American Journal of Emergency Medicine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Is it dangerous to treat acute ischemic stroke by thrombolytic therapy in patients with comorbid intracranial aneurysms?☆,☆☆

Jiayue Ding, Jie Han *, Zhe Jing, Yue Jiang

Neurology Intensive Care Unit, First Affiliated Hospital of Dalian Medical University, Dalian, China

ARTICLE INFO

Article history:
Received 14 November 2015
Accepted 15 December 2015
Available online xxxx

ABSTRACT

Objectives: The safety of cerebral ischemic stroke patients with comorbid intracranial aneurysms treated by thrombolysis is still an unsolved mystery. We aimed to perform a secondary analysis and review to provide evidence on whether stroke patients with intracranial aneurysms have worse outcomes after thrombolysis.
Methods: We searched almost all the relevant English articles published before June 21, 2015, using databases such as Medline, Embase, and Cochrane and tracked the acquired references to include the available articles. Data were processed using RevMan5.0 software provided by Cochrane collaboration, and relevant clinical guidelines, theory, retrospective studies, and case reports were summarized.
Results: We included 5 retrospective studies totaling 767 patients who met the inclusion and analytical criteria, which included 78 people with intracranial aneurysms. The total relative risk for patients with unruptured intracranial aneurysms developing intracranial hemorrhage after thrombolysis was 0.98 (95% confidence interval [CI], 0.60-1.58; $P = .92$; $I^2 = 22\%$). The total relative risk for symptomatic intracranial hemorrhage was 0.97 (95% CI, 0.37-2.57; $P = .95$; $I^2 = 40\%$). The total relative risk for mortality during hospitalization was 1.09 (95% CI, 0.36-3.31; $P = .21$; $I^2 = 36\%$). We collected 13 case reports for reference.
Conclusion: The presence of unruptured intracranial aneurysms was not associated with a statistically significant increased risk of intracranial hemorrhage, symptomatic intracranial hemorrhage, and inhospital death after intravenous thrombolysis, although some theories and guidelines had opposite views. We suggest to perform more clinical trials with larger samples, multiple centers, and higher level of evidence to draw more reliable conclusions.

1. Introduction

The incidence rate of intracranial aneurysms (IAs) in patients with acute ischemic cerebral stroke is approximately 6.6% [1], which is higher than the normal crowd (3.6%-6%) [2,3]. It has been indicated that aneurysms, especially saccular aneurysms that are very thin to block the blood flow, cause rupture of IAs, resulting in intracranial hemorrhage (ICH). A meta-analysis on the relationship between postthrombolytic ICH and associated risk factors has been published, and thrombolytic drugs such as recombinant tissue type plasminogen activator (rt.-PA) and urokinase might lead to secondary ICH [4]. For patients with aneurysm, rupture and bleeding are risk factors, and thrombolytic therapy may cause similar bleeding, which is considered an adventure in the eyes of clinical workers. However, in recent years, some physicians found that patients with aneurysms who have received thrombolysis had good outcomes and no events of aneurysm rupture when they did not know the risk before postthrombolysis imaging. As the relevant case reports and retrospective studies were covered continually, thrombolysis prone to rupture of aneurysms has been a subject of debate among medical specialists, that is, whether stroke patients with comorbid aneurysms should undergo thrombolysis, which is still a dilemma among doctors. Studies have shown that approximately 9.3% postthrombolysis patients have IAs, and some of them have good outcomes with unruptured aneurysms, whereas the others have disastrous events with ruptured aneurysms resulting in ICH or even death. Given this, we decided to perform a secondary analysis and review to analyze whether stroke patients with IAs have an increased risk of ICH, symptomatic intracranial hemorrhage (sICH), and mortality after thrombolytic therapy for clinical decision.

2. Methods

We embraced items of Cochrane systematic review and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [5].

☆ Conflicts of interest: The authors confirm that this article content has no conflicts of interest.
☆☆ Funding: None.

* Corresponding author at: Neurology Intensive Care Unit, First Affiliated Hospital of Dalian Medical University, 222 Zhongshan Street, Dalian, 116011, China. Tel.: +86 18098876278.
E-mail address: sjnkzz@163.com (J. Han).

http://dx.doi.org/10.1016/j.ajem.2015.12.025
0735-6757/

2.1. Search method

We searched almost all the relevant English articles published before June 21, 2015, using databases such as Medline, Embase, and Cochrane and tracked the acquired references to get a more complete data. We searched PubMed comprehensively using the terms *aneurysm*, *malformation*, and *thrombolysis*. In other databases, generally, we used the following search terms: aneurysm(s), malformation, thrombolysis, thrombolytic, thrombolyse(s), fibrinolysis, fibrinolystic, fibrinolyse(s), tissue plasminogen activator, rt.-PA, t-PA, alteplase, urokinase, streptodornase. Two authors (ZJ and YJ) selected the relevant articles, resolving any conflicts by involving JD.

