Tenecteplase versus alteplase for acute ischemic stroke thrombolysis: a systematic review and meta-analysis

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Abstract

Background: Intravenous thrombolysis is the preferred clinical treatment for acute ischemic stroke. Alteplase is an intravenous thrombolytic drug used in clinical practice. Recently, studies have shown the efficacy of another intravenous thrombolytic drug, tenecteplase, and have reported that the risk of bleeding is low. However, at present, Chinese and international research has yielded controversial results regarding the efficacy and risks of tenecteplase. Therefore, this systematic review and meta-analysis of the efficacy and safety of tenecteplase were performed. **Methods:** PubMed, the Cochrane Library, MEDLINE, the Wanfang Database and CNKI were searched for all studies on the thrombolytic treatment of acute ischemic stroke. All studies published in English prior to March 2021 were retrieved. The studies were screened and selected based on the inclusion and exclusion criteria. Then, the data were extracted and recorded by trained researchers. RevMan 5.4 statistical software was used to analyze the data on the 24h recanalization rate, early neurological improvement (24h reduction in the National Institutes of Health Stroke Scale [NIHSS] score of at least 8 points or 24 h NIHSS score of 0~1 point), mRS score at 90 days, intracranial hemorrhage, symptomatic intracranial hemorrhage and mortality in the tenecteplase group and alteplase group. **Results:** A total of 565 related studies were identified through the initial searches in each database. The citations of meta-analyses and related reviews were screened for additional eligible articles. Eventually, 9 high-quality English-language articles that included 2149 patients with acute ischemic stroke (including 1035 in the tenecteplase group and 1046 in the alteplase group) were included in this meta-analysis. The meta-analysis results were as follows: (1) Efficacy: The 24 h recanalization rate with regard to vascular recanalization was significantly better in the tenecteplase group than in the alteplase group (OR = 1.83, 95% CI: 1.23~2.72, $z = 2.97$, $P = 0.003$). There was significantly greater improvement in early neurological function in the tenecteplase group than in the alteplase group (OR = 1.34, 95% CI: 1.11~1.63, $Z = 3.00$, $P = 0.003$). There were no significant differences in 90-day mRS scores between the two groups (mRS score = 0-1, OR = 1.20, 95% CI: 0.99~1.46, $z = 1.82$, $p = 0.07$; mRS score = 0-2, OR = 1.17, 95% CI: 0.94~1.45, $z = 1.38$, $p = 0.17$). However, the subgroup analysis showed that the 90-day mRS score of the 0.25 mg/kg tenecteplase group was significantly different from that of groups treated with other doses of tenecteplase (OR = 1.48, 95% CI: 1.01~2.03, $z = 2.03$, $p = 0.04$). (2) Safety: The incidences of any intracranial hemorrhage (OR = 0.91, 95% CI: 0.55~1.49, $z = 0.39$, $p = 0.70$), symptomatic intracranial hemorrhage (OR = 1.21, 95% CI: 0.63~2.32, $z = 0.56$, $P = 0.57$), and mortality (OR = 0.85, 95% CI: 0.57~1.26, $z = 0.82$, $p = 0.41$) were not significantly different between the tenecteplase and alteplase groups.

Conclusions: Tenecteplase can significantly increase the 24-hour vascular recanalization rate and improve the neurological prognosis of patients with acute ischemic stroke and it does not increase the risk of intracranial hemorrhage or mortality.

Keywords: Acute ischemic stroke, intravenous thrombolysis, tenecteplase, alteplase, meta-analysis

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INTRODUCTION

Stroke is one of the main causes of death and disability worldwide. The lifelong risk and disease burden of stroke are as high as 39.3% in China, which ranks first globally.¹ Ischemic stroke is the main type, accounting for 81.9% of all strokes.² Alteplase is the most effective intravenous thrombolytic therapy and is the preferred treatment for acute ischemic stroke. However, studies have shown that^{3,4} the success rate of the treatment of acute ischemic stroke with alteplase is low, and there is a high risk of hemorrhagic transformation. Tenecteplase is a new third-generation thrombolytic drug. It is a modified recombinant plasminogen activator, and can promote the conversion of fibrinogen and plasminogen into fibrin and plasmin.

