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Original Article

The treatment efficacy of recombinant tissue plasminogen agonist in thrombolysis of acute cerebral ischemic stroke

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Abstract: Acute cerebral ischemic stroke is a common cerebral vascular disease and, under most situations, require the thrombolysis as its primary treatment. Recombinant tissue plasminogen agonist (rt-PA) has been proved for treating acute cerebral ischemic stroke in multiple countries. This study compared the treatment efficacy of rt-PA, via various routes including artery, venous and combined thrombolysis, in an attempt to find an optimal plan for ischemic stroke in clinical practice. A total of 150 cases of acute cerebral ischemic stroke patients were retrospectively studied to analyze the treatment efficacy of artery, venous or combined application of rt-PA, via the analysis of vessel repass rate, ESS score, thrombolysis effects and incidence of complications. The vessel repass rates internal carotid artery in type I, II and IIIa patients were significantly higher than other sub-types ($P<0.05$). The repass rate was also remarkably higher in combined thrombolysis group compared to artery or venous thrombolysis group, along with higher ESS score, obvious effect and overall effective rate ($P<0.05$). No significant difference, however, has been identified between artery and venous injection group ($P>0.05$). The thrombolysis treatment using rt-PA by combined application can improve the vessel repass rate, ESS score, obvious effect and overall effective rate, and decrease the incidence of postoperative complications.

Keywords: Recombinant tissue plasminogen agonist, acute cerebral ischemic stroke, thrombolysis treatment

Introduction

Acute cerebral ischemic stroke has high mobility and mortality rates, severely affecting patients' lives [1]. Thrombolysis is the most effective treatment measure to recover the blood flow of cerebral vessels to date. Among all medicines used for thrombolysis, recombinant tissue plasminogen agonist (rt-PA) has unique advantages [2]. In clinical practice, thrombolysis medicine is commonly applied by intravenous injection. This method, however, may not obtain satisfactory efficacy as the medicine cannot reach the blockage site of target vessels. With the advancement of intravascular treatment, artery injection or artery/venous combined method has been used in clinical thrombolysis. This study retrospectively investigated the treatment efficacy of rt-PA thrombolysis on acute cerebral ischemic stroke patients, among different injection routes, in an attempt to compare the overall effective rates among those methods.

Materials and methods

General information

A total of 150 patients with acute cerebral ischemic stroke between January 2014 and January 2015 in our hospital were recruited and retrospectively studied. All patients had thrombolysis treatment using rt-PA, including 50 cases of artery thrombolysis (22 males, 28 females, aging between 34~75 years old, average age = 56.2±5.2 years), 50 cases of venous thrombolysis (31 males, 19 females, aging between 33~75 years old, average age = 60.1±4.2 years) and 50 cases of combined thrombolysis (24 males, 26 females, aging between 40~74 years old, average age = 59.3±6.3 years).

The study protocol was approved by the Research Ethics Committee of our hospital, and all patients gave their informed consent before study commencement.

The typing of ischemia followed established guidelines [3]: Type I, blockage of internal carotid artery but not affected Willis circle or lenticulostriate artery; Type II, blockage of cerebral cortex vessels but not lenticulostriate artery; Type IIIa, blockage of middle cerebral artery and partial lenticulostriate artery; Type IIIb, blockage of middle cerebral artery and lenticulostriate artery; Type IIIc, complete blockage of lenticulostriate artery. Inclusive criteria: (1) Ages between 18~80 years old; (2) Received thrombolysis within 6 hours of onset; (3) Manifestation of brain dysfunctions for more than one hour. Exclusive criteria: (1) Patients having history of intracerebral hemorrhage, cerebral trauma, active bleeding, gastrointestinal hemorrhage or surgery; (2) Those who were taking anti-coagulation medicines; (3) With severe multi-organ dysfunctions; (4) Palate count less than 100×109/L.

Thrombolysis treatment

Combined thrombolysis: Rt-PA (10~20 mg) were applied via intravenous injection within 6 hours of disease onset. Meanwhile, an intra-artery cannulation inside internal carotid artery and vertebral artery was performed via femoral artery puncture. Under the help of cerebral angiography and heparinization, the catheter was inserted to the thrombus site. Rt-PA (20~30 mg) was continuously applied within 30~60 min. Total dosage of rt-PA was not more than 50 mg. Heparinization was maintained for 24 hours, with the monitor of blood coagulation indexes.

Artery thrombolysis: An artery cannulation was performed via femoral artery puncture within 6 hours of disease onset. Rt-PA (20-30 mg) was applied for thrombolysis under heparinization condition, with monitoring of blood coagulation.

