This study was approved by the Ethics Committee of Dongyang Hospital Affiliated with Wenzhou Medical University.

Inclusion criteria: All patients were diagnosed with acute stroke by CT and MRI. Time of onset was no more than 6 h. Patients had clear consciousness or occasional drowsiness. Their expected survival was more than 6 months. Patients had no mental illness or communication disorders. Informed consent was signed by patients and their family who were included in this study.

Exclusion criteria: Patients were allergic to alteplase. Patients had organ damage (such as liver, kidney). Patients had a history of intracranial hemorrhage and gastrointestinal bleeding.

Methods

Patients in two groups received blood pressure regulation and water-electrolyte balance upon admission. The thrombolysis group was treated with alteplase (RK20180329n, Boehringer Ingelheim Pharmaceuticals Co., Ltd., Germany) with a total dose of 0.9 mg/kg. The first 10% of the total dose was injected within 1 min. The remaining dose was given via intravenous infusion and was completed within no more than 60 min. After thrombolysis, targeted treatment was provided according to patient's conditions assessed by brain CT scan.

The combined group was treated with solitaire AB stents thrombectomy based on alteplase thrombolysis. In a supine position, the patients were locally anesthetized bilaterally in their groin area after disinfection. The right femoral artery was punctured with the Seldinger technique. The blood vessel and the guide tube were moved to a 6F vascular sheath after angiography. The micro-catheter in the occlusion section, combined with the micro-guide wire was slowly inserted to break up the thrombus. After angiography, the patency of blood vessels was checked. Solitaire AB stents (Micro Therapeutics Inc. dba ev3 Neurovascular, USA) were placed in the occlusion vessel. Once the stents were opened, the embolism was removed. With the blood vessels were unblocked, the stents were collapsed and withdrawn with the micro-catheter. The heart rate and blood pressure of patients in the two groups were observed at all times during treatment. Additionally, calcium ion antagonists and antiplatelet therapy were given to the patients after surgery.

Outcome measures

Main outcome measures: (1) Before treatment, at 1 day and 1 week after treatment, fasting venous blood (5 mL) was collected, and centrifuged (3,000 r/min, 15 min). The levels of glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), S100β, C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) were detected by enzyme-linked immunosorbent assay. The kits used were all provided by Wuhan Elite Biotechnology Co., Ltd. (2) Before treatment, at 1 day and 1 week after treatment, the National Institutes of Health Stroke Scale (NIHSS) score was used to evaluate the nerve function. A score of 0-1 was classified as normal, a score of 2-4 was classified as mild injury, a score of 5-15 was classified as moderate injury, a score of 16-20 was classified as moderate-to-severe injury, and a score of 21-42 was classified as severe injury [9]. (3) Modified Rankin Scale (mRS) was adopted to assess patient prognosis [10]. A score of 0 was defined as no symptoms/normal; a score of 1 was defined as no significant disability despite symptoms and able to carry out all usual duties and activities; a score of 2 was defined as slight disability, but able to look after their own affairs without assistance; a score of 3 was defined as moderate disability, requiring some help, but able to walk without assistance; a score of 4 was defined as moderately severe disability, unable to walk or attend to own bodily needs without assistance; a score of 5 was defined as

Table 1. Comparison of general information ($\bar{x}$ ± SD)

General information	Thrombolysis group	Combined group	t/x^2	P
Male/Female (n)	36/24	34/26	0.137	0.711
Average age (year)	59.1±10.1	58.9±10.6	0.106	0.916
Mean course (h)	3.5±0.8	3.8±0.9	1.930	0.056
Body mass index (kg/m^2)	23.52±2.63	23.86±2.25	0.761	0.448
White blood cell count (×10^9)	8.1±2.9	7.9±2.9	0.378	0.706
Neutrophil (%)	68.9±13.3	68.1±13.7	0.325	0.746
Infarct site ≥2 (n)	36	33	0.307	0.580
Atrial fibrillation (n)	19	22	0.333	0.564
Hypertension (n)	35	32	0.304	0.581
Hyperlipidemia (n)	35	37	0.139	0.709
Diabetes mellitus (n)	20	22	0.147	0.702
Homocysteine (n)	30	28	0.313	0.715
Obesity (n)	28	26	0.135	0.714
Smoking (n)	32	30	0.133	0.715

severe disability, bedridden, and requiring constant nursing care and attention. The scores of 0-1 points meant that the patient has a good prognosis, otherwise, indicating a poor prognosis.

Secondary outcome measures: (1) Via cerebral angiography, the recanalization rate of the patients in the two groups at 1 week after treatment was recorded. Recanalization rate = number of recanalization cases/total number of cases * 100%.