In recent years, the number of clinical studies comparing the efficacy and safety of tenecteplase and alteplase as intravenous thrombolytic therapies for the treatment of acute ischemic stroke has gradually increased, and most studies have shown that tenecteplase is not inferior in terms of efficacy and safety. Some studies showed that tenecteplase had a certain advantage with regard to improving vascular recanalization and early neurological function,⁵⁻⁷ but the conclusions varied among the studies. Therefore, this analysis was performed to clarify the recent evidence regarding the efficacy and safety of intravenous thrombolysis with tenecteplase.

METHODS

Literature search

We conducted a literature search in PubMed, the Cochrane Library, MEDLINE, the Wanfang Database and CNKI to identify all studies on the efficacy and safety of intravenous thrombolysis with tenecteplase and alteplase for the treatment of acute ischemic stroke. The deadline for the retrieval of studies was March 2021. The language was restricted to English. The keywords were as follows: “acute ischemic stroke”, “acute cerebral infarction”, “tenecteplase”, and “alteplase”. Manual screening of the references of a previously published meta-analysis was also performed.

Study inclusion and exclusion criteria

Inclusion criteria: The following were the inclusion criteria: (1) clinical studies comparing the efficacy and safety of intravenous thrombolysis with tenecteplase and alteplase for the treatment

of acute ischemic stroke. (2) Intravenous thrombolytic therapy with tenecteplase was administered to the experimental intervention group, intravenous thrombolytic therapy with alteplase was administered to the control group, and the subjects had not used other thrombolytic drugs before enrollment. (3) At least one of the following outcomes was reported: 90-day modified Rankin Scale (mRS) score of 0~1 point or 0~2 points, early neurological improvement (24 h reduction in the National Institutes of Health Stroke Scale [NIHSS] score of at least 8 points or 24 h NIHSS score of 0~1 points), 24 h recanalization rate (full or partial recanalization of the occluded blood vessels at 24 h or an initial angiographic evaluation after thrombolysis with the blood flow restored to more than 50% of the original infarct area without a recoverable thrombus), symptomatic intracranial bleeding, any intracranial hemorrhage and mortality. There were strict parameters for the outcomes of the studies.

Exclusion criteria: The exclusion criteria were as follows: (1) summaries, meta-analyses, case reports, subgroup analyses of clinical studies and animal experiments; (2) studies with incomplete data or unclear outcomes; (3) studies with defective designs or poor quality.

Data extraction

Two researchers conducted the literature search, read the articles, applied the inclusion and exclusion criteria to select the eligible articles, and extracted and summarized the relevant data from the included studies. A third researcher checked and reviewed the collected data and discussed any discrepancies with the researcher who entered the data to arrive at a solution. The data extracted from the studies were as follows: (1) basic study information, such as the first author, country, publication date and design; (2) basic information about the experimental group and control group patients, including sample size, age, sex, baseline NIHSS score, time from onset to thrombolysis and relevant risk factors; (3) intervention measures, including the specific doses of tenecteplase and alteplase used for intravenous thrombolysis; and (4) outcome indicators as mentioned above in the inclusion criteria.

Literature quality evaluation criteria

The quality of the included literature was independently scored by two trained reviewers. The quality of cohort studies was evaluated with

the Newcastle-Ottawa Scale, while the quality of randomized controlled trials (RCTs) was evaluated with the modified Jadad 7-point scale. Disagreements were resolved through discussion or with the assistance of a third researcher.

