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Safety outcomes after thrombolysis for acute ischemic stroke in patients with prior recent stroke: A meta-analysis of observational studies

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Abstract

Objective: This investigation sought to evaluate the safety outcomes after thrombolysis for acute ischemic stroke in patients with prior recent stroke through meta-analysis. *Methods:* The databases were systematically searched for were observational studies of intravenous thrombolysis for stroke in patients with prior stroke in the past 3 months, the risk of intracranial hemorrhage and mortality. Data from eligible studies were analyzed using RevMan5.3. *Results:* A total of 7 studies were included in the analysis. The adjusted OR of the analysis indicated that prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke would not increase the risk of intracranial hemorrhage (6 studies, the treatment group contains 1,037 and the control group 51,788) and mortality at three months (4 studies, the treatment group contains 977 and the control group 51,361 subjects). Based on the number of events, we could conclude that thrombolysis does not increase the risk of intracranial hemorrhage (3 studies, the treatment group contains 834 and the control group 48,452 subjects) and mortality at three months (3 studies, the treatment group contains 834 and the control group 48,452 subjects).
Conclusion: A review of the current published literature indicates that prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke does not increase the risk of intracranial hemorrhage and the 3-month mortality of patients.

Keywords: Intravenous thrombolysis, previous stroke, early recurrent stroke, meta-analysis

INTRODUCTION

Intravenous thrombolysis is one of the effective treatments for acute stroke and is believed to improve the functional prognosis of patients significantly[1-3], which has aroused increasingly attention in recent years. The thrombolysis time window was initially 3 hours, and is now extended to within 4.5 hours.[4] Although the treatment is beneficial, there are also many contraindications preventing some patients from receiving intravenous thrombolysis.[5] It is a common understanding that the risk of stroke recurrence is high, especially within first month after a stroke.[6] Patients with stroke in the past 3 months have been excluded from intravenous thrombolysis as it is believed to increase the risk of cerebral hemorrhage and result in higher mortality of patients.[7] Thus, this excludes a large proportion of patients. Although some studies have shown that patients with stroke in the past 3 months receiving intravenous thrombolysis have increased risk of intracranial hemorrhage[8-9], these studies were mostly retrospective with relatively small sample size. Patients with prior stroke within the last 3 months have been excluded from most large randomized trials and registries of intravenous thrombolysis. So, there is limited data and it is uncertain whether prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke is associated with an increased risk of adverse outcomes. In this meta-analysis, we aim to identify studies of thrombolysis for acute ischemic stroke in patients with recent stroke, to determine the outcome at the 3-6 months' follow-up. With analysis of the relevant literature, we hope to gain a comprehensive understanding of

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the safety outcomes after thrombolysis for acute ischemic stroke in patients with recent stroke.

METHODS

Search Strategy

The databases of PUBMED, EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register) were searched for relevant studies. We used all search terms, including "intravenous thrombolysis", "bridging thrombolysis", "previous stroke", "early recurrent stroke". Studies were restricted to those published in English language from January 1980 to January 2020, the date the searches were conducted. The protocol of this meta-analysis has been registered in the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/prospero, CRD42020149912).

Study selection criteria

To be included in the meta-analysis, studies were required to include a randomized controlled trial comparing outcomes of intravenous thrombolysis between new stroke with prior stroke within 3 months, and the control, with report of the adverse outcomes. Studies were excluded if (1) they were case reports, editorials, reviews, letters without original data, critiques or commentaries; or (2) they failed to report adequate data to gain a comprehensive understanding of safety outcomes after thrombolysis for patients with recent stroke and control groups.

Data extraction

Two authors (Yu Shen and Min Li) independently searched the literature databases and extracted data. Any inconsistencies were resolved through consultation with the third author Lijun Xu. The data collected from the studies[10-16] for the review as shown in Table 1 are: first author, year of publication, country of study cohort, types of studies. The corresponding odds ratios (ORs) were calculated to express the comparison of event occurrence risk. Where applicable, we also performed adjusted analyses for adjusted for age; gender, hypertension, atrial fibrillation, congestive heart failure, hyperlipidemia, prestroke disability, prestroke use of antiplatelets, baseline blood glucose, baseline NIHSS score, and administration of intravenous antihypertensives before thrombolysis; estimated the corresponding OR ($OR_{adjusted}$) for all available outcomes. A more comprehensive assessment through the incidence of events were also conducted.