Statistical analysis

SPSS 20.0 statistical software was used for statistical processing. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± SD). Repeated measures analysis of variance was adopted for comparison among multiple time points. Bonferroni correction was used for post-hoc pairwise comparisons. Independent t-test was used for comparison between groups. Enumeration data were expressed in cases/percent (n/%). P<0.05 was considered statistically significant.

Results

Comparison of general information

As shown in **Table 1**, the two groups of patients were not statistically different in the general information, which indicated that the groups were comparable (all P> 0.05).

Effects of alteplase thrombolysis combined with solitaire AB stents on the levels of GFAP, NSE and S100β

As shown in **Table 2**, there were no significant differences in the levels of GFAP, NSE and S100β before treatment between the two groups (all P>0.05). After treatment, the levels of GFAP, NSE and S100β in the two groups were reduced, and the levels of which were even significantly lower at 1 week after treatment than at 1 day after treatment (all P<0.05). Compared with the thrombolysis group, the combined treatment group had lower levels of GFAP, NSE and S100β, at both 1 day and 1 week after treatment (all P<0.05).

Effects of alteplase thrombolysis combined with solitaire AB stents on NIHSS and mRS scores

There was no significant difference in NIHSS and mRS scores before treatment between two groups (P>0.05). NIHSS scores and mRS in the two groups were lower at 1 day and became much lower 1 week after treatment (all P<0.05). In comparison to the thrombolysis group, the combined treatment group had lower NIHSS and mRS scores before treatment, at 1 day and 1 week after treatment (all P<0.05). See **Table 3**.

Effects of alteplase thrombolysis combined with solitaire AB stents on inflammatory factors

As shown in **Table 4**, the levels of CRP and TNF-α before treatment between two groups were similar (both P>0.05). After treatment, the levels of CRP and TNF-α showed a decreased tendency at 1 day after treatment and were further reduced at 1 week after treatment (all P<0.05). The above indicators were lower in the combined treatment group than those in the thrombolysis group after treatment (all P<0.05).

Table 2. Comparison of the levels of GFAP, NSE and S100β ($\bar{x}$ ± SD)

Group		Thrombolysis group (n=60)	Combined group (n=60)	*t*	P
GFAP (pg/mL)	Before treatment	4.12±1.57	4.16±1.51	0.142	0.887
	At 1 day after treatment	3.85±1.05*	3.10±0.85*	4.3	0.001
	At 1 week after treatment	3.37±0.44*,#	2.06±0.25*,#	20.05	0.001
NSE (ng/mL)	Before treatment	45.52±10.11	45.46±10.18	0.032	0.974
	At 1 day after treatment	40.12±8.62*	36.62±5.15*	2.7	0.008
	At 1 week after treatment	38.86±5.15*,#	21.35±3.29*,#	22.19	0.001
S100β (ng/mL)	Before treatment	2.15±0.89	2.16±0.80	0.065	0.949
	At 1 day after treatment	2.02±0.40*	1.79±0.28*	3.649	0.001
	At 1 week after treatment	1.89±0.25*,#	1.25±0.17*,#	16.4	0.001

Note: Compared with the same group before treatment, *P<0.05; compared with the same group at 1 d after treatment, #P<0.05. GFAP: glial fibrillary acidic protein; NSE: neuron specific enolase.

Table 3. Comparison of NIHSS and mRS ($\bar{x}$ ± SD)

Group	NIHSS score (points)			mRS (points)		
	Before treatment	At 1 day after treatment	At 1 week after treatment	Before treatment	At 1 day after treatment	At 1 week after treatment
Thrombolysis group (n=60)	31.25±6.36	23.33±3.35*	15.63±2.44*,#	1.97±0.13	1.68±0.52	1.40±0.44#
Combined group (n=60)	31.52±5.57	19.62±3.86*	9.88±2.31*,#	1.95±0.15	1.10±0.40	0.89±0.22#
t	0.247	5.623	13.260	0.781	6.848	8.030
P	0.805	0.001	0.001	0.437	0.001	0.001

Note: Compared with the same group before treatment, *P<0.05; compared with the same group at 1 d after treatment, #P<0.05. NIHSS, National Institutes of Health Stroke Scale; mRS, modified ranki scale.

