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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.

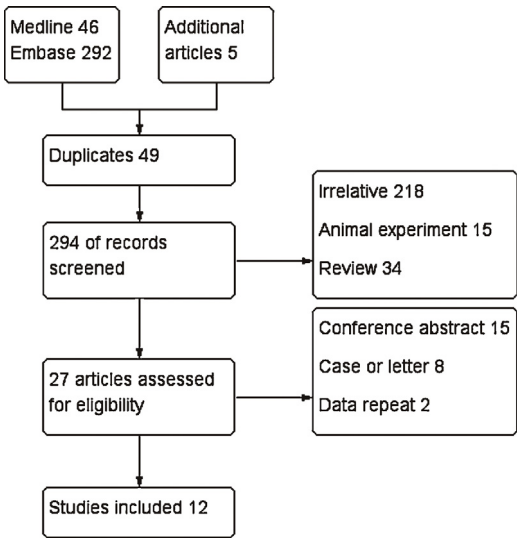

Fig. 1. Flowchart.

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.

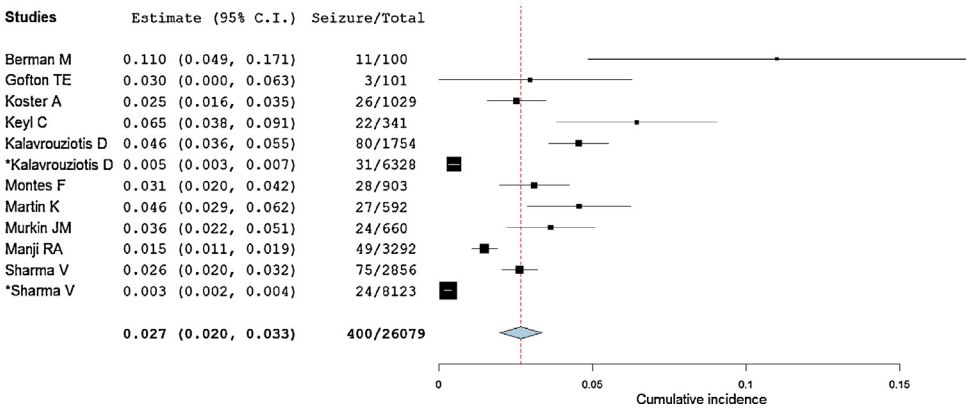

Fig. 2. Cumulative incidence rate of tranexamic acid (TXA) associated seizure. *Data of different TXA doses from the same studies.

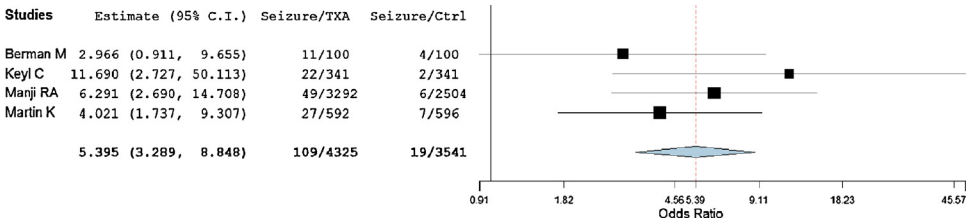

Fig. 3. The odds ratio of tranexamic acid-associated seizure.

3.2. Incidence rate of TXA-associated seizures

All studies [3–12] reported the incidence rate. The cumulative incidence rate of TXA-associated seizures is 2.7% (95%CI: 2.0–3.3%; $I^2 = 96\%$; $P < 0.001$) (Fig. 2).

3.3. The odds ratio comparing with non-TXA exposure

Five studies [3,6–9] reported the data of patients with non-TXA exposure. The odds ratio of seizure is 3.91 (95%CI: 2.22–3.91; $I^2 = 56\%$; $P < 0.001$) in patients with TXA exposure vs patients with non-TXA exposure. In the sensitivity analysis, we found the result was changed if we removed the study [8]. The odds ratio of seizure changed to 5.39 (95%CI: 3.29–8.85; $I^2 = 0\%$; $P < 0.001$) (Fig. 3).

3.4. The dose–effect response of TXA-associated seizures

Because there was a high heterogeneity between the results in Section 3.2, we performed a subgroup analysis. We first divided all doses into three levels including low, middle and high dose (Table 1). 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. Then we pooled the incidences of the three dose levels due to heterogeneity all studies using OpenMeta. The incidence rates in low dose level, middle dose level and high dose level are respectively 1.4% (95%CI: 0.2–2.5%; $I^2 = 96\%$), 2.4% (95%CI: 0.4–4.4%; $I^2 = 97\%$), and 5.3% (95%CI: 3.3–7.3%; $I^2 = 56\%$). After performing the sensitivity analysis, the result of the risk of seizure in high TXA dose is stable. Finally, we calculated the relationship between dose and the incidence rate of TXA-associated seizures. The result showing the incidence rate of TXA-associated seizures increased when the dose levels increased (Fig. 4).

