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Prophylactic Use of Tranexamic Acid for Postpartum Bleeding Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Despite multimodal approaches to treatment, postpartum hemorrhage (PPH) is a life-threatening condition whose incidence continues to rise. In developing areas, such as sub-Saharan Africa, PPH is the leading cause of maternal mortality. Tranexamic acid (TXA) is a possible prophylactic treatment for the prevention of PPH. We performed a systematic review and meta-analysis of randomized trials comparing prophylactic TXA vs placebo or no treatment in term parturients to quantify the effects of prophylactic TXA administration on peripartum bleeding outcomes. The meta-analysis was performed using a random-effects model. The outcomes assessed were (i) incidence of PPH, (ii) mean blood loss (in milliliters) within 24 hours, (iii) incidence of red blood cell transfusion within 24 hours, (iv) use of additional uterotonics, (v) minor side effects (ie, nausea, vomiting, headache, etc), (vi) major venous thromboembolism, (vii) length of hospital stay, and (viii) mortality. Eighteen trials (3846 subjects) were included in the quantitative analysis, with 1935 patients receiving TXA. The studies were of poor to moderate quality. Prophylactic TXA administration was associated with a decreased incidence of PPH after delivery (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.17-0.59; $P = .0006$), a reduction in mean blood loss by 149.1 mL (95% CI, 112.9-185.2; $P < .00001$), and a reduction in red blood cell transfusions (OR, 0.28; 95% CI, 0.15-0.49; $P < .00001$) while also being associated with a reduction in the use of additional uterotonics (OR, 0.45; 95% CI, 0.30-0.66; $P < .00001$). Minor side effects were more common in those who received TXA (OR, 2.51; 95% CI, 1.69-3.74; $P < .00001$). There appeared to be no increased risk of venous thromboembolism and no difference in length of hospital stay associated with TXA use. Although prophylactic TXA administration may be associated with improved peripartum bleeding, existing evidence is insufficient for any definitive recommendations secondary to the poor to moderate quality of the literature. A large well-designed, methodologically sound, randomized controlled trial is needed to better delineate the true effect size and address potential safety concerns.

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality and is responsible for one-quarter of all maternal death worldwide [1]. Most maternal mortality due to PPH occurs in developing nations, where greater than one-third of all parturients are affected [1]. In developed nations, although maternal mortality is rare, PPH may be implicated in up to 27% of cases [2]. In addition, the incidence of PPH is on the rise in many of these countries [3–5]. Although a number of effective treatments exist, women still develop severe hemorrhage. In countries with limited health care resources, a safe, low-cost, effective therapy that can be administered in a wide range of health care settings is needed to help reduce the incidence of PPH and its associated morbidity and mortality [6].

Tranexamic acid (TXA) is an antifibrinolytic agent that prevents the conversion of plasminogen to plasmin stabilizing clot formation in bleeding patients. TXA has been shown to reduce blood loss, transfusion requirements, and mortality in multiple perioperative settings including cardiac surgery, liver surgery, major orthopedic surgery, and trauma [7–10]. Given the pathophysiology of PPH, TXA is a promising therapy. It is economical [11], has a good safety profile [12], and can be administered in multitude of health care settings where tertiary obstetrical care is not available [13].

The World Maternal Antifibrinolytic Trial, a large pragmatic international randomized, placebo-controlled trial modeled after the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage trial, is in progress to determine if TXA can reduce mortality in patients with diagnosed PPH [12]. To date, more than 15000 patients have been randomized with recruitment scheduled to proceed until early 2016. However, this trial does not assess the efficacy of prophylactic TXA in preventing the onset of PPH. There have been a number of small randomized-controlled trials that have examined whether

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prophylactic TXA can reduce the incidence of PPH among parturients. However, no firm conclusions regarding the efficacy and safety of routine, prophylactic TXA in the prevention of PPH have been reached. This is particularly important, as the prophylactic use of TXA is not an approved indication for use by regulatory bodies.

A recent systematic review and mathematical model estimated that almost 22 000 deaths per year could be averted worldwide if TXA were used prophylactically or for treatment of PPH (assuming a 30% effect size) [13]. The purpose of this systematic review and meta-analysis is to determine if the prophylactic administration of TXA is associated with an improvement in peripartum hemorrhage rates, morbidity, and mortality and whether there are any adverse events associated with its use.

Methods

This meta-analysis conforms to the reporting guidelines according to the 2009 PRISMA statement (http://www.prisma-statement.org/).