2.2. Eligibility criteria

Based on participants interventions comparisons outcomes study (PICOS) recommended by Cochrane collaboration, we listed the following criteria:

(1) Participants (P): Patients with cerebral thrombosis or embolism, which have received arterial or intravenous thrombolytic therapy.
(2) Interventions (I): IAs found by computed tomography angiography (CTA), magnetic resonance angiography (MRA), conventional angiography, catheter arteriography, and more, including ruptured or unruptured, operated or unoperated, and even operating IAs.
(3) Comparisons (C): Patients without IAs determined by CTA, MRA, conventional angiography, and catheter arteriography.
(4) Outcomes (O): We got the outcomes as follows: ICH, sICH, subarachnoid hemorrhage (SAH), prognosis, National Institute of Health Stroke Scale (NIHSS) score, and death during hospitalization. According to imaging manifestations, investigators estimated recanalization and ICH after thrombolysis. Meanwhile based on signs and symptoms of patients, they knew whether neurologic function had improved. Most of studies used European-Australasian Acute Stroke Study (ECASS) II or National Institute of Neurological Disorders and Stroke rt.-PA Stroke Study Group (NINDS) criteria to determine the diagnosis of sICH.
(5) Study (S): The second-level clinical researches (prospective, controlled, failing to be mastered: such as cohort study, before-and-after study, nonrandomized controlled trial), the third-level researches (controlled, failing to be mastered: such as case-control study, cross-sectional study), the fourth-level researches (narrative, noncontrolled: such as case report, expert review).

Two authors (ZJ and YJ) looked through all titles and abstracts of relevant articles to extract some uncorrelated articles. Two authors (JD and JH) read through the full text of the rest to classify each article type and simultaneously removed the uncorrelated articles. All conflicts were resolved through discussion.

2.3. Quality evaluation

We consulted Newcastle-Ottawa Quality Assessment Scale (NOS) items provided by Cochrane collaboration [6], with 1 point for each item. The higher the score of a study, the higher is the quality of the study.

Selection: (1) Is the case definition adequate? (2) Representativeness of the cases. (3) Selection of controls. (4) Definition of controls.

Comparability: Comparability of cases and controls based on the design or analysis.

Exposure: (1) Ascertainment of exposure. (2) Same method of ascertainment for cases and controls. (3) Nonresponse rate.

Two authors (JD and ZJ) were involved in this work.

2.4. Statistical analysis

Data were processed using RevMan5.0 software provided by Cochrane collaboration. Dichotomous variable was expressed as relative risk (RR) to reach the outcome statistics. Fixed-effects model used Mantel-Haenszel method and random-effects model used DerSimonian and Laird method for calculation. Every effect size was expressed as 95% confidence interval (CI). Hypothesis test was *U* test expressed by Z and P. $P \le .05$ was considered significantly different. We used χ^2 test to assess the heterogeneity of data. Only if the heterogeneity is available ($P > .05$; $I^2 \le 50\%$), using fixed-effects model is valid for meta-analysis. On the contrary, the heterogeneity is too hard to be accepted ($P < .05$; $I^2 > 50\%$). It is necessary to find out the reason of unexpected heterogeneity and estimate whether random-effects model is appropriate. Subgroup analysis is recommended strongly to make the heterogeneity diminished. Publication bias was calculated and shown using a funnel plot. We gathered all relevant case reports to be used as references for the results of meta-analysis giving an exact suggestion to clinical decision.

3. Results

3.1. Search results

After the initial search, we removed duplicates and animal studies, and based on titles and abstracts, we excluded the irrelevant articles. Finally, 66 articles were shortlisted. We glanced over all these articles to screen further, by eliminating nonaneurysm and nonthrombolytic therapy articles. Finally, we brought 18 studies into our systematic review. The included articles encompassed 5 retrospective studies and 13 case reports. We combined the retrospective studies to conduct the meta-analysis.

3.2. Characteristics of included studies

We got 7 retrospective studies containing 5 articles on existing unruptured IAs in acute ischemic stroke patients after receiving

Table 1
Characteristics of included studies

Study	Kim et al [7]	Edwards et al [8]	Sheth et al [9]	Mittal et al [10]	Zhang et al [11]
Design	Retrospective, single center	Retrospective, 2 centers	Retrospective, single center	Retrospective, multicenter	Retrospective, single center
Image for IAs identification	CTA, MRA, conventional angiography	CTA, MRA	CTA, MRA	CTA, MRA, catheter arteriography	CTA, MRA
Treatment strategy	All the researchers consulted AHA/ASA: rt.-PA intravenous thrombolytic therapy				
Definition of sICH	ECASS II	ECASS II	NINDS	ECASS II	ECASS II
Outcome	ICH, sICH, SAH	ICH, sICH, SAH	ICH, sICH, mortality	ICH, sICH, SAH, mortality[a], 3-mo mRS	ICH, sICH, non-sICH, mortality[a], good outcome
NOS score	6	6	6	6	7

Abbreviation: AHA/ASA, American Heart Association/American Stroke Association.
[a] Mortality means mortality in hospitalization.

Please cite this article as: Ding J, et al, Is it dangerous to treat acute ischemic stroke by thrombolytic therapy in patients with comorbid intracranial aneurysms? Am J Emerg Med (2015), http://dx.doi.org/10.1016/j.ajem.2015.12.025