International Journal of Gynecology and Obstetrics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

www.figo.org

CLINICAL ARTICLE

A randomized placebo-controlled trial of preoperative tranexamic acid among women undergoing elective cesarean delivery

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ARTICLE INFO

Article history:
Received 8 January 2015
Received in revised form 11 May 2015
Accepted 5 August 2015

Keywords:
Blood loss
Elective cesarean delivery
Tranexamic acid

ABSTRACT

Objective: To study the efficacy and safety of preoperative intravenous tranexamic acid to reduce blood loss during and after elective lower-segment cesarean delivery. *Methods:* A single-blind, randomized placebo-controlled study was undertaken of women undergoing elective lower-segment cesarean delivery of a full-term singleton pregnancy at a center in Cairo, Egypt, between November 2013 and November 2014. Patients were randomly assigned (1:1) using computer-generated random numbers to receive either 1 g tranexamic acid or 5% glucose 15 minutes before surgery. Preoperative and postoperative complete blood count, hematocrit values, and maternal weight were used to calculate the estimated blood loss (EBL) during cesarean, which was the primary outcome. Analyses included women who received their assigned treatment, whose surgery was 90 minutes or less, and who completed follow-up. *Results:* Analyses included 100 women in each group. Mean EBL was significantly higher in the placebo group (700.3 ± 143.9 mL) than in the tranexamic acid group (459.4 ± 75.4 mL; $P < 0.001$). Only six women, all in the placebo group, experienced an EBL of more than 1000 mL. There were no reports of thromboembolic events up to 4 weeks postoperatively. *Conclusion:* Preoperative administration of tranexamic acid safely reduces blood loss during elective lower-segment cesarean delivery. **Australian New Zealand Clinical Trials Registry: ACTRN12615000312549.**

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1. Introduction

Worldwide, 15% of deliveries occur by cesarean [1]. In the USA, one in three women deliver by cesarean [2]. Although cesarean delivery is intended to be a lifesaving procedure, reducing both maternal and fetal morbidity and mortality [3], blood loss during cesarean is twice that of vaginal delivery (1000 mL vs 500 mL) [4]. Severe anemia after postpartum bleeding is a leading contributor to maternal morbidity, increasing the likelihood of fatal postpartum hemorrhage in future pregnancies [5]. Therefore, medications such as oxytocin, ergometrine, prostaglandin F2α, and misoprostol are commonly used to minimize intraoperative and postoperative bleeding during cesarean delivery [6,7].

Tranexamic acid is a synthetic lysine derivative that inhibits fibrinolysis by preventing binding of plasminogen and plasmin to the fibrin substrate through blockage of the lysine-binding sites [8]. Additionally, the drug inhibits conversion of plasminogen to plasmin [9]. The drug theoretically increases the risk of thromboembolic events, although a systematic review of its use in surgery showed no significant increases in this risk [10]. In 2011, the CRASH-2 trial [11] showed that early administration of tranexamic acid significantly reduces mortality in trauma patients with hemorrhage. As a result of this trial, the drug was included in the WHO Model List of Essential Medicines [12].

Tranexamic acid is routinely used to reduce intraoperative and postoperative blood loss in several surgical procedures, including coronary artery bypass, oral surgery, total hip or knee arthroplasty, and urinary tract surgery [13]. In obstetric and gynecologic practice, tranexamic acid is most commonly used in the management of pregnancy-associated bleeding (threatened abortion and placenta previa), postpartum hemorrhage, and idiopathic menorrhagia [14,15].

When the placenta separates from the uterine wall during delivery, strong myometrial contractions occur along with increased platelet activity and a release of coagulant factors. Fibrinolytic activity also increases during placental delivery and can continue for 6–10 hours after delivery [16]. Thus, antifibrinolytic agents such as tranexamic acid can be used to reduce bleeding. Randomized controlled studies have shown that tranexamic acid reduces blood loss during and after cesarean [9,17,18], indicating that its use effectively prevents and treats bleeding. Nevertheless, these studies are limited and have small sample sizes compared with those assessing efficacy of tranexamic acid in blood loss reduction during other surgical interventions.

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http://dx.doi.org/10.1016/j.ijgo.2015.05.027
0020-7292/© 2015 Published by Elsevier Ireland Ltd. on behalf of International Federation of Gynecology and Obstetrics.

Please cite this article as: Maged AM, et al, A randomized placebo-controlled trial of preoperative tranexamic acid among women undergoing elective cesarean delivery, Int J Gynecol Obstet (2015), http://dx.doi.org/10.1016/j.ijgo.2015.05.027

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The aim of the present study was to evaluate the efficacy and safety of preoperative intravenous tranexamic acid for the reduction of blood loss during and after elective lower-segment cesarean delivery.

2. Materials and methods

A prospective, single-blind, randomized placebo-controlled study was performed at the Obstetrics and Gynecology Department of Kasr El Aini University Hospital, Cairo, Egypt, between November 1, 2013, and November 30, 2014. Women with full-term singleton pregnancies who were scheduled to undergo an elective lower-segment cesarean delivery were eligible for inclusion. Exclusion criteria included anemia (hemoglobin <90 g/L), maternal medical disorders (e.g. cardiac, renal, and hepatic diseases, or coagulopathies), history of thromboembolic events, or known allergy to tranexamic acid. Patients with an increased risk of obstetric hemorrhage (e.g. prepartum hemorrhage, abnormal placentation, previous history of uterine atony or postpartum hemorrhage, polyhydramnios, and uterine fibroids) were also excluded.