Venous thrombolysis: Rt-PA (0.9 mg/kg body weight) was applied with intravenous injection (10% dosage) and continuously pumping for 60 min (90% dosage).

Vessel repass rate evaluation

Under cerebral angiography, the vessel repass status was graded as: (1) Grade 0, no observable change; (2) Grade I, no improvement of perfusion, but slight movement of thrombus; (3) Grade II, re-perfusion (<50%) in the ischemic region; (4) Grade III, complete re-perfusion of ischemic region. A complete thrombolysis was defined under grade III, while partial thrombolysis was identified under grade II. Grade 0 and I represented as unsuccessful thrombolysis [4].

European stroke scale (ESS)

We used ESS to evaluate the neurological functional of patients at different time points: before thrombolysis, 24 hours after treatment, 7 days afterwards and 30 days later. Severe conditions were defined when ESS score was less than 50 points, while mild condition and recovery were identified for ESS score between 50~94 and more than 95, respectively.

Treatment efficacy evaluation

The treatment effective rate was evaluated as previously documented [5]: (1) Complete recovery, when ESS decreased by 91%~100%; (2) Significant improvement, when ESS decreased between 46%~90% and having grade I~III morbidity; (3) Improvement, when ESS decreased by 18%~45% and with grade III or above morbidity; (4) No change, when ESS decreased by 0%~17%; (5) Aggravation, when ESS increased; and (6) Death. Obvious effects were defined for those having complete recovery and significant improvement, while efficacy was defined for those with complete recovery improvement, significant improvement or improvement.

Data analysis

SPSS 17.0 software package was used to analyze all collected data, of which measurement data were presented as mean ± standard deviation (SD). Between-group comparison for enumeration data was performed by chi-square test. A statistical significance was defined when $P<0.05$.

Results

Vessel repass rates

We compared the blood vessel repass rates among three groups using different thrombolysis methods. Results showed significantly elevated repass rates in type I (78.57%), type II (75%) and type IIIa (72.73%) ischemic stroke when using combined thrombolysis method as

Table 1. Vessel repass rate among three thrombolysis methods

Group	N	Complete repass	Partial repass	No repass	Repass rate (%)
Combined thrombolysis	50				
Internal carotid thrombus					
Type I	14	7	4	3	78.57*,#
Type II	12	7	2	3	75*,#
Type IIIa	11	5	3	3	72.73*,#
Type IIIb	6	0	2	4	33.33*,#
Type IIIc	0	0	0	0	0
Vertebral artery thrombus	7	1	2	4	42.86*,#
Artery thrombolysis	50				
Internal carotid thrombus					
Type I	16	0	5	11	31.25
Type II	11	1	3	7	36.36
Type IIIa	9	1	3	5	44.44
Type IIIb	5	0	1	4	25
Type IIIc	0	0	0	0	0
Vertebral artery thrombus	9	0	2	7	22.22
Venous thrombolysis	50				
Internal carotid thrombus					
Type I	14	0	5	9	35.71
Type II	10	1	3	6	40
Type IIIa	8	1	2	5	37.5
Type IIIb	7	0	1	6	14.29
Type IIIc	0	0	0	0	0
Vertebral artery thrombus	11	0	4	7	36.36

Note; *, P<0.05 compared to the artery thrombolysis group; #, P<0.05 compared to the venous thrombolysis group.

Table 2. ESS scores after thrombolysis

Group	N	Before	After thrombolysis			
			6 h	24 h	7 d	30 d
Combined group	50	40±14	81±19*,#	82±21*,#	87±26*,#	89±21*,#
Artery group	50	41±11	71±15	73±17	78±18	81±13
Venous group	50	40±17	72±12	73±19	79±14	82±10

Note; *, P<0.05 compared to the artery thrombolysis group; #, P<0.05 compared to the venous thrombolysis group.

compared to the other two methods (**Table 1**, P<0.05). This method, however, had lower repass rates in type IIIb (33.33%), type IIIc (0%) and vertebral basal artery thrombus. The comparison between artery and venous thrombolysis group had no statistically significant results (P>0.05).

ESS scores

No significant difference of ESS scores existed among three groups before the thrombolysis. The intervention obtained significant improvement of ESS scores in all three groups. The combined thrombolysis method gained the most significant improvements of ESS scores in all time points checked (6 hours later, 81±19; 24 hours later, 81±19; 7 days later, 87±26; 30 days later, 89±21). All those scores were significantly higher than those in artery or venous intervention group (**Table 2**, P<0.05). No significant difference regarding improvements of ESS scores between artery and venous injection groups (P>0.05).

