Safety and Efficacy of Repeated Thrombolysis with Alteplase in Early Recurrent Ischemic Stroke: A Systematic Review

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Background and Aim: The current American Heart Association guidelines for the management of acute ischemic stroke advise against the use of intravenous (IV) alteplase in patients with recurrent stroke occurring within 90 days of their index event. Following these guidelines strictly, patients having early recurrent ischemic stroke would be unable to avail of this reperfusion strategy that has been proven to confer superior clinical outcomes. While some registry-based studies have demonstrated the safety of IV alteplase in this subgroup of patients, data on the repeated use of the drug are lacking. Thus, we aim to determine the safety and efficacy of repeated thrombolysis in patients with early recurrent ischemic strokes. *Methods:* The following electronic databases were searched for relevant studies: the Cochrane Central Register for Controlled Trials by The Cochrane Library, MEDLINE by PubMed, Health Research and Development Information Network, Scopus, and ClinicalTrials.gov. Data on symptomatic intracranial hemorrhage, 90-day clinical outcomes, systemic hemorrhage and allergic reactionswere synthesized. *Results:* Ten articles with 33 patients in total were included in our review. One patient developed symptomatic intracranial hemorrhage after the second reperfusion attempt and subsequently died from pneumonia. Another died from spontaneous rupture of previously unidentified infrarenal aortic aneurysm. Six of the 13 patients with available follow-up data had good clinical outcomes (Modified Rankin Score 0-2). There were no allergic reactions and other drug-related adverse events noted. *Conclusions:* Repeated IV alteplase can be safe and efficacious in patients who have early recurrent ischemic stroke. Larger studies, trials, or registry-based data are needed to ascertain the encouraging findings of our review.

Key Words: Ischemic stroke—recurrence—thrombolysis—off label use—recombinant tissue-type plasminogen activator—alteplase

Introduction

Stroke is the second most common cause of death worldwide and the third major cause of permanent disability.[1] In 2005, 5.7 million people died from stroke while 16 million had their first stroke. These numbers are projected to reach 7.8 million and 23 million respectively by 2030.[2] Intravenous (IV) alteplase and endovascular thrombectomy are considered standard-of-care reperfusion strategies in the management of stroke.[3] Both strategies have been proven by multiple randomized controlled trials[4,5] to result in better 90-day clinical outcomes in acute ischemic stroke patients undergoing the interventions compared to those in the control arm.

Complications associated with IV alteplase include symptomatic intracranial hemorrhage (sICH) and death.[6]

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In an effort to prevent these, the American Heart Association guidelines advised against the use of IV alteplase in some clinical scenarios such as the history of stroke in the past 90 days.[3] Like most exclusion criteria of IV thrombolysis, this recommendation is based on criteria set by the landmark National Institute of Neurological Disorders and Stroke (NINDS) IV alteplase study.[7] Despite these published guidelines, a recent survey of stroke experts within the Specialized Program of Translational Research in Acute Stroke have found some variations in which exclusion criteria were followed.[8]

Hemorrhagic transformation after IV alteplase has been associated with a molecular cascade triggered by the drug that leads to increased permeability of the blood brain barrier.[9] In addition, reperfusion brought about by IV alteplase can also result in the influx of oxygen, a potent substrate of superoxide, which may further aggravate the vessel damage brought about by free radicals native to ischemic tissue.[10,11] These 2 possible mechanisms of intracranial hemorrhage in the setting of IV alteplase for ischemic stroke caution against the repeated use of the drug in recent stroke.

Several observational series have already shown that IV alteplase can be safely and effectively administered to these patients with early recurrent stroke.[12,13] Taking only the pharmacokinetic properties of IV alteplase into account, the repeated use of the drug should not lead to compounding effects because of its short half-life (6 minutes) elimination of more than 80% of the compound via urine 18 hours after administration.[14,15] Evidence derived from cardiopulmonary literature also shows that repeated administration of systemic thrombolysis may be effective and safe.[16,17]

The rate of stroke recurrence within 90 days of the index event can be as high as 14.5%-18.3%.[18,19] With recent advances in best medical management, this figure has decreased to 5.0%-7.5%.[20,21] Strictly following the guidelines, patients with early recurrent ischemic stroke would not be treated with IV alteplase. Knowing the superior 90-day clinical outcomes of acute ischemic stroke patients who receive IV alteplase compared to those who do not,[5] it is important to review the use of the drug in this subgroup of patients.