Statistical analysis

RevMan 5.4 software was used for the statistical analysis. The χ^2 test and the I^2 statistic were used to test the heterogeneity among the studies. If P was <0.05 and I^2 was $>50\%$, there was significant heterogeneity among the studies, and the possible causes of heterogeneity were determined by subgroup analyses. If I^2 was $\leq 50\%$, there was no significant heterogeneity among the studies, and the fixed-effects model was used; otherwise, the random-effects model was used. The relative risk (RR) and its 95% confidence intervals (CIs) were used for the dichotomous variables. A funnel plot was constructed to assess bias in the meta-analysis. Asymmetry in the funnel plot is an indicator of bias. The more pronounced the asymmetry is, the greater the degree of bias is. $P<0.05$ indicated a significant difference.

RESULTS

Study selection

Initially, 565 studies were retrieved. By reading the titles and abstracts, 534 irrelevant studies were eliminated. Additional screening led to the exclusion of 10 meta-analyses⁸⁻¹⁷ related to tenecteplase and 12 studies¹⁸⁻²⁹ reporting subgroup analyses of clinical studies and control groups that were not administered alteplase. Ultimately,

a total of 9 studies^{5-7,30-35} were included in this meta-analysis, and all of them were published in English. The literature screening process is shown in Figure 1.

This analysis included 2,149 patients, with 1,098 patients in the tenecteplase group and 1,051 patients in the alteplase group. Nine studies were included; 4 studies reported the use of 0.25 mg/kg tenecteplase, 2 reported the use of 0.4 mg/kg tenecteplase, 1 reported the use of 0.1 mg/kg tenecteplase, and two reported using different doses of tenecteplase (0.1, 0.4 mg/kg and 0.1, 0.25, 0.4 mg/kg). For the basic information and data from the studies, see Table 1A, 1B and 1C.

Analysis of the effectiveness of intravenous thrombolysis with tenecteplase

Early neurological improvement after intravenous thrombolysis

A total of 7 studies investigated the improvement of early neurological function in patients treated with intravenous thrombolytics.^{6,7,30-33,35} The results show that $I^2 = 42\%$, indicating an overall moderate level of heterogeneity; therefore, the fixed-effects model was selected. There was a significant difference in early neurological improvement between the two groups ($OR = 1.34$, 95% CI: 1.11 ~ 1.63, $z = 3.00$, $P = 0.003$).

The subgroup analysis was stratified by the dose of tenecteplase, which could be divided into four groups: the low-dose group (0.1 mg/kg), two medium-dose groups (0.2 mg/kg and 0.25 mg/kg) and the high-dose group (0.4 mg/kg). Among the low-dose group, the high-dose group

Figure 1. Literature selection flow chart

Table 1A: The characteristics of the included studies

Studies	QA	Study type	Location	Patients (n)		Sex (male/ female)		Age* (y)		Baseline NIHSS score*						Time to treatment*		Ischemic stroke or TIA (n)		
				TNK	rt-PA	TNK	rt-PA	TNK mg/kg	TNK mg/kg	TNK mg/kg	rt-PA	TNK mg/kg	rt-PA	TNK mg/kg	rt-PA	TNK mg/kg	rt-PA	TNK mg/kg	rt-PA	
Parsons <i>et al.</i> ⁶	5‡	RCT	Australia	50	25	26/24	12/13	72±6.9	68±9.4	/	70±8.4	14.5±2.3	14.6±2.3	3.1±0.9 (h)	3.0±0.7 (h)	/	2.7±0.8 (h)	/	/	
Huang <i>et al.</i> ³¹	5‡	RCT	UK	47	49	30/17	31/18	/	71±13	/	71±12	/	12 (9-18)	/	184±44 (min)	/	192±45 (min)	12	11	
Campbell <i>et al.</i> ³³	6‡	RCT	Australia	101	101	58/43	52/49	/	70.4±15.1	/	71.9±13.7	/	17	/	125 (min)	/	134 (min)	/	/	
Logallo <i>et al.</i> ³²	7‡	RCT	Norway	549	551	321/228	339/212	/	/	/	/	/	/	5.6 ±5.4	5.8± 5.2	/	118 (79–180) (min)	/	/	
Parsons <i>et al.</i> ⁵	6†	Pro- spective cohort	Australia	15	35	/	/	73.0±9.5	/	/	69.4±13.5	14 (13-17)	/	/	15 (11-18)	3.4±0.4 (h)	2.3±0.4 (h)	/	/	
Haley <i>et al.</i> ³⁰	6‡	RCT	USA	81	31	41/40	17/14	67 ±19	69 ±15	68 ±16	72 ±16	8 (5–11)	10 (6–15)	9 (5–17)	13 (5–17)	/	/	21	4	
Rajappa <i>et al.</i> ³⁵	6‡	RCT	India	42	84	/	/	/	/	/	/	/	/	/	/	/	/	/	/	
Seners <i>et al.</i> ³⁴	5‡	RCT	France	131	131	/	/	/	74 (58–82)	/	69 (54–80)	/	16 (11–20)	/	15 (9–20)	/	145 (123–175) (min)	149 (120–180) (min)	/	/
Psychogios <i>et al.</i> ⁷	6†	Pro- spective cohort	Greece	19	39	44/508	14/25	/	69 (51–78)	/	70 (63–77)	/	19 (12–23)	/	16 (10–20)	/	165 (105–230) (min)	165 (130–220) (min)	3	3