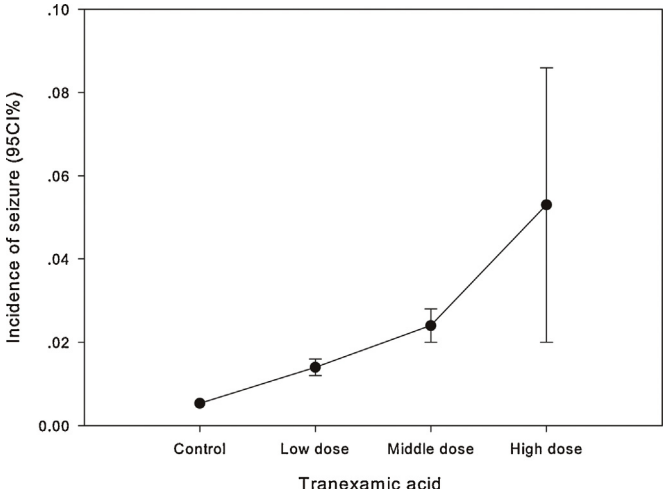

Fig. 4. Dose–effect response of tranexamic acid-associated seizure.

4. Discussion

The present meta-analysis summarized the findings regarding TXA-associated seizures on patients with TXA exposure. After the meta-analysis, we found that: (1) The cumulative incidence rate of TXA-associated seizures is 2.7%; (2) The risk of seizure increased in patients with TXA exposure and (3) the incidence rate of TXA-associated seizures increased when the dose levels increased. In addition, the incidence of seizures in controls is 0.5% in the case–control study (Fig. 3). Although positive sensitivity analysis existed in the incidence rate of low and middle TXA doses, the incidence is at least 0.9% whatever remove any studies. The subgroup analysis of different TXA dose levels showing the odds ratio was at least 3.45 (95%CI: 1.42, 8.41, $I^2 = 61\%$, $P = 0.06$). Therefore, the results of our meta-analysis support the evidences that three dose levels, especially high TXA dose, increase the risk of seizure.

Our result suggest that incidence rate of TXA-associated seizures is 2.7%, which is coincident with the findings of other studies [4,12]. However, the overall incidence rate of acute seizures is 0.1% in general population which has similar age as

TXA-exposure patients [3]. Even in the case-control study (Fig. 3), the incidence of acute seizures of controls is only 0.5%. In addition, patients with TXA exposure have a more than three times increased risk comparing with patients who have a similar surgery but non-TXA exposure. Therefore, it may be concluded that TXA is a decided risk factor of increasing seizure in patients with cardiac surgery or pulmonary endarterectomy. We also found that the dose–effect response between incidence rate of TXA-associated seizures and TXA dosage. To our best knowledge, it is therefore suggested that TXA should be carefully used even in low dose level.

Several potentially confounding factors may contribute or attenuate to our findings and they need to be discussed. First, all studies only included the populations with cardiac surgery or pulmonary endarterectomy. However, anesthetics reverse tranexamic acid inhibition of glycine receptors which may be an important molecular mechanism of TXA-associated seizures [1,13]. The actual incidence rate of TXA-associated seizures therefore may be higher. Second, mean age of the most included populations is >60 years old. Kidney volume and renal function decreased in parallel with increasing age [14]. Therefore, the elimination half-life increased in the elderly. Decreased renal function may induce higher TXA blood concentration which may increase the risk of seizure than that of general population. For example, a patient, with chronic renal failure, who was treated with TXA experienced a generalized seizure [15]. Third, the percentage of males is more than a half. On the average, women have a lower body weight than men, therefore, it may induce a lower blood TXA concentration when they are treated with equal dosage. This, therefore, decrease the incidence rate of seizure.

Some studies have investigated the molecular mechanisms of TXA-associated seizures. First, gama-aminobutyric acid type A (GABAA) receptors and glycine receptor, which are two major mediators of inhibition in the CNS, can be inhibited by TXA [13,16]. Furtmuller et al. [17] first found that hyperexcitability induced by TXA was completely blocked by GABA(A) receptor agonist muscimol. Kratzer et al. [16] demonstrated that TXA enhanced neuronal excitation by antagonizing inhibitory GABAergic neurotransmission [16]. Furthermore, another study reported that TXA concentrations in the CSF of patients inhibited glycine receptors [13]. Second, Furtmuller et al. [17] and Kratzer et al. [16] also suggested that TXA did not interfere with N-methyl-D-aspartate receptor and impact glutamatergic synaptic transmission [16]. Thus, the convulsant property of TXA is likely mediated by disinhibition.

The present meta-analysis has several limitations. First, a general limitation of meta-analyses is that no ideal data collection can be performed. For example, publication bias existed because null or difficult-to-interpret results might be unpublished. Similarly, because of the nature of meta-analyses, we had to perform a statistical analysis by relying only upon the included studies. This might result in less-accurate results. Second, the number of studies included was insufficient. Additionally, we were unable to perform any subgroup analysis with different design, disease, age, or sex. Third, there was heterogeneity in the studies, which might be caused by methodology. The random effects model we used might reduce the effect of heterogeneity, but we could not remove it. Therefore, these results should be interpreted carefully. A random controlled trail with large sample is needed for further study.

5. Conclusions

The risk of seizure increased in patients with TXA exposure and the incidence rate of TXA-associated seizures increased when the dose levels increased.

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Conflict of interest statement

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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