Going beyond the use of IV alteplase in patients with recent stroke, the aim of this systematic review is to determine the safety and efficacy of repeated thrombolysis in patients who have a recurrent ischemic stroke within 3 months of their prior event in terms of sICH, 90-day functional outcomes, and other adverse drug events.

Materials and Methods

The Preferred Reporting for Items for Systematic Reviews and Meta-Analyses guidelines were followed for this review.[22]

Criteria for Considering Studies for This Review

Case reports, case series, prospective/retrospective cohort, case control, cross-sectional trials, and randomized controlled trials were all considered. Studies involving adult patients who underwent repeated thrombolysis for early recurrent ischemic strokes (within 90 days of index ischemic stroke) were included. No restrictions were implemented in terms of sex, ethnicity, severity of disease, and comorbid conditions. Studies administering IV alteplase at nonstandard doses and using the drug with other reperfusion modalities were not excluded. The outcome measures for this review were 90-day Modified Rankin Score (mRS), sICH as defined by NINDS,[23] and other adverse events such as major systemic bleeding and allergic reactions.

Search Methods for Identification of Studies

The Cochrane Central Register for Controlled Trials (CENTRAL) by The Cochrane Library, MEDLINE by PubMed, Health Research and Development Information Network, ClinicalTrials.gov, and SCOPUS were systematically searched for relevant studies from conception until August 2018. Key search terms used included the following: "recurrent stroke," "ischemic stroke" "alteplase," and "thrombolysis." The full search strategy done is detailed in Appendix 1. Reference lists from eligible articles were likewise reviewed.

Study Selection, Data Collection, and Analysis

Two review authors (RJCS and AIE) independently screened the titles and abstracts generated from the systematic search using predetermined screening criteria. Relevant articles were retrieved in full-text and were subjected to predetermined eligibility criteria by 2 authors (RJCS and AIE). Discrepancies in the fulfillment of both the screening and eligibility criteria were discussed with the other review authors, if warranted (JDBD and MCSJ). Studies which fulfilled the eligibility criteria were included in the qualitative analyses. Data collection was done by 2 authors (RJCS and JDBD) using pilot-tested data collection forms. The number of patients who experienced the outcome of interest and the total number of patients were obtained for all the dichotomous outcomes considered for this review.

Results

Search Results

The initial database search identified 33 articles (the Cochrane Central Register for Controlled Trials 5; PubMed 13; Health Research and Development Information Network 0; ClinicalTrials.gov 0, and SCOPUS 15). Three duplicate articles were discarded. Of these 30 studies, 10 met our inclusion criteria and were subsequently analyzed for this systematic review. The flow diagram of information is displayed in Figure 1.