Treatment efficacy of thrombolysis

In an evaluation of different thrombolysis methods, we found 13 cases of complete recovery and 8 cases with significant improvement after combined thrombolysis, making the obvious effect at 42% and overall effective rate at 56%. All those percentages were significantly elevated when compared to either artery or venous thrombolysis group (**Table 3**, P<0.05). No significant difference of effective rate has been discovered between artery and venous group (P>0.05).

Incidence of complications

We also observed the occurrence of various complications in all patients. Results showed 2 cases (4%) of intracranial hemorrhage in combined thrombolysis group. This was significantly lower than that in artery or venous injection group (**Table 4**, P<0.05). No significant difference of incidence of intracranial hemorrhage or death rate has been found between artery and venous group (P>0.05).

Discussion

Acute cerebral ischemic stroke has now become one of the most important reasons causing mortality worldwide, making it a great

Table 3. Thrombolysis efficacy comparison

Group	N	Complete recovery	Significant improve	Improvement	No change	Aggravation	Death	Obvious effect (%)	Effective rate (%)
Combined group	50	13	8	7	18	3	1	42*,#	56*,#
Artery group	50	5	6	9	24	5	1	22	40
Venous group	50	4	5	11	25	4	1	18	40

Note; *, P<0.05 compared to the artery thrombolysis group; #, P<0.05 compared to the venous thrombolysis group.

Table 4. Incidence of complication after thrombolysis

Group	N	Intracranial hemorrhage		Death rate	
		N	Percentage	N	Percentage
Combined group	50	2	4*,#	1	2*,#
Artery group	50	4	8	1	2
Venous group	50	5	10	1	2

Note; *, P<0.05 compared to the artery thrombolysis group; #, P<0.05 compared to the venous thrombolysis group.

challenge for effective decrease of morbidity and mortality rate [6]. The safety and efficacy of rt-PA in thrombolysis has been repeated proved by clinical trials [7]. The neglect of early symptoms of ischemic stroke, however, often make the patient miss the optimal treatment window of thrombolysis, as only 6% of acute cerebral ischemic stroke patients received rt-PA thrombolysis treatment [8, 9]. Clinical researches have confirmed the safety and efficacy of thrombolysis within 4.5 hours of the onset of ischemic stroke [10, 11], including venous, artery or combined intervention [12]. Among all these routes of drug introduction, artery cannulation can achieve a higher local concentration of rt-PA, but with a delay of treatment for about 2 hours, thus compromising the efficacy and alleviation of hypercoagulable state of cerebral blood vessel. Venous thrombolysis can exert its effect in a short time, but only has a vessel repass rate of internal carotid artery at about 10% [13, 14]. Therefore, the combined thrombolysis can achieve a rapid treatment with retaining the advantage of higher repass rate of large vessel by artery method [15].

This study retrospectively investigated the vessel repass rates among all those three types of rt-PA introduction routes in thrombolysis and found significantly elevated repass rates in internal carotid artery type I, type II and type IIIa thrombus. Such higher repass rate was not related with certain treatment method. A further comparison among different methods found significantly elevated repass rate in combined thrombolysis group when compared to either artery or venous group, suggesting better treatment efficacy of combined therapy. This was consistent with previous study, which reported the repass rate of combined thrombolysis as high as 64.0%~88.9% [16].

After thrombolysis, ESS scores in all groups had improvements when compared to those before treatment. Further comparison showed that, at the same time point after treatment, patients with combined therapy had higher ESS scores compared to artery or venous group, both of which, however, had no between-group difference. An evaluation of thrombolysis efficacy revealed more satisfactory effects and lower incidence of complications of combined group than the other two methods. These results suggested that the venous-artery combined thrombolysis can improve patients' ESS score, facilitate the recovery of neurological function, improve the efficacy of thrombolysis and decrease the incidence of complication, contributing to a more favorable prognosis. Previous studies reported the rate of intracranial hemorrhage after combined thrombolysis between 5.6%~20.0%, while the percentage of favorable prognosis at 60.0%~66.7% [17]. No significant difference of thrombolysis efficacy has been discovered between artery and venous intervention, while the venous injection did not increase the incidence of complication [18, 19]. The neurological score was significantly elevated 3 month after rt-PA thrombolysis treatment [20, 21], which is consistent with this study.

In summary, the application of rt-PA by artery-venous combined thrombolysis in treating acute cerebral ischemic stroke can elevate the vessel repass rate, improve ESS score, facilitate the recovery of neurological function, increase the effective rate and decrease the

incidence of complication, making it a better treatment plan for clinical practice.

Disclosure of conflict of interest

None.

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