Table 4. Comparison of CRP and TNF-α levels before and after treatment ($\bar{x}$ ± SD)

Group	CRP (mg/L)			TNF-α (ng/L)		
	Before treatment	At 1 day after treatment	At 1 week after treatment	Before treatment	At 1 day after treatment	At 1 week after treatment
Thrombolysis group (n=60)	11.30±2.25	10.52±2.26*	9.38±1.15*,#	55.62±7.67	50.52±5.52*	41.25±5.52*,#
Combined group (n=60)	11.40±2.20	8.85±1.12*	5.05±0.99*,#	56.05±7.60	36.63±5.57*	26.30±4.20*,#
t	0.246	5.129	22.100	0.372	13.720	16.700
P	0.806	0.001	0.001	0.710	0.001	0.001

Note: Compared with the same group before treatment, *P<0.05; compared with the same group at 1 d after treatment, #P<0.05. CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

Table 5. Comparison of the incidence of adverse events (n, %)

Group	Intracranial hemorrhage	Re-occlusion	Spontaneous intracerebral hemorrhage	Hemorrhagic thrombosis	Adverse event
Thrombolysis group (n=60)	3 (5.00)	2 (3.33)	2 (3.33)	3 (5.00)	10 (16.67)
Combined group (n=60)	3 (5.00)	4 (6.67)	4 (6.67)	4 (6.67)	15 (25.00)
x^2	0.000	0.702	0.702	0.152	1.263
P	1.000	0.402	0.402	0.697	0.261

Effects of alteplase thrombolysis combined with solitaire AB stents on the incidence of adverse event rate

The combined group showed a similar incidence of adverse events when compared to the thrombolysis group (P>0.05). See **Table 5**.

Effects of alteplase thrombolysis combined with solitaire AB stents on recanalization

The recanalization rate (81.67%, (49/60)) of the combined treatment group was higher than that of the thrombolytic group (63.33%, (38/60)) (x^2=5.057, P=0.025). See **Figure 1**.

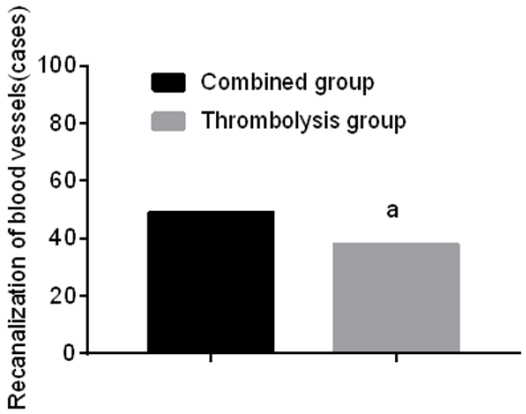

Figure 1. Comparison of recanalization. Compared with the combined group, [a]P<0.05.

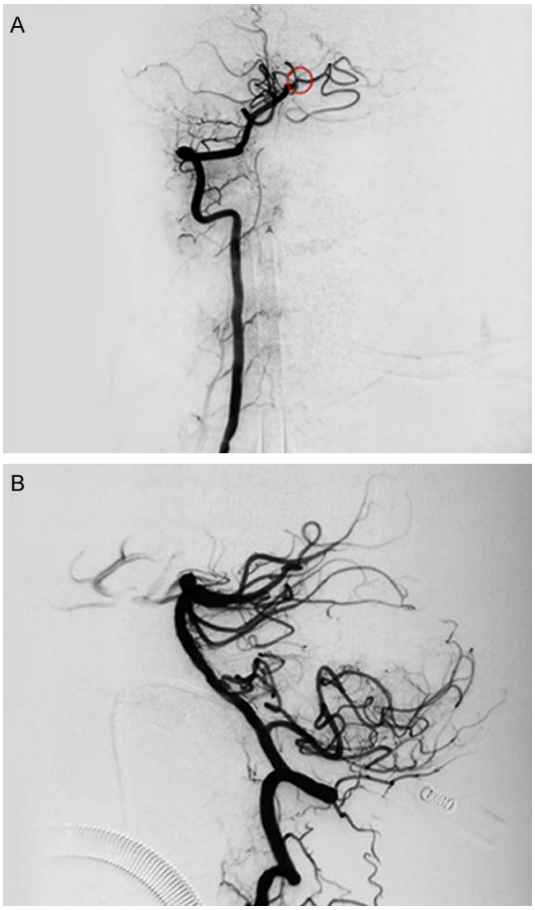

Figure 2. Recanalization cerebral angiography before and after treatment in patients treated with alteplase thrombolysis combined with stent arterial thrombectomy. A. Before treatment; B. After treatment. The red circle is the patient's vascular occlusion site.