Search Strategy

The following electronic databases were searched in duplicate: (i) MEDLINE (1946–January 2015), (ii) EMBASE (1947–January 2015), and (iii) Cochrane Central Register of Controlled Trials (2005–January 2015). The following MeSH search terms were used with the definition exploded: "postpartum hemorrhage" with the "AND function combining 'tranexamic acid.'" Identified abstracts were screened and full-text articles meeting the inclusion criteria described below were retrieved. The references of all retrieved articles were manually searched to identify studies not found in the initial electronic search. All available abstracts from major meetings from the Web sites of major international associations including the American Society of Anesthesiologists (ASA), Society of Obstetrics and Gynaecologists of Canada (SOGC), Society for Obstetric Anesthesia and Perinatology (SOAP), The American Congress of Obstetricians and Gynecologists (ACOG), and Royal College of Obstetricians & Gynecologists (RCOG) were searched. Published protocols on www.clinicaltrials.gov were also searched.

Selection criteria

Studies meeting the following criteria were included: (i) prospective with randomized allocation, (ii) comparison of prophylactic use of TXA (intervention) vs placebo or no treatment (control) for cesarean section (CS) or spontaneous vaginal deliveries (SVDs), and (iii) adult (>18 years) patients. Attempts were made to contact study authors, particularly for meeting abstracts, to elicit information regarding methodology, missing data, and other study details relevant to this review and to enable more accurate risk of bias estimates. Abstracts were planned for inclusion if an adequate risk of bias assessment could be performed. Studies were planned for inclusion regardless of whether regulatory approval (US Investigational New Drug or national equivalent) was sought by authors.

Data Extraction

Two independent reviewers (A.A. and S.C.) performed the data extraction in duplicate. The following demographic data were extracted: primary author, year of publication, specific obstetric population (types of parturients), delivery type (CS vs SVD), sample size, and dose and timing of TXA administered. Procedures for of risk of bias assessments are detailed in the following sections.

Reconciliation of Study Procedures

All activities including the literature search, inclusion of studies, grading study quality, and data extraction were carried out independently and in duplicate by the 2 authors (A.A. and S.C.). Disagreements between reviewers were resolved through discussion.

Outcomes Assessed

The primary outcome was (1) onset of primary PPH as defined by a blood loss greater than 500 mL in an SVD or greater than 1000 mL in CS (as traditionally defined as per ACOG guidelines) or sustained blood loss leading to hemodynamic instability [14]. The secondary outcomes were as follows: (2) mean blood loss (mL) in a 24-hour period; (3) transfusion of red blood cells (RBCs) in a 24-hour period; (4) use of additional medications to control PPH; (5) mild side effects of TXA such as nausea, vomiting, headache, and skin reactions; (6) major thromboembolic events including myocardial infarction, stroke, pulmonary embolism, and proximal deep venous thrombosis; (7) length of stay (LOS); and (8) mortality.

Assessment for Risk of Bias and Methods for Measuring Heterogeneity

Each included study was assessed for risk of bias according to the Cochrane Collaboration's Risk of Bias Tool for randomized controlled trials (http://handbook.cochrane.org). Heterogeneity was assessed using the I^2 statistic. Studies were pooled for the meta-analysis using a random-effects model.

Analysis and Plans to Summarize Results

Meta-analysis was performed with RevMan 5.3 (Cochrane Library, Oxford, UK) using a random-effects model. The Summary of Findings table was generated using GRADEpro, the GRADE working group guideline development tool (www.http://ims.cochrane.org/revman/gradepro). Results for dichotomous data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous data, the mean difference with 95% CIs is presented. Differences were considered statistically significant if $P < .05$, and the 95% CI excluded 1 for the OR and 0 for the mean difference. Subgroup analysis was planned based on delivery type, SVD or CS. The *a priori* hypothesis regarding subgroup effects was that TXA would have a greater effect in patients undergoing CS.

Results

The search yielded 273 records after removal of duplicates identified between databases. Among these, 21 studies were included in the systematic review [15–35]. Two hundred twenty-four records were excluded because they did not fulfill the criteria for a clinical trial or had no analyzable data. Three studies were excluded from the quantitative analysis with the rationale discussed below [33–35]. In total, 18 studies were included in the quantitative meta-analysis. The PRISMA flow diagram is presented in Figure 1. Details including TXA dose, treatment arms (placebo or no treatment), outcomes assessed, and other pertinent details of each study are given in Table 1. Most of studies used a TXA dose of either 1 g or 10 mg/kg administered prior to incision or anesthesia during CS or at delivery of anterior shoulder in SVD. Overall, 3846 patients were included in the meta-analysis, of which 1935 received TXA. The Summary of Findings table gives estimates of the effects of TXA on reported outcomes as well as grading the level of evidence (Table 2).

None of the included studies sought or obtained regulatory approval for the off-label use of TXA. Authors of 7 studies were contacted to obtain further information regarding either methodological issues related to risk of bias or to acquire data to allow better determination of mean/SD from median/interquartile range. Responses were received from 3 authors [23,26,28] and no response from 4 authors [15,18,30,32].

Three studies were excluded from the meta-analysis (see Table 1) because they did not provide procedures for measuring blood loss or how PPH was defined [33–35]. These studies were published as abstracts and reported statistically significant reductions in blood loss