Quality assessment of studies

Two reviewers Yu Shen and Min Li independently assessed the quality of studies using the Newcastle-Ottawa quality assessment scale (NOS score). Discrepancies were resolved through consultation with a third reviewer Lijun Xu. While differences were resolved with consensus; scores≥6 indicated that a study was of high quality, and scores of 4 or 5 points indicate moderate quality.[17]

Statistical analysis

I^2 was calculated to evaluate heterogeneity across studies. $I^2 < 25\%$ considered homogeneity; $25\% \leq I^2 < 50\%$ considered low heterogeneity; $50\% \leq I^2 < 75\%$ considered moderate heterogeneity; and $I^2 \geq 75\%$ considered substantial heterogeneity.[18] Data were analyzed using a fixed-effect model if they were homogeneous or of low heterogeneity, and a random-effect model were used if they showed moderate or substantial heterogeneity.[19] All meta-analyses were conducted using Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Literature search and the included studies

One hundred and forty two articles were identified from all databases initially, in which 126 articles were eliminated after reading the title and abstract, and 16 articles were retained to access the full text. After reading the full text, 7 articles were excluded because they were meta-analysis or review, 1 article was excluded because the control group was not patients with intravenous thrombolysis who had a stroke for the first time, and one other article was excluded because it did not state that the previous stroke occurred within 3 months. Finally 7 articles that meet the inclusion criteria were analyzed. In total, there were 1,054 patients who received intravenous thrombolysis treatment for stroke, who had recent stroke in the previous 3 months, and 52,988 patients met the requirements for the control group. The studies were from Poland, the United States and other European and American countries (Table 1). A statistical correlation analysis was performed to

Table 1: Characteristics of included studies

References	country	Total		Types of studies	intracranial hemorrhage			mortality at three months		
		Experimental	Control		OR(95%CI)	Value(N)		OR(95%CI)	Value(N)	
						Experimental	Control		Experimental	Control
Breuer L 2011[10]	Germany	50	190	prospective	9.619(0.94-98.38)	NA	NA	NA	NA	NA
KarlinskiM1 2012[11]	Poland	14	681	observational study	4.07(0.97-17.1)	NA	NA	3.48(0.96-12.7)	NA	NA
Karlinski M 2012[12]	Poland	146	3428	observational study	1.84(0·64-5·32)	NA	NA	1.24(.54-2.85)	NA	NA
Karlinski M 2015[13]	Poland	249	11221	observational study	0.74(0.35-1.56)	15(244)	540(10987)	0.69(0.41-1.16)	37(189)	1485(7546)
Merkler AE 2017[14]	USA	568	36031	retrospective cohort	0.9(0.6-1.4)	24(568)	1768(36031)	1.5(1.2-1.9)	84(568)	3839(36031)
CappellariM 2014[15]	USA	10	237	retrospective analysis	1.72(0.33-8.91)	NA	NA	NA	NA	NA
Heldner MR 2014[16]	Switzerland	17	1200	retrospective analysis	NA	2(17)	72(1191)	NA	7(17)	245(1077)

Abbreviations: NA: not available.

determine whether intravenous thrombolysis of stroke patients with recent stroke in the past 3 months would increase the risk of intracranial hemorrhage and mortality.

The NOS score was 9 points for four studies[10,12,13,16], 8 points for two[11,14], and 7 points for one[15] (Table 2). According to the criteria described above, all of the studies were of high quality, which indicated that all of the included studies were reliable.[10-16]

The risk of intracranial hemorrhage in patients receiving intravenous thrombolysis for stroke, who has prior stroke within the recent 3 months

The definition of symptomatic intracranial hemorrhage (sICH) was according to European Cooperative Acute Stroke Study (ECASS) II. The main clinical manifestations were drowsiness or aggravation of hemiplegia. The most objective indicator was the increase of NHISS score by 4 points or more. Brain CT was examined 24 hours and 7 days after intravenous thrombolysis.[13] This review was mainly analyzed from two aspects. Firstly, it was based on the adjusted OR ($OR_{adjusted}$) analysis. For the outcome indicator of sICH, 6 of the 7 studies contained adjusted OR, thus the final results were obtained and assembled through these studies. Due to the low heterogeneity (I2 = 49%), a fixed-effects model was used in the meta-analysis. The results could be drawn from the forest plot, which showed that prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke did not increase the risk of intracranial hemorrhage (OR 1.07, 95%CI 0.78-1.47, P = 0.68; Figure 1). Upon removing the studies one by one, there was no significant change in the results of the study. Since 3 of the 7 studies provided the number of cases of cerebral hemorrhage, so the second analysis was based on these three studies which used a fixed-effect model in the meta-analysis for their homogeneity (I^2=10%). After evaluating and assembling the results from the three studies, we could conclude that the forest plot basically did not increase the risk of intracranial hemorrhage (OR 1.00, 95%CI 0.73-1.38, P = 0.99; Figure 2). Both analysis showed no apparent publication deviation on funnel plots. Overall, it could be seen from the two analyses that prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke did not increase the risk of intracranial hemorrhage, and was not a risk factor for intracranial hemorrhage.