Before treatment, NIHSS scores reached 25, indicating the high risk of large vessel occlusion. After brain CT and CTP, CTA examination, it was confirmed that the patients had a basilar artery embolism, with the beginning of the basilar artery occluded and the distal blood flow restricted (**Figure 2A**). After treatment, the positive blood flow of the basilar artery was restored, and the cerebral arteries in the bilateral posterior area were well developed, which was determined as being a TICI-III grade and fully perfused. After reexamination, direct and lateral blood flow was normal, and no intracranial hemorrhage was observed by immediate CT scan (**Figure 2B**).

Discussion

Some research suggests that with an acute stroke, the rupture of neuronal cells and glial cells are promoted as a result of cerebral ischemia and hypoxia, causing damage to the nervous system in patients with acute stroke [11]. NSE and S100β are of great significance in assessing the degree of nerve damage. NSE is an important metabolic enzyme that regulates energy metabolism in nerve cells; S100β protein helps maintain calcium homeostasis in nerve cells [12, 13]. GFAP, an essential component of the glial cytoskeleton, will be largely released once the cytoskeleton is destroyed under hypoxic conditions [14, 15]. In this study, after treatment, the levels of GFAP, NSE and S100β were decreased and the combined treatment group showed significantly lower levels than the thrombolysis group on 1 day and 1 week after treatment, suggesting that combined treatment can better restore the above indicators and prevent nerve damage.

In this study, after treatment, NIHSS and mRS scores were decreased in both groups, which showed better improvement in the combined treatment group than in the thrombolysis group, indicating that alteplase thrombolysis combined with solitaire AB stents thrombectomy can improve patient's nerve function and prognosis. A study also supported these results showing that the administration of alteplase thrombolysis in patients within 6 hours can largely contribute to a better prognosis and lower NIHSS score [16]. Local thrombosis has a direct impact on the patient's intracranial arterial blood flow. Thrombolytic therapy can promote the restoration of blood flow perfusion by thrombus clearance in the artery [17, 18].

CRP is a type of acute protein, having a low level in healthy bodies. When the body is infected, CRP levels sharply increase and participate in immune reactions. In the inflammatory reaction, a large amount of TNF-α accumulates to promote the inflammatory reactivity of cells, with the help of pro-inflammatory factors, thereby seriously damaging the tissues. In this study, the levels of CRP and TNF-α in the two groups decreased to different degrees at 1 day and 1 week after treatment especially in the combined treatment group. This suggested that alteplase thrombolysis combined with solitaire AB stents thrombectomy can improve inflammatory response, control disease progression, and promote patient recovery.

The recanalization rate of the combined treatment group increased, confirming the efficacy of the combined treatment. The mechanical thrombectomy can help patients with faster vascular dredging. The effect of alteplase on arterial thrombosis can play a role within a certain time window to prevent penumbra tissue damage [19, 20]. In this study, the combined treatment group had slightly higher incidence of adverse events than the thrombolytic group with no significant difference, reminding about the risk of the solitaire AB stents thrombectomy. This result was inconsistent with the opinion of Zhou [21].

In summary, alteplase thrombolysis combined with solitaire AB stents thrombectomy for acute stroke has obvious clinical efficacy, restores patient's nerve function, improves recanalization rate, reduces adverse events and improves the treatment safety, which provides new research directions for clinical treatment of acute stroke. However, due to the small size of the cases, we found a higher incidence of adverse events in the combined treatment. Thus, the results of this research should be confirmed with further study.

Disclosure of conflict of interest

None.

Address correspondence to: Haihong Zhang, Department of Emergency, Dongyang Hospital Affiliated to Wenzhou Medical University, No.60 Wuning West Road, Dongyang 322100, Zhejiang Province, China. Tel: +86-15925961496; E-mail: zhanghaihong36dy@163.com

