INPLASY PROTOCOL

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None declared.

Efficacy and safety of tranexamic acid in spontaneous intracerebral hemorrhage: a systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **To evaluate the available literature to determine the efficacy and safety of tranexamic acid in spontaneous intracerebral hemorrhage.**
Condition being studied: **Spontaneous intracerebral hemorrhage is one of the leading causes of disability and death worldwide constituting serious global public health and socioeconomic burdens. Although organised inpatient care has been shown to contribute to reduced disability and mortality, there are no strongly evidence-based acute therapies specific to spontaneous intracerebral hemorrhage. Tranexamic acid is an anti-fibrinolytic agent that reduces bleeding by inhibiting plasminogen activation and fibrinolysis. It has been shown to reduce perioperative blood loss and risk of blood transfusion. Several randomized controlled trials examining the efficacy and safety of tranexamic acid in spontaneous intracerebral hemorrhage patients have been performed in recent years. However, an in-depth meta-analysis of the latest results of these larger randomized controlled trials is lacking.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 July 2021 and was last updated on 11 July 2021 (registration number INPLASY202170032).

INTRODUCTION

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METHODS

Search strategy: Controlled vocabulary (i.e., MeSH and Emtree) and keywords were used. Search terms included those related to 'Tranexamic Acid', 'Intracerebral Hemorrhage', 'Randomized Controlled Trials', and their variants.

Participant or population: Adult patients (aged ≥18) with spontaneous intracerebral hemorrhage and were treatable within 24 h of symptom onset.

Intervention: Tranexamic acid at any dose.

Comparator: Placebo or no treatment.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: (i) Types of studies: Randomized controlled trial; (ii) Types of participants: Adult patients (aged ≥18) with spontaneous intracerebral hemorrhage and were treatable within 24 h of symptom onset; (iii) Types of interventions: Tranexamic acid at any dose versus placebo or no treatment; (iv) Types of outcome measures: The outcomes of interest were hematoma expansion defined as hematoma growth >33% and/or >6ml, 3-month poor functional outcome defined as modified Rankin Scale score 4-6, 3-month mortality, and major thromboembolic events.

Information sources: We conducted a comprehensive search of PubMed, Embase, Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform, and the ClinicalTrials.gov. In addition, we manually screened the reference lists of eligible trials and previous relevant reviews for additional studies.

Main outcome(s): The outcomes of interest were hematoma expansion defined as hematoma growth >33% and/or >6ml, 3-month poor functional outcome defined as modified Rankin Scale score 4-6, and 3-month mortality.

Additional outcome(s): None.

Data management: After records were imported into the Zotero reference management software, and duplicate records were manually removed. Two reviewers independently screened the titles and abstracts for relevance, and labeled records as probably included and excluded in duplicate. If records were deemed potentially relevant by either screener, the full-text articles were retrieved to assess eligibility. Disagreements were resolved by consensus, and third-party adjudication if required.

Quality assessment / Risk of bias analysis: Two reviewers assessed risk of bias of each trial independently and in duplicate using the Cochrane Collaboration's tool based on the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention. We examined the following risk of bias domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias (such as stopping early and funding source) and rated as "high risk", "unclear risk", or "low risk". Disagreements were resolved by consensus, and third-party adjudication if required. Two reviewers assessed the

overall certainty of evidence for each outcome using the Grading Recommendations Assessment, Development and Evaluation system. The domains assessed included risk of bias, inconsistency, indirectness, imprecision, and publication bias; the evidence quality was classified as "very low", "low", "moderate", or "high".

Strategy of data synthesis: Odds ratios with corresponding 95% confidence intervals were used as summary statistics. Meta-analyses were performed using a random-effects model accounting for clinical heterogeneity. We assessed heterogeneity between trials using the Cochran Q test (with $p < 0.1$ indicating significance) and quantified by the I2 statistic (for which a value of 50% or greater was considered to represent significant heterogeneity). Publication bias across individual trials was graphically evaluated using a funnel plot and with the Egger linear regression test at a significance level of $p < 0.10$.

Subgroup analysis: Subgroup analyses were carried out according to the risk of hematoma expansion (with or without the CT markers). CT markers, including black hole sign, blend sign, island sign, and spot sign, have been used as reliable predictors for early hematoma growth in patients with intracerebral hemorrhage.

Sensitivity analysis: We also performed two post hoc sensitivity analyses, one deleting each study separately and another transforming the random effect model to fixed effect, to test the robustness of our findings.

Language: No language restriction.

Country(ies) involved: China.

Keywords: Cerebral hemorrhage; hematoma; tranexamic acid; randomized controlled trial; meta-analysis.

Contributions of each author:

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