Table 1B: The characteristics of the included studies

Studies	QA	Study type	Location	Hypertension (n)		Diabetes (n)		CHD (n)		Atrial fibrillation (n)		Dyslipidemia (n)		Smoking (n)		Large vessel occlusion (n)				
				TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	0.1 mg/kg	TNK	0.25 mg/kg	TNK
Parsons <i>et al.</i> ⁶	5‡	RCT	Australia	32	15	14	1	/	/	22	6	28	9	14	1	24	25	/	/	23
Huang <i>et al.</i> ³¹	5‡	RCT	UK	20	28	7	7	/	/	19	15	4	7	13	10	/	35	/	/	38
Campbell <i>et al.</i> ³³	6‡	RCT	Australia	/	/	/	/	/	/	/	/	/	/	/	/	/	21	/	/	18
Logallo <i>et al.</i> ³²	7‡	RCT	Norway	246	236	72	74	58	82	50	69	61	65	282	297	/	/	/	92	94
Parsons <i>et al.</i> ⁵	6†	Prospective cohort	Australia	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Haley <i>et al.</i> ³⁰	6‡	RCT	USA	67	22	17	4	45	24	/	/	39	17	9	7	3	9	5	2	2
Rajappa <i>et al.</i> ³⁵	6‡	RCT	India	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Seners <i>et al.</i> ³⁴	5‡	RCT	France	/	/	/	/	/	/	/	/	/	/	/	/	/	131	/	131	131
Psychogios <i>et al.</i> ⁷	6†	Prospective cohort	Greece	15	25	2	13	3	15	/	/	9	17	7	11	/	19	/	39	39

Table 1C: The characteristics of the included studies

Studies	QA	Study type	Location	Early neurological improvement (n)		mRS score of 0-1 at 90 days (n)		mRS score of 0-2 at 90 days (n)		24 h Recanalization (n)		Mortality (n)		ANY ICH (n)		S-ICH (n)	
				TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	rt-PA	TNK	rt-PA
Parsons <i>et al.</i> ⁶	5‡	RCT	Australia	32	9	27	10	36	11	28/48	8/22	4	3	/	/	2	3
Huang <i>et al.</i> ³¹	5‡	RCT	UK	19	12	13	10	17	19	21/32	26/35	8	6	8/52	14/51	3/52	4/51
Campbell <i>et al.</i> ³³	6‡	RCT	Australia	72	69	49	41	63	50	22	10	10	18	/	/	1	1
Logallo <i>et al.</i> ³²	7‡	RCT	Norway	229	214	354	345	421	432	/	/	29	26	47	50	15	13
Parsons <i>et al.</i> ⁵	6†	Prospective cohort	Australia	/	/	9	12	/	/	13	15/29	/	/	/	/	/	/
Haley <i>et al.</i> ³⁰	6‡	RCT	USA	22	5	14	13	/	/	/	/	12	8	12	5	5	1
Rajappa <i>et al.</i> ³⁵	6‡	RCT	India	11	16	/	/	32	48	20	29	2	1	/	/	1	2
Seners <i>et al.</i> ³⁴	5‡	RCT	France	/	/	/	/	/	/	127	127	/	/	/	/	/	/
Psychogios <i>et al.</i> ⁷	6†	Prospective cohort	Greece	12	13	7	15	11	19	/	/	2	7	4	3	3	2