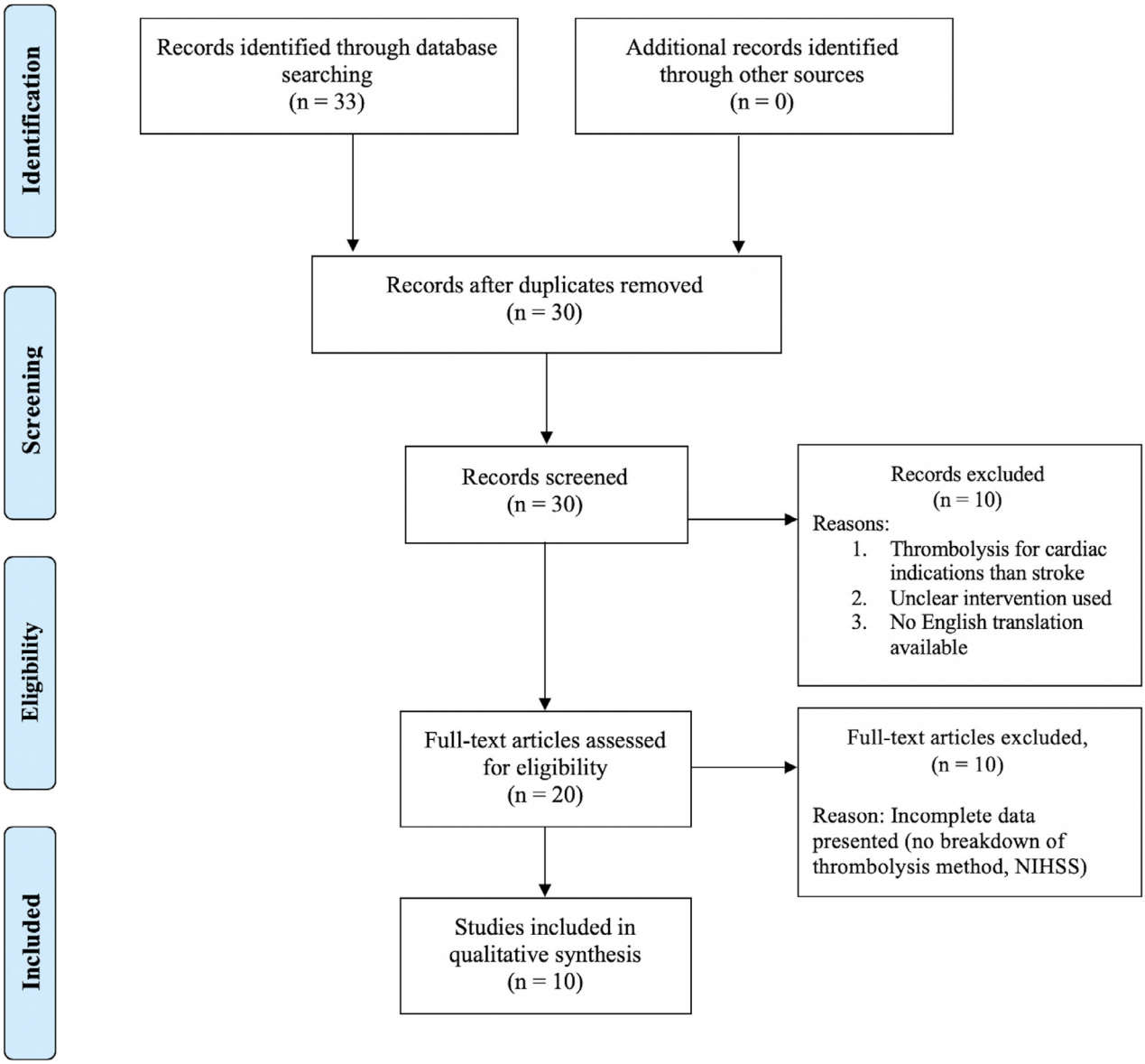

Figure 1. *PRISMA flow diagram of study selection.*

Included Studies

A total of 10 articles were included in this review. Six of the studies were case reports while 4 were case series. The population of Kahles' case series accounted for most of the patients in the review.[24] Unfortunately, individual patient level data was not available for this study; consequently, the pooled summary from the 19 patients of the series were used for analysis.

Population Characteristics in the Included Studies

In summary, a total of 33 patients from 10 different studies were analyzed (see Table 1). The shortest interthrombolysis time was 6 hours for a patient who was had recurrent basilar artery occlusion. Nine patients had the same artery occluded during the first- and second thrombolysis.

Interventions Employed in the Included Studies

In most of the studies, IV alteplase was given at the recommended dose of .9 mg/kg during the first- and second thrombolysis. One series[25] used a smaller dose of .6 mg/kg while another case used tenecteplase instead of alteplase for the second thrombolysis.[26] Other variations in reperfusion therapy were the use of intra-arterial thrombolysis[27] and mechanical thrombectomy.[28] Only 4 cases dealt with posterior circulation stroke.[24,29]

Effects of the Intervention

The effects of the intervention are summarized in Table 2. The sICH rate for this group of patient is 3.0% (1/33), on account of 1 patient who had a parenchymal hematoma occupying more than 30% of the infarcted

