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Review

Tranexamic acid-associated seizures: A meta-analysis

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ABSTRACT

Purpose: To investigate the incidence rate of tranexamic acid (TXA)-associated seizures.
Methods: Two electronic databases (Medline and Embase) were searched. We looked for additional studies in the references of all identified publications. The cutoff day was 2015 Dec 06. Two authors independently reviewed the titles and abstracts of the publications identified firstly. Odds ratio (OR) and 95% confidence interval (CI) were used to compare discontinuous variables.
Results: Ten studies enrolling 26,079 patients with TXA exposure and 7395 patients with non-TXA exposure were included. The cumulative incidence rate of TXA-associated seizures is 2.7%. The odds ratio of seizure is 5.39 (95%CI: 3.29–8.85; $I^2 = 0\%$; $P < 0.001$) in patients with TXA exposure vs patients with non-TXA exposure. The incidence rate of TXA-associated seizures increased when the dose levels increased.
Conclusion: The risk of seizure increased in patients with TXA exposure and the incidence rate of TXA-associated seizures increased when the dose levels increased.

1. Introduction

Tranexamic acid (TXA) is a worldwide antifibrinolytic drug that is effective in decreasing bleeding [1]. TXA acts by binding to plasminogen and blocking the interaction of plasmin (ogen) with fibrin, thereby reducing the degradation of the fibrin clot [2]. As a lysine analog, TXA can cross the blood–brain barrier [2,3]. Therefore, TXA may act on neurons and glia cells and induce disorders of brain. In fact, many studies have reported that TXA was associated with an increased incidence rate of postoperative seizures [4,5]. However, the prevalence and the odds ratio comparing with non-TXA exposure with dose–effect response of tranexamic acid-associated seizures have still kept no consensus. To provide the best available evidence for these questions, we conducted a meta-analysis in the present article.

2. Methods

2.1. Study identification and selection

Two electronic databases (Medline and Embase) were searched. We looked for additional studies in the references of all identified publications. The following MeSH terms and text words were used without language restrictions: 'tranexamic acid', 'TXA', 'seizure', 'convulsion', and 'epilepsy'. The cutoff day was 2015 Dec 06. We selected studies which reported the prevalence or odds ratio. In addition, the articles published in English and having an available full text could only be included. Two authors independently reviewed the titles and abstracts identified in the search.

2.2. Data extraction

The two same reviewers independently extracted relevant information from each eligible study by using a standardized form. For each of the included studies, the first author, the study design, the inclusion criteria of patients, the dosage of TXA, the percentage of males and the age were recorded. If there was any disagreement about article selection, it would be resolved through discussion by all authors. Missing data were calculated according to the statistic method published in the Cochrane handbook.

2.3. Statistical analysis

All statistical analyses were performed using Review Manager 5.3 (Cochrane Collaboration) and OpenMeta (www.cebm.brown.edu). Odds ratio (OR) and 95% confidence interval (CI) were used to compare discontinuous variables. The I^2 was used to examine between-study heterogenicity. If $I^2 > 50\%$, the heterogeneity was unacceptable. The data were analyzed by using a random-effects

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model. If $I^2 < 50\%$, the heterogeneity was acceptable and the data were analyzed with a fixed-effects model. Sensitivity analysis was performed to test the reliability of the results of significant findings by a cycle way that we removed single different study and repeated the analysis once. If the result of the study did not change significantly before and after removing this study, it had a high stability. Outcome measures were prevalence and odds ratio, and the dose–effect response. The result was presented as statistical significance when $P < 0.05$.

3. Results

3.1. Study identification and selection

A flow diagram of the identification of studies was shown in Fig. 1. Ten studies [3–12] enrolling 26,079 patients with TXA exposure and 7395 patients with non-TXA exposure were included. The features of included studies were presented in Table 1. Mean age of most patients was >60 years old and the percentage of males was more than a half. All patients had a cardiac surgery or pulmonary endarterectomy.

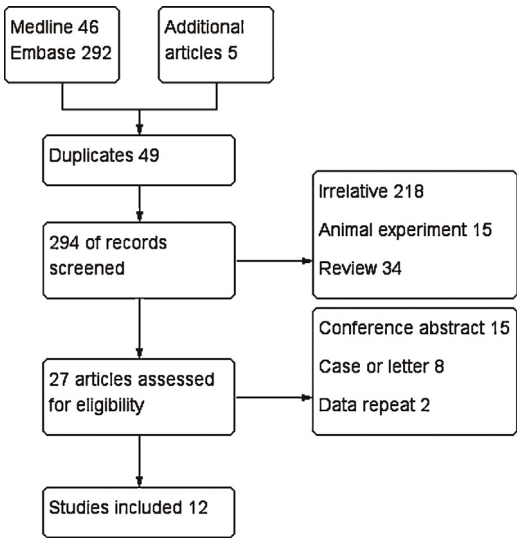

Fig. 1. Flowchart.

Table 1
Features of the included studies.

Author	Design	Disease	EEG	Seizure type	Seizure(*n*)/TXA (*N*) Seizure(*n*)/control (*N*)	Age*	Male (%)	Dose
Berman M	Retrospective cohort study	Pulmonary endarterectomy	No	–	11/100	56.1 (16.6)	58.0	[a]High (30 mg/kg + 15 mg/kg h)
					4/100	55.8 (16.6)	57.0	–
Gofton TE	Prospective observational study	Cardiac surgery	Yes	–	3/101	65.4 (10.6)	72.0	High (80 mg/kg)
					No control	–	–	–
Koster A	Retrospective cohort study	Cardiac surgery	No	Clonic movement	26/1029	70.3	59.9	Low (24 mg/kg)
					46/3854	69.5	58.2	–
Keyl C	Retrospective cohort study	Cardiac surgery	No	GTCS only	22/341	73.0 (9.3)	55.4	High (100 mg/kg)
					2/341	73.7 (8.5)	53.6	–
Kalavrouziotis D	Retrospective cohort study	Cardiac surgery	No	GTCS only	31/6328 and	–	–	Middle (59 mg/kg)
					80/1754	–	–	High (109 mg/kg)
					No control	–	–	–
Martin K	Prospective cohort study	Cardiac surgery	No	–	27/592	66.0 (12.2)	68.6	Middle (4 g + 0.5 g/h)
					7/596	66.7 (11.7)	69.0	–
Montes F	Retrospective cohort study	Cardiac surgery	No	Generalized convulsive seizures	28/903	–	–	–
					No control	–	–	–
Manji RA	Retrospective cohort study	Cardiac surgery	Yes	–	49/3292	–	–	Low (45 mg/kg)
					6/2504	–	–	–
Murkin JM	Retrospective study	Cardiac surgery	No	–	24/660	–	–	–
					No control	–	–	–
Sharma V	Prospective observational study	Cardiac surgery	Yes	Generalized and focal seizure	75/2856	–	–	Middle (32 mg/kg + 16 mg/kg h)
					24/8123	–	–	Low (50 mg/kg)
					No control	–	–	–

* Data were shown by mean and standard deviation.
[a] Cumulative TXA dosage is high dose level because cardiopulmonary bypass time is long.
High TXA doses included 30 mg/kg (loading dose) plus 15 mg/kg h (continuous infusion during operation) and 80–109 mg/kg; middle TXA doses included 59 mg/kg, 4 g plus 0.5 g/h, and 32 mg/kg plus 16 mg/kg h; low TXA doses included 24–50 mg/kg.
EEG = electroencephalogram; TXA = tranexamic acid; GTCS = generalized tonic–clonic seizures.