References

[1] Kim LJ. Editorial: acute stroke intervention. Neurosurg Focus 2017; 42: E9.
[2] Sung EK, Farris C, Abdalkader M and Mian A. Acute neurologic syndromes beyond stroke: the role of emergent MR imaging. Neuroimaging Clin N Am 2018; 28: 375-395.
[3] Derex L and Cho TH. Mechanical thrombectomy in acute ischemic stroke. Rev Neurol (Paris) 2017; 173: 106-113.
[4] Huang WL, Gong SJ, Wu ZS and Hong QL. Linical effect analysis of bridging treatment and mechanical thrombectomy in patients with acute cerebral infarction complicated with precirculation large vessel occlusion. J Apoplexy Nerv Dis 2019; 36: 53-55.
[5] Paciaroni M and Pantoni L. Thrombolysis in dementia patients with acute stroke: is it justified? Neurol Sci 2017; 38: 27-31.
[6] Murao A, Endo T, Nisii T, Tamari Y, Tamai H and Terao S. Thrombolytic recombinant tissue plasminogen activator (rt-PA) treatment in the acute ischemic stroke with limb arterial embolism; three case reports. Rinsho Shinkeigaku 2020; 60: 223-228.
[7] Chen HA, Ma YH, Hsu TY and Chen JP. Preparation of peptide and recombinant tissue plasminogen activator conjugated poly(Lactic-Co-Glycolic Acid) (PLGA) magnetic nanoparticles for dual targeted thrombolytic therapy. Int J Mol Sci 2020; 21.
[8] Ringleb P, Bendszus M, Bluhmki E, Donnan G, Eschenfelder C, Fatar M, Kessler C, Molina C, Leys D, Muddegowda G, Poli S, Schellinger P, Schwab S, Serena J, Toni D, Wahlgren N and Hacke W. Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection. Int J Stroke 2019; 14: 483-490.
[9] Tan HH, Huang ZW and Yang QF. Correlation between T cell subsets and NIHSS score in patients with acute ischemic stroke. Hainan Medicine 2018; 29: 1690-1692.
[10] He PC, Xu ZY and Yao QY. Effects of serum homocysteine and vitamin B12 levels on cognitive function and prognosis of patients with acute ischemic stroke. J of Practical Clinical Medicine 2019; 23: 27-30.
[11] Morotti A, Poli L and Costa P. Acute stroke. Semin Neurol 2019; 39: 61-72.
[12] Kozak HH, Uğuz F, Kılınç İ, Uca AU, Tokgöz OS, Güney F and Özer N. A cross-sectional study to assess the association between major depression and inflammatory markers in patients with acute ischemic stroke. Indian J Psychiatry 2019; 61: 283-289.

[13] He Y, Cai Z and Chen Y. Role of S-100β in stroke. Int J Neurosci 2018; 128: 1180-1187.
[14] Han B, Zhang Y, Bai Y, Chen X, Huang R, Wu F, Leng S, Chao J, Zhang JH, Hu G and Yao H. Novel insight into circular RNA HECTD1 in astrocyte activation via autophagy by targeting MIR142-TIPARP: implications for cerebral ischemic stroke. Autophagy 2018; 14: 1164-1184.
[15] Neri M, Frati A, Turillazzi E, Cantatore S, Cipolloni L, Di Paolo M, Frati P, La Russa R, Maiese A, Scopetti M, Santurro A, Sessa F, Zamparese R and Fineschi V. Immunohistochemical evaluation of aquaporin-4 and its correlation with CD68, IBA-1, HIF-1α, GFAP, and CD15 expressions in fatal traumatic brain injury. Int J Mol Sci 2018; 19.
[16] Al Khathaami AM, Al Bdah B, Tarawneh M, Alskaini M, Alotaibi F, Alshalan A, Almuhraj M, Aldaham D and Alotaibi N. Utilization of intravenous tissue plasminogen activator and reasons for nonuse in acute ischemic stroke in saudi arabia. J Stroke Cerebrovasc Dis 2020; 29: 104761.
[17] Li Y, Wang H, Zhao L, Jian Y, Dang M, Jiang Y, Zhang Y, Zhang L, Zhang R, Chen M and Zhang G. A case report of thrombolysis resistance: thrombus ultrastructure in an ischemic stroke patient. BMC Neurol 2020; 20: 135.
[18] Holliday E, Lillicrap T, Kleinig T, Choi PMC, Maguire J, Bivard A, Lincz LF, Hamilton-Bruce MA, Rao SR, Snel MF, Trim PJ, Lin L, Parsons MW, Worrall BB, Koblar S, Attia J and Levi C. Developing a multivariable prediction model for functional outcome after reperfusion therapy for acute ischaemic stroke: study protocol for the Targeting Optimal Thrombolysis Outcomes (TOTO) multicentre cohort study. BMJ Open 2020; 10: e038180.
[19] Margolin EA, Rai A, Goldfarb J, Zaslavsky K, Kohly R and Nicholson P. Dramatic recovery of vision in patient with acute central retinal artery occlusion treated with local intra-arterial tissue plasminogen activator. BMJ Case Rep 2020; 13.
[20] Marko M, Posekany A, Szabo S, Scharer S, Kiechl S, Knoflach M, Serles W, Ferrari J, Lang W, Sommer P and Greisenegger S. Trends of r-tPA (Recombinant Tissue-Type Plasminogen Activator) treatment and treatment-influencing factors in acute ischemic stroke. Stroke 2020; 51: 1240-1247.
[21] Zhou HM, Wang YD, Guo Y, Liao L and Han YY. Effects of intravenous thrombolysis and bridging therapy on prognosis in acute stroke. J Medical Forum 2019; 40: 111-113.