Table 1. *Characteristics of included studies*

Study, year, age/sex	Risk factors	OTT 1st thrombolysis (min)	1st dose details	Other intervention	NIHSS score	Artery	No. of days between thrombolysis	OTT 2nd thrombolysis (min)	2nd dose details	Other intervention	NIHSS score	Artery
Topakian et al[24] 2005 50/F	NR	120	Alteplase .9 mg/kg	None	9	R MCA	4	85	Alteplase 50mg	None	6	R MCA artery
Smadja et al[25] 2008 74/M	HTN	240	Alteplase .9 mg/kg	None	6	BA	.25	60	Tenecteplase .4 mg/kg	None	22	Basilar artery
Sauer et al[26] 2010 84/F	NR	120	NR	None	12	MCA + ACA combined	90	120	NR	None	12	MCA + ACA combined
Cappellari et al[27] 2011 75/F	HTN AF	175	Alteplase .9 mg/kg	None	4	R MCA	2	35	Alteplase .9 mg/kg	None	15	L MCA
Alhazza et al[28] 2013 81/F	AF	NR	Alteplase .9 mg/kg	None	NR	R MCA	6	NR	Alteplase .9 mg/kg	None	23	R MCA
83/F	CAD, smoking	NR	Alteplase .9 mg/kg	None	NR	R MCA	70	NR	Alteplase .9 mg/kg	None	9	R MCA
97/F	HTN, CAD, HL smoking	NR	Alteplase .9 mg/kg	None	NR	R MCA	70	NR	Alteplase .9 mg/kg	None	4	R MCA
Sposato et al[29] 2013 76/F	HTN, HL, AF, CHF	120	Altepalse .9 mg/kg	None	18	R MCA	4	240	Alteplase .9 mg/kg	None	22	L MCA
Yoo et al[30] 2013 73/F	DM	70	Alteplase .9 mg/kg	+ IA Urokinase 100,000 + Mechanical thrombectomy	12	L MCA	90	55	Alteplase .9 mg/kg	None	12	L MCA
Laible et al[31] 2015 80/M	NR	NR	Alteplase .9 mg/kg	+ IA	19	BA	30	420	Alteplase IV .9 mg/kg	None	18	L MCA
51/F		350	Alteplase	None	11	L MCA	73	119	Alteplase	+ IA	14	L MCA
48/M		NR	Alteplase	IA	2	L MCA	66	220	Alteplase	None	2	L MCA
Qureshi et al[32] 2015 73/M	HTN, HL	NR	Alteplase .9 mg/kg	None	NR	NR	6	NR	Alteplase .9 mg/kg	None	NR	R ICA
54/M	NR	NR	Alteplase .9 mg/kg	None	NR	L MCA	49	NR	Alteplase .9 mg/kg	None	NR	L MCA
Kahles et al[33] 2016 (19 patients) 68±12 37% F	HTN, DM, HL, CAD, TIA	153 ±78	Alteplase .9 mg/kg	NR*	7 (4-10)	NR*	30 (13-50)	125 (44)	Alteplase .9 mg/kg	None	10 (7-13)	NR*

*Arteries involved in the series were the middle cerebral artery (15), vertebrobasilar territory (3), and multiple territories (1).

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; F, female; HL, hyperlipidemia; HTN, hypertension; IA, intra-arterial; M, male; NR, not reported; TIA, transient ischemic attack.

Table 2. *Efficacy and safety of the intervention*

Study, year patient no.	ICH 1st thrombolysis	sICH 2nd thrombolysis	3-month functional outcome (mRS)	Major systemic bleeding	Anaphylactoid/ anaphylactic reaction
Topakian et al[24] 1	None	None	1	No	None
Smadja et al[25] 2	None	None	NR	No	None
Sauer et al[26] 3	None	None	3	No	None
Cappellari et al[27] 4	None	None	NR	No	None
Alhazza et al[28] 5	None	None	5	No	None
6	None	None	5	No	None
7	None	None	1	No	None
Sposato et al[29] 8	None	Present	6	No	None
Yoo et al[30] 9	None	None	0	No	None
Laible et al[31] 10	None	None	5	No	None
11	None	None	4	No	None
12	None	None	0	No	None
Qureshi et al[32] 13	None	None	0	No	None
14	None	None	0	No	None
Kahles et al[33] 15-33	None	None	6 for one patient but NR for others	Present (infrarenal aneurysm rupture)	None