The risk of mortality at 3 months in patients receiving intravenous thrombolysis for stroke, who has prior stroke within the recent 3 months

Some studies have concluded that although prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke may not increase the risk of intracranial hemorrhage, it could increase the risk of death within 3 months.[15] Therefore, we defined death within 3 months of thrombolysis treatment, to determine the mortality effect of intravenous thrombolysis. We also classified according to adjusted OR ($OR_{adjusted}$) and the number of mortality at three months. A total of 4 studies of adjusted OR were included in the analysis. We analyzed using the random effect model as the heterogeneity is moderate (I^2=68%). The results could be drawn from the forest plot, which indicated that prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke did not increase the risk of death for 3 months (OR 1.27, 95%CI 0.75-2.14, P = 0.37; Figure 3). Also, by using a one-by-one elimination method for sensitivity analysis, the results also did not show significant changes. From the analysis of number of mortality at three months. Only 3 of the 7 studies contained such data, similar results were obtained, but it tends to increase the risk of death for 3 months (OR 1.33, 95%CI 0.93-1.89, P = 0.12; Figure 4). In addition, both types of analysis showed no significant risk of publication bias on funnel plots.

DISCUSSION

As far as we know, this is the first meta-analysis to assess the safety of prior stroke within 3 months when receiving intravenous thrombolysis for acute ischemic stroke. We have shown in our meta-analysis that prior stroke within 3 months of receiving intravenous thrombolysis did not increase the risk of intracranial hemorrhage. It also did not increase the mortality. However, those with prior stroke may still have higher disability upon discharge from the hospital that require more care, due to cumulative disability from the second strokes.[14] Nevertheless, it is too early to conclude from our meta-analysis that prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke is safe.

In 1996, the US Food and Drug Administration approved the intravenous thrombolytic treatment for patients with acute ischemic stroke.[20] Since then, for the last 25 years, abundant real-world data has repeatedly demonstrated its safety. The

Table 2: NOS score

Authors (year)	Selection				Comparability	Outcome			Total
	Representativeness of exposed cohort (maximum: *)	Selection of nonexposed cohort (maximum: *)	Ascertainment of exposure (maximum: *)	Demonstration that outcome of interest was not present at start of study (maximum: *)	Comparability of cohorts in terms of design or analysis (maximum: **)	Assessment of outcome (maximum: *)	Follow up was long enough for outcomes to occur (maximum: *)	Adequacy of follow up of cohorts (maximum: *)	
Breuer L 2011[10]	*	*	*	*	**	*	*	*	*********
Karlinski M1 2012[11]	*	*	*	*	*	/	*	*	*******
Karlinski M 2012[12]	*	*	*	*	*	*	*	*	********
Karlinski M 2015[13]	*	*	*	*	**	*	*	*	*********
Merkler AE 2017[14]	*	*	*	*	**	*	*	*	*********
Cappellari M 2014[15]	*	*	*	*	*	*	*	*	********
Heldner MR 2014[16]	*	*	*	*	**	*	*	*	*********

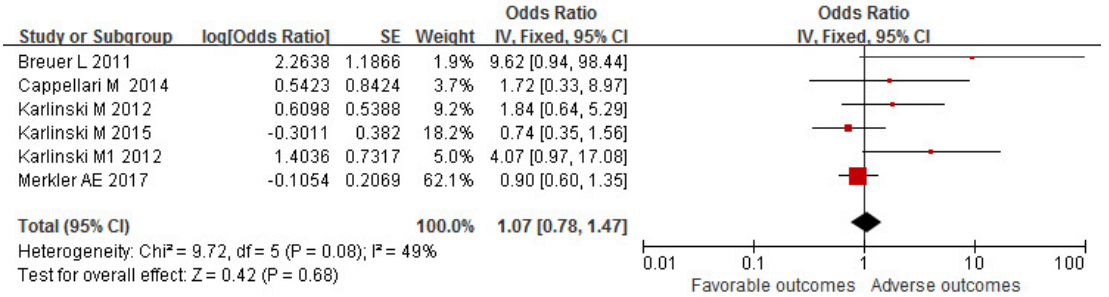
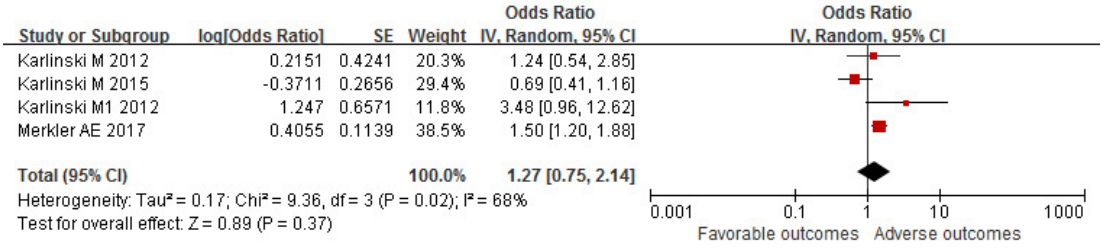


Figure 1 and Figure 2. Forest plot of prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke and risk of intracranial hemorrhage.