*Data are expressed as the means ± SDs or medians (interquartile ranges). †Assessed by the Newcastle-Ottawa Scale for cohort studies. ‡Assessed by the modified Jadad 7-point scale. NIHSS=National Institutes of Health Stroke Scale. TNK=Tenecteplase. rt-PA=recombinant tissue-type plasminogen activator/alteplase. mRS=modified Rankin scale. S-ICH=symptomatic intracranial hemorrhage. ANY-ICH=any symptomatic intracranial hemorrhage. CHD=coronary heart disease. TIA=transient ischemic attack. QA=quality assessment. RCT=randomized controlled trial

The data of 'Ischemic stroke or TIA' in Table 1A refers to 'The number of patients with a previous history of ischemic stroke or TIA'.

Figure 2. Forest plot for early neurological improvement

and the 0.2 mg/kg tenecteplase group, there were no significant differences in early neurological function (OR = 1.45, 95% CI: 0.62 ~ 3.38, $z=0.86$ $P=0.39$; OR = 1.13, 95% CI: 0.89 ~ 1.44, $z=1.03$, $P=0.30$; OR = 1.51, 95% CI: 0.63 ~ 3.63, $Z=0.92$, $P=0.36$). Tenecteplase administered at 0.25 mg/kg) significantly improved early neurological function (OR = 2.05, 95% CI: 1.38 ~ 3.04, $z=3.56$, $p=0.0004$) (Figure 2).

24 h recanalization rate after intravenous thrombolysis

Six studies investigated the 24 h recanalization rate in patients after intravenous thrombolysis.^{5,6,31,33-35}

The I^2 statistic was 31%, indicating that there was moderate heterogeneity among the studies; therefore, a fixed-effects model was used. There was a significant difference in the 24 h recanalization rate between the two groups (OR= 1.83, 95% CI: 1.23–2.72, $Z=2.97$, $P=0.003$) Figure 3.

Prognosis at 90 days after intravenous thrombolysis

mRS score of 0-1

Seven studies^{5-7,30-33} reported the proportions of patients with mRS scores of 0-1 at 90 days, and I^2

Figure 3. Forest plot for the 24 h recanalization rate

Figure 4. Forest plot for mRS 0-1 at 90 days

was 0%, indicating that there was no heterogeneity among the studies; therefore, a fixed-effects model was used. There was no significant difference between the two groups (OR= 1.20, 95% CI: 0.99–1.46, Z=1.82, P=0.07). A subgroup analysis was performed stratified by the dose of tenecteplase. A significantly higher proportion of the patients who received 0.25 mg/kg tenecteplase had a mRS score of 0-1 at 90 days than the patients who received alteplase (OR= 1.48, 95% CI: 1.01–2.16, Z=2.03, P=0.04). There was no significant difference in other subgroups (0.1 mg/kg: OR= 1.64, 95% CI: 0.76–3.55, Z=1.25, P=0.21; 0.4 mg/kg: OR= 1.07, 95% CI: 0.84–1.36, Z=0.56, P=0.58) (Figure 4).

mRS score of 0-2

Six studies^{6,7,31-33,35} reported the proportions of patients with mRS scores of 0-2 at 90 days, and I² was 59%, indicating that there was moderate

heterogeneity among the studies; therefore, the random-effects model was used. There was no significant difference between the two groups (OR= 1.45, 95% CI: 0.94–2.24, Z=1.67, P=0.09) (Figure 5).