The study was approved by the Hospital Ethical Committee. All participants provided informed written consent following a discussion on the nature of the study as well as the expected value, outcome, and possible adverse effects.

On the day of their scheduled surgery, participants were randomly assigned in a 1:1 ratio to receive either intravenous tranexamic acid or intravenous glucose before cesarean delivery. Randomization was performed using computer-generated random numbers. Only the participants were masked to the group allocation.

A full medical history was obtained from all participants. Obstetric ultrasonography and laboratory tests were performed, including prothrombin time, prothrombin concentration, complete blood count, and liver and kidney function tests. Maternal body weight and vital signs (heart rate, blood pressure, and respiratory rate) were checked 30 minutes before surgery. According to group assignment, either 1 g (10 mL) tranexamic acid (Kapron, Amoun, Egypt; stored in a dry container at 15 °C–30 °C) diluted in 20 mL of 5% glucose or 30 mL of 5% glucose was slowly administered intravenously 15 minutes before skin incision over a 5-minute period.

Following delivery, patients in both groups received an intravenous bolus of 5 IU oxytocin (Syntocinon, Novartis, Basel, Switzerland), 1 mL (0.2 mg) intramuscular ergometrine (Methergin, Novartis, Basel, Switzerland), and 20 IU oxytocin in 500 mL lactated Ringer's solution (infused at a rate of 125 mL/h). Fluid monitoring was performed through rate of infusion and urine output. A complete blood count test was performed 24 hours after delivery.

On discharge, patients who received tranexamic acid were given a brief orientation regarding symptoms and signs of a thromboembolic event and were instructed to contact the investigators immediately if any occurred. All patients were examined for thromboembolic events at the 1- and 4-week follow-up visits.

The primary outcome measure was the estimated blood loss (EBL) during cesarean delivery. Secondary outcome measures were excessive blood loss (>1000 mL), use of additional ecbolics denoting uterine atony (e.g. additional 5 IU intravenous bolus oxytocin and 1 mL [0.2 mg] intramuscular ergometrine with or without 600 mg rectal prostaglandin E1), and the occurrence of any maternal thromboembolic event. EBL was calculated according to the formula:

$$\text{EBL} = \text{EBV} \times \frac{\text{Preoperative hematocrit} - \text{Postoperative hematocrit}}{\text{Preoperative hematocrit}}$$

where EBV is estimated blood volume (mL; weight in kg × 85).

For a two-tailed test at an α level of 0.05, the difference between the two groups regarding the primary outcome measure (EBL) had a power of 1.0 (100%) in a post hoc calculation. Data were analyzed using SPSS version 20.0 (IBM, Armonk, NY, USA). Analyses were per protocol: women with a cesarean delivery of more than 90 minutes and those lost to follow-up were excluded from analyses. Numerical data were expressed as mean and standard deviation or median and range, as appropriate. Categorical data were expressed as frequency and percentage. The χ^2 test was used to examine the relation between qualitative variables. For quantitative data, comparison between the two groups was performed using an independent sample t test or the Mann–Whitney test. $P < 0.05$ was considered significant. Power analysis was performed using G-Power package version 3.1.5.

3. Results

Overall, 214 patients underwent randomization (Fig. 1). Analyses included 200 patients (100 in each group). No differences between groups were noted in maternal age, weight, gravidity, parity, number of previous spontaneous abortions, and number of previous cesareans (Table 1).

EBL was significantly higher in the placebo group than in the tranexamic acid group ($P < 0.001$) (Table 2). Only 12% of women in the tranexamic acid group had an EBL of 500–1000 mL compared with

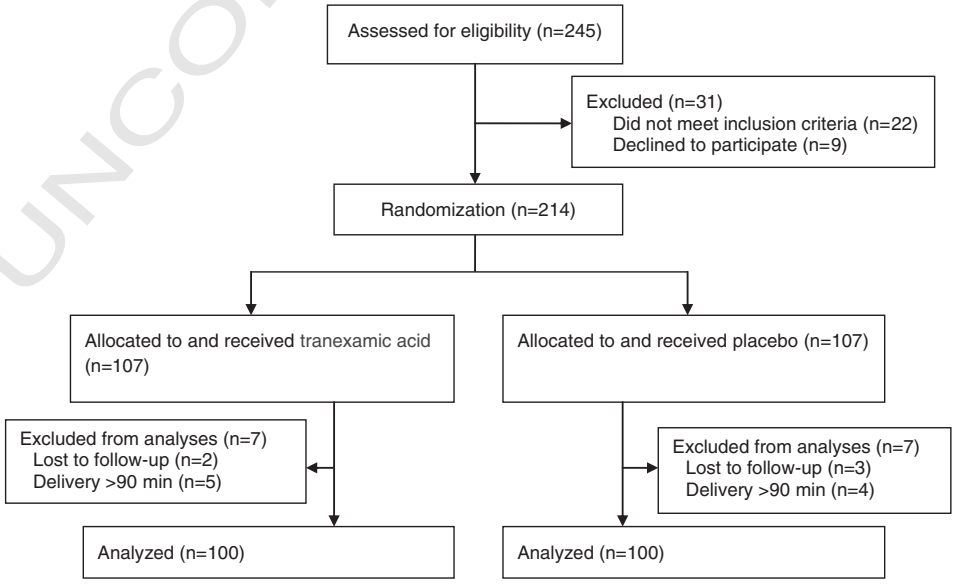

Fig. 1. Flow of patients through the study.

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