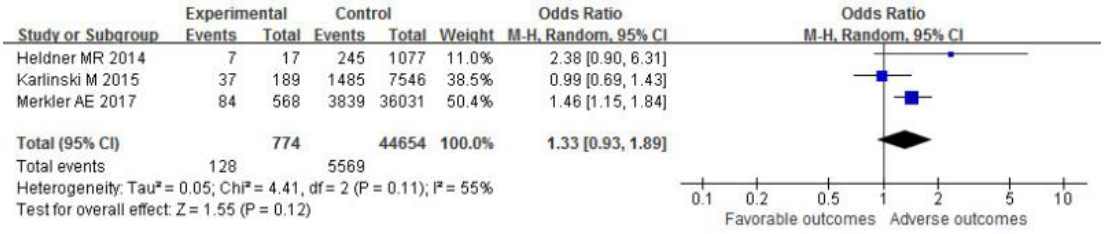


Figure 3 and Figure 4. Forest plot of prior stroke within 3 months of receiving intravenous thrombolysis for acute ischemic stroke and risk of mortality at three months.

NINDS trial[7], which started in 1991, considered that intravenous thrombolysis for a recurrence acute ischemic stroke within 3 months may increase the risk of intracranial hemorrhage. Some subsequent studies have repeated similar protocol based on the thrombolytic window and r-tPA dose of the NINDS study, with similar conclusions.[21-23] However, more studies to-date have drawn a different conclusion. There was a randomized controlled trial that included 399 historical strokes greater than 14 days and found no adverse outcomes.[24] Moreover, there are many studies which reported that intravenous thrombolysis in patients with prior strokes in preceding 3 months that did not increase the risk of ICH[8,10,25-28], which is consistent with the results of our meta-analysis.

From the pathophysiological point of view,

although various mechanisms and factors involved in excessive perfusion after local vascular occlusion and recanalization can result in the destruction of the blood-brain barrier and vascular basal dysfunction, which may lead to ICH[29-30], experiments in mice have shown that when the blood-brain barrier is damaged, in most cases, the integrity of the blood-brain barrier can be restored within 10-30 minutes.[31] Even though studies of patients with acute ischemic stroke have shown that the blood-brain barrier is destroyed early in ischemia, it can gradually recover after a few days.[32] Therefore, through the above findings, we speculate that intravenous thrombolysis for a period of time after an acute stroke does increase the risk of intracranial hemorrhage, but the period may not be three months, it may be a week or a month. So, the conclusion that has remained unchanged for more than 20 years may have to be re-evaluated and modified.

The strengths of the current meta-analysis are, firstly, this is the largest systematic review and meta-analysis on safety outcomes after thrombolysis for acute ischemic stroke in patients with recent stroke. In addition, both the safety of short-term cerebral hemorrhage and the long-term mortality was evaluated and analyzed, which was a comprehensive evaluation of safety.

There are several limitations of this meta-analysis: First, the included literature has no randomized controlled trial, and they are all retrospective or observational studies. There are some confounding factors associated with the retrospective or observational studies, including missing data, and baseline factors, which need to be corrected statistically. Second, the criteria of some control groups is unclear, and there are many factors which may skewed the results. Third, there may be a publication bias as the absence of causing intracranial hemorrhage in thrombolysis may not have been reported. Fourth, the number of studies evaluated is relatively small. This is partly because prior stroke has always been considered an absolute contraindication for thrombolysis treatment. Finally, there may be some language bias, as there could be appropriate studies published in non-English languages that was omitted by this meta-analysis.

Therefore, whilst this meta-analysis may not be insufficient to prove that thrombolysis in the presence of recent prior stroke is safe, but the exclusion of this group of patients could have excluded many patients who could potentially benefited from this treatments. A better founded conclusion based on a well conducted large-scale, multi-center RCT is necessary. The intended study should include the following aspects[5]: The data on the treatment of the first infarct, as well as the size and prognosis of the infarct. This is because the size and prognosis of the previous stroke is likely to affect the outcome of subsequent intravenous thrombolysis; infarct location and severity; duration between the two strokes. We need more studies to clarify the benefits and risks of thrombolysis in the varying intervals between the two stroke, and its resultant functional recovery (mRS) score; whether there is any intracranial hemorrhage after the first stroke; and the intravenous thrombolysis dose.

DISCLOSURE

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