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Tranexamic acid for the prevention of postpartum hemorrhage in women undergoing cesarean delivery: an updated meta-analysis

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ABSTRACT

Postpartum hemorrhage represents a major complication of cesarean delivery, leading to significant rates of maternal morbidity and mortality. Previous meta-analyses have provided inconclusive evidence regarding the clinical utility of tranexamic acid therapy prior to caesarean delivery due to methodological limitations of studies and lack of follow-up for thromboembolic events. The present meta-analysis aims to accumulate current literature knowledge in the field and provide an updated synthesis of evidence concerning the efficacy and safety of prophylactic tranexamic acid for the prevention of postpartum hemorrhage in women undergoing cesarean delivery. Medline, Scopus, CENTRAL, Web of Science and Clinicaltrials.gov will be systematically searched from inception. Women undergoing cesarean delivery receiving standard uterotonic agent prophylaxis and tranexamic acid or placebo will be comapred in terms of postoperative blood loss (in ml), blood loss >1000 ml, red-cell transfusion, number of red-cell units transfused, hemoglobin and hematocrit decrease, additional administration of uterotonic agents, thromboembolic events. Only randomized controlled trials will be included. A random-effects model using restricted maximum likelihood will be fitted in order to provide pooled estimates of odds ratios and 95% confidence intervals.

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1 Background Postpartum hemorrhage represents a major complication of cesarean delivery, leading to significant rates of maternal morbidity and mortality. Blood loss often necessitates resuscitation with red-cell transfusion, exposing

patients at risk of hemolytic, anaphylactoid and infectious complications. To this end, the administration of a uterotonic agent is recommended aiming to limit postpartum blood loss. Tranexamic acid is a synthetic competitive lysine receptor inhibitor, serving as an antifibrinolytic agent by inhibiting plasmin-fibrin interactions and fibrin matrix stabilization. Previous meta-analyses have provided inconclusive evidence regarding the clinical utility of tranexamic acid therapy prior to caesarean delivery due to methodological limitations of studies and lack of follow-up for thromboembolic events. The present meta-analysis aims to accumulate current literature knowledge in the field and provide an updated synthesis of evidence concerning the efficacy and safety of prophylactic tranexamic acid for the prevention of postpartum hemorrhage in women undergoing cesarean delivery.

2 Study design The meta-analysis will be conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

3 Search strategy Medline, Scopus, CENTRAL, Web of Science and Clinicaltrials.gov will be systematically searched from inception. Google Scholar will be searched to provide grey literature coverage. The full reference list of the retrieved studies will also be searched to identify potential additional sources (“snowball” method). Search will be based on Medical Subject Headings (MeSH) terms ("Cesarean Section"[Mesh], "Postpartum Hemorrhage"[Mesh], "Tranexamic Acid"[Mesh]), combined with a list of key-words (“cesarean”, “cesarean”, “postpartum hemorrhage”, “blood loos”, “transfus*”, “tranexamic”, “TXA”, “antifibrinolytic”). No date or language restriction will be applied.

4 Eligibility criteria Population: Women undergoing cesarean delivery receiving standard uterotonic agent prophylaxis Intervention: Tranexamic acid Comparator: Placebo Outcomes: Postoperative blood loss (in ml), blood loss >1000 ml, red-cell transfusion, number of red-cell units transfused, hemoglobin and hematocrit decrease, additional administration of uterotonic agents, thromboembolic events Study type: Randomized controlled trials Exclusion criteria: Observational studies, review articles, animal studies, in vitro studies, vaginal delivery, no uterotonic agent prophylaxis

5 Study selection The studies will be selected following 3 consecutive stages. Firstly, the titles and abstracts of the articles identified by database search will be screened to assess for potential eligibility. Subsequently, all studies that will be presumed to meet the pre-specified inclusion criteria will be retrieved as full-texts. Then, studies that will meet any of the exclusion criteria will be identified and will not be included in the review.

6 Data extraction Data extraction will be performed independently by two researchers. The following data will be extracted: name of first author, publication date, country, study design, inclusion and exclusion criteria, tranexamic acid dose, patients’ number, age, previous cesarean delivery, multiple pregnancy, hypertensive disorders of pregnancy, timing of cesarean delivery, type of prophylactic uterotonic agent, anticoagulant prophylaxis after delivery, as well as data regarding outcomes of interest.

7 Quality assessment The quality of studies will be assessed with the RoB-2 tool for randomized controlled trials, which takes into account the following domains: randomization, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. The credibility of evidence will be judged with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluating the domains of inconsistency, indirectness, imprecision and publication bias.

8 Data analysis A random-effects model using restricted maximum likelihood will be fitted in order to provide pooled estimates of odds ratios and 95% confidence intervals. Heterogeneity will be evaluated with the inconsistency index (I2) and the 95% predictive intervals will be calculated to provide estimates of the effects to be expected by future studies. Publication bias will be assessed with the visual inspection of funnel plots along with the significance of the Egger’s regression test (p-value <0.10). Subgroup analysis is planned depending on study date, location and drug dosage. Moreover, sensitivity analyses will be performed by separately pooling women undergoing elective caesarean delivery, as well as those at high risk of postpartum hemorrhage. As an additional sensitivity analysis, the summary effect estimates will be estimated using 2 one-stage generalized linear mixed models (modified Simmonds-Higgins and hypergeometric-normal model).

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