Abbreviations: MRS, Modified Rankin Score; SICH, symptomatic ICH.

territory after the second thrombolysis.[29] The same patient was 1 of 2 mortalities in the review. She, however, did not die from brain herniation but rather from complications brought about by pneumonia. Asymptomatic hemorrhagic conversion was found in the 24-hour routine repeat computed tomography scans in 2 patients.[26,30]

Among the 13 patients with reported 3-month functional outcomes after the second thrombolysis, 6 patients recovered and achieved no symptoms to minimal disability (mRS 0-1),[25,27,28,30,31] 2 had moderate disability (mRS 3-4),[27,32] 3 had severe disability (mRS 5),[27,30] and 2 patients died (mRS 6).[24,29] The other mortality is that of a patient who died from spontaneous rupture of a previously unidentified infrarenal aortic aneurysm within 24 hours of the second IV thrombolysis.[24]

Discussion

The findings of this review suggest that functional outcomes and sICH rate in patients undergoing repeat thrombolysis are similar to published data on thrombolysed patients without a recent stroke. A meta-analysis of the landmark IV alteplase trials for acute ischemic showed that 32.9% (259/787) of patients in the treatment arm had good (mRS 0-1) 3-month functional outcome and 6.8% (231/3391) developed sICH.[5] A series of patients undergoing IV alteplase within 3 months of an ischemic stroke showed a similar sICH rate of 6.2% (15/244).[12] In comparison, half of the patients in our review with reported 3-month functional outcomes (6/12) had good outcomes. The lone case (1/33) with sICH[29] had factors that already predispose to sICH regardless of any reperfusion attempt[33]: severe stroke (NIHSS score 22), a cardioembolic mechanism, and the use of low molecular weight heparin.

In the NINDS IV alteplase trials, serious systemic hemorrhage occurred in approximately 1.6% of IV alteplase-treated patients.[7] The risk of this complication is still unknown in the subset of patients who undergo repeated systemic thrombolytic therapy for stroke or other conditions.[34] One patient in our review died after rupture of a previously unidentified infrarenal aortic aneurysm after the second dose of IV alteplase.[24] A study dealing with patients with unruptured intracranial aneurysms who receive IV alteplase did not demonstrate an increased risk for developing sICH.[35]

Alteplase is a purified human glycoprotein. Studies in various animal models demonstrate antibody formation inducing altered pharmacokinetic properties and sensitization on re-exposure.[36] One case report documented preexisting IgE antibodies against IV alteplase in a patient who developed severe anaphylaxis after alteplase.[37] Despite the theoretical risk of developing allergic

reactions after repeated use of IV alteplase, none were documented in the patients in our review.

The main limitation of this systematic review is the small number of documented cases of repeat IV alteplase for early recurrent with only half providing 3-month outcomes. Hence, a definitive conclusion about the efficacy and safety of IV alteplase in early recurrent ischemic stroke cannot be made. Another limitation is the design of the included studies which have an inherent bias due to lack of randomization and comparator groups. Our review suggests that repeated IV alteplase may not be as hazardous as previously thought.[38] Randomized trials for infrequent clinical scenarios like ours are unlikely to come to fruition. Thus, large stroke registries with provisions for monitoring the use of IV alteplase for early recurrent ischemic stroke are needed.

Conclusions

This systematic review suggests that repeated IV alteplase may be safe and efficacious in patients who develop a new ischemic stroke within 3 months from their prior event. The sICH, 3-month clinical outcomes, major systemic bleeding, and allergic reactions found in our review were comparable to that of randomized trials of IV alteplase for acute stroke.[5] Larger studies are needed to support the use of IV alteplase in this subgroup of patients.

Conflict of Interest

All the authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.07.006.

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