Safety of tenecteplase

Any intracranial hemorrhage after intravenous thrombolysis

Four studies^{7,30-32} reported the incidence of intracranial hemorrhage after intravenous thrombolysis, and I² was 25%, indicating that there was slight heterogeneity among the studies; therefore, the fixed-effects model was used. There was no significant difference between the two groups (OR= 0.90, 95% CI: 0.64–1.29, Z=0.56, P=0.58) (Fig. 6).

Figure 5. Forest plot for mRS 0-2 at 90 days

Figure 6. Forest plot for any intracranial hemorrhage

Symptomatic intracranial hemorrhage after intravenous thrombolysis

Six studies^{6,7,30-33,35} reported the incidence of symptomatic intracranial hemorrhage after intravenous thrombolysis, and I² was 17%, indicating that there was slight heterogeneity among the studies; therefore the fixed-effects model was used. There was no significant difference between the two groups (OR= 1.27, 95% CI: 0.78–2.07, Z=0.95, P=0.34).

Patients who developed symptomatic

intracranial hemorrhage were analyzed in subgroups according to the dose of tenecteplase. There was no significant difference in the occurrence of symptomatic intracranial hemorrhage among the groups stratified by dose (0.1 mg/kg: OR= 0.31, 95% CI: 0.05–2.07, Z=1.21, P =0.23; 0.2 mg/kg: OR= 1.00, 95% CI: 0.09–11.35, Z=0.00, P =1.00; 0.25 mg/kg: OR= 1.07, 95% CI: 0.45–2.56, Z=0.15, P =0.88; 0.4 mg/kg: OR= 1.76, 95% CI: 0.90–3.44, Z=1.66, P =0.10) (Figure 7).

Figure 7. Forest plot for symptomatic intracranial hemorrhage

Figure 8. Forest plot for mortality

Mortality after intravenous thrombolysis

There were 7 studies^{6,7,30-33,35} that reported mortality after intravenous thrombolysis, and I² was 8%, indicating that there was no heterogeneity among the studies; therefore, the random-effects model was used. There was no significant difference in mortality after thrombolysis between the two groups (OR = 0.86, 95% CI: 0.60 - 1.24, Z = 0.80, P = 0.42) (Figure 8).

Publication bias

In this study, funnel plots were used to assess publication bias. If a funnel plot has a standard symmetrical distribution, there is no publication bias. If a funnel plot has a nonstandard or asymmetric distribution, there is publication bias. As shown in the figure below, each funnel plot has the basic standard inverted distribution, indicating that there is no publication bias in the included literature (Figure 9).

Sensitivity analysis

In this study, a sensitivity analysis was performed

using the leave-one-out method. After excluding one study,³² the significant difference in the proportion of patients with mRS scores of 0-2 at 90 days between the two groups disappeared. The exclusion of three studies^{6,31,33} resulted in the disappearance of the significant difference in the proportion of patients with mRS scores of 0-1 between the 0.25 mg/kg tenecteplase group and the alteplase group; the exclusion of the other studies had no effect on the original results.

DISCUSSION

This study showed that the early neurological improvement was significantly better in the tenecteplase group than in the alteplase group, probably due to the higher vascular recanalization rate in the former group. In this study, 6 articles^{5,6,31,33-35} reported the 24 h recanalization rate, which was significantly higher in the tenecteplase group than in the alteplase group. Tenecteplase is a new third-generation intravenous thrombolytic drug and a modified recombinant plasminogen activator. This drug can be rapidly administered in a one-time bolus; additionally, it

Figure 9. Funnel plots for efficacy and safety outcomes

has higher fibrin specificity and can enhance the resistance of plasminogen activator inhibitor-1, its plasma clearance is slower, and its half-life is significantly longer than that of alteplase.³⁶ Therefore, tenecteplase has a better thrombolytic effect and is associated with a higher rate of early recanalization. In addition, this study showed that tenecteplase has a dose-effect relationship with regard to the improvement of early neurological function. The moderate dose (0.25 mg/kg) had the best clinical efficacy, which was significantly different from the alteplase group. There were no significant differences in early neurological improvement between patients in the low-dose tenecteplase group (0.1 mg/kg) and high-dose tenecteplase group (0.4 mg/kg) and those in the group receiving the standard dose of alteplase (0.9 mg/kg). This is mainly due to the limited thrombolytic effect and low recanalization rate associated with the low dose of 0.1 mg/kg. Although tenecteplase at a dose of 0.4 mg/kg has a better thrombolytic effect and a higher recanalization rate, it is associated with an increased risk of intracranial hemorrhage. The latest European Stroke Organization (ESO) 2021 acute ischemic stroke intravenous thrombolysis guidelines also recommend an intravenous bolus injection of tenecteplase at a dose of 0.25 mg/kg as a form of bridging treatment plan before mechanical thrombectomy in patients with ischemic stroke caused by acute aortic occlusion.³⁷ The results of the comparison of activities of daily living showed that there was no significant difference in the proportions of patients with a mRS score of 0-1 and a mRS score of 0-2 between the two groups at 90 days. The subgroup analysis showed that the proportion of patients with a mRS score of 0-1 in the moderate-dose (0.25 mg/kg) tenecteplase group was relatively higher ($P=0.04$), but the results were not stable. The sensitivity analysis showed that the exclusion of three studies^{6,31,33} led to the disappearance of that significant difference, possibly due to the small sample sizes in the included studies.

The safety analysis showed that there was no significant difference in the overall incidence of intracranial hemorrhage, symptomatic intracranial hemorrhage or mortality between the two groups of patients. The above results about safety show that the safety of tenecteplase and alteplase for the treatment of acute ischemic stroke is similar. However, the subgroup analysis showed that as the dose of tenecteplase increased, the incidence of symptomatic intracranial hemorrhage tended to gradually increase (0.1mg/kg,1.79%;0.2mg/

kg,2.38%;0.25mg/kg,4.39%; 0.4mg/kg,3.8%).

This meta-analysis investigated the outcomes reported in the literature, such as early neurological improvement, the 24 h recanalization rate, the mRS score and the incidences of any intracranial hemorrhage, symptomatic intracranial hemorrhage, and mortality. The funnel plots showed that there was no obvious publication bias. However, this meta-analysis also had certain flaws, such as the following: (1) the numbers of included studies and cases were small, which led to instability of the results, as shown in the sensitivity analysis;^{6,31-33} (2) the designs of the included studies varied, which may have affected the results; (3) the baseline data, such as sex, age, and NIHSS scores, varied among the studies,^{6,7,30} which may have affected the results; and (4) most of the studies included in this analysis were performed in Europe and the United States, and the conclusions may only be generalizable to patients in European and American countries. More high-quality clinical studies in non-European and American countries are needed to clarify the overall efficacy of tenecteplase.

In summary, treatment with tenecteplase resulted in better early neurological improvement and a higher 24 h recanalization rate than treatment with alteplase. The proportions of patients with mRS scores of 0-1 and 0-2 and overall mortality at 90 days were not inferior in the tenecteplase group compared with the alteplase group, and the use of tenecteplase did not increase the incidence of serious adverse events, such as symptomatic intracranial hemorrhage. Tenecteplase at a dose of 0.25 mg/kg had the best effect. However, in view of the shortcomings and deficiencies of this study, more high-quality clinical studies are still needed to further clarify the clinical efficacy and safety of tenecteplase as a method of intravenous thrombolysis in the treatment of acute ischemic stroke.

DISCLOSURE

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