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A comparison of two doses of tranexamic acid to reduce blood loss during cesarean delivery

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Abstract

Introduction: Per partum hemorrhage is one of the most common, life-threatening complications during delivery. Recently, many studies have found tranexamic acid to be efficient to prevent severe hemorrhage during cesarean delivery. Up to now, the optimal dose to be given is still unknown.

Objective: The aim of our study is to compare the effect of two doses of intravenous tranexamic acid on blood loss during and after cesarean delivery.

Patients and methods: we led a prospective, randomized, double-blinded, controlled study. Fifty-two informed and consent parturient, scheduled for cesarean section were randomized into two groups to receive either 10 mg/kg or 15 mg/kg of tranexamic acid intravenously. The primary outcome of our study was the amount of blood loss at 6 hours postoperative. This total blood loss volume was estimated according to the Gross's formula. The secondary outcomes were the postoperative hemoglobin levels and the total dose of oxytocin given. Data were recorded, tabulated and analyzed using Statistical package for social sciences (SPSS® version 17). Numerical variables were presented as mean and standard deviation (SD). Student t-test was used for comparison between groups as regard quantitative variables. A difference with a P value <0.05 was considered as statistically significant.

Results: We found no significant difference in both groups regarding mean age, BMI, gravid, parity, mean term of pregnancy, mean preoperative hemoglobin level and hematocrit value, fluid administration and duration of surgery. The mean blood loss was significantly lower, and the mean postoperative hemoglobin level higher, in the group who received 15 mg of Tranexamic acid. In addition, oxytocin consumption tended to be lower in that group.

Conclusion: The 15 mg/kg-dose of Tranexamic acid was found to be more efficient on blood loss during and after cesarean section than the 10 mg/kg-dose, with higher postoperative hemoglobin rates and less recourse to oxytocin.

Introduction

Cesarean section rates are increasing all over the world. Per partum hemorrhage is one of the most common, life-threatening complications of this procedure [1]. Reducing bleeding during and after caesarian directly improve the outcomes of cesarean delivery, especially maternal mortality and morbidity. Tranexamic acid is a fibrinolysis inhibitor that has been used for many years to reduce bleeding in various surgical procedures [2,3]. Recently, many studies have found tranexamic acid to be efficient to prevent severe hemorrhage during cesarean delivery. Up to now, the optimal dose to be given is still unknown [4]. The aim of our study is to compare the effect of two doses of intravenous tranexamic acid on blood loss during and after cesarean delivery.

Methods

We led a prospective, randomized, double-blinded, controlled study at the Tunis maternity and neonatology center from June to December 2013. After approval of institute ethics committee, 52 informed and consent parturient, scheduled for cesarean section (CS) were randomized into two groups to receive either 10 mg/kg (TXA 1 group) or 15 mg/kg (TXA 2 group) of tranexamic acid (Exacyl®, SANOFI-AVENTIS, France) intravenously. We only included women who were categorized as class 1 according the American Society of Anesthesiologists (ASA 1), with regular perinatal care and scheduled for elective CS via Pfannenstiel incision under spinal anesthesia. We did not include parturient with known allergy to TAX, parturient with any medical history involving heart, liver, kidneys, or brain disease, clotting disorders such as thrombophilia. Women with anemia, abnormal site of the placenta (ultrasound detected), preeclampsia, macrosomia, polyhydramnios or twin pregnancy were not included. Randomization was performed immediately before CS, according to a random table, to have two groups of 26 parturient. All solutions were prepared and given by an anesthetist who was not involved in patient management or assessment. TXA was given five minutes before CS. Anesthetic protocol was the same in all patients and consisted of spinal anesthesia with 10 mg of hyperbaric Bupivacaine 0.5% (Bupicaine 0.5%®, UNIMED, TUNISIA) and 5 Ug of Sufentanil (Sufentanil®, MEDIS, TUNISIA). All patients received a co-loading with 20 ml/kg of 0.9% saline solution. 10 UI of Oxytocin (Syntocinon®, ROTEXMEDICA, Germany) were given intravenously immediately after delivery then 15 UI were infused during 6 hours postoperatively. A complementary dose of oxytocin was given preoperatively upon request of the surgeon who was not aware of the study. Recorded data were age, body mass index (BMI), gravid, parity, term of pregnancy, preoperative hemoglobin rate and hematocrit value, fluid administration, total dose of oxytocin and duration of surgery. We performed a second complete blood

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cells count (CBC) at 6 hours postoperative so that we could calculate the difference of hemoglobin rate in each parturient and the blood volume lost during and up to 6 hours after the CS. This total blood loss volume was estimated according to the "Gross's formula" [5]:

Total blood loss=(Estimated blood volume)/[(Hct start - Hct final)/ Hct average](Hctstart: peroprative hematocrit; Hctfinal: postoperative hematocrit).

Primary outcome: the primary outcome of our study was the amount of total blood loss at 6 hours postoperative

Secondary outcomes: the secondary outcomes were the postoperative hemoglobin levels and the total dose of oxytocin given.

Statistical analysis: sample size was computed using a power at 90% and an α value at 0.05 to allow detect a minimal blood loss difference of 100 ml. We found that we need 22 patients at least in each group but we included all the randomized patients (26 in each group). Data were recorded, tabulated and analyzed using Statistical package for social sciences (SPSS® version 17). Normal distribution was checked before analysis. Numerical variables were presented as mean and standard deviation (SD). Student t-test was used for comparison between groups as regard quantitative variables. A difference with a P value <0.05 was considered as statistically significant.

Results

The main indication for cesarean section was uterine scar in both groups with 52% in TXA1 group versus 48% in TXA2 group (p=0.36). The mean total given doses of TXA were of 702 ± 164 mg in TXA1 group versus 977 ± 161 mg in TXA2 group ($p<<10^{-3}$). We found no significant difference in both groups regarding mean age, BMI, gravid, parity, mean term of pregnancy, mean preoperative hemoglobin level and hematocrit value, fluid administration and duration of surgery (Table 1). The mean blood loss was significantly lower in the TXA2 group (p=0.017). The mean postoperative hemoglobin level was higher in the TXA2 group (p=0.022). The mean hematocrit value were similar in both groups (p=0.081). The mean total dose of oxytocin given tended to be lower in the TXA2 group (p=0.05) (Table 2). No perioperative complications were noted in both groups, especially no allergic reactions, no early postoperative thromboembolism.

Table 1. Preoperative characteristics.

	TAX1 (n=30)	TAX2 (n=30)	P
Age (year)	32.2 ± 4	32 ± 5	0.97
Term of pregnancy (week)	37.8 ± 1.4	38.1 ± 1.6	0.53
BMI (Kg/m²)	26.7 ± 4	25.8 ± 3	0.34
Gravid (mean)	2.3 ± 1	1.8 ± 1	0.14
Parity (mean)	1.9 ± 0.9	1.6 ± 0.7	0.25
Intraoperative fluid (ml)	1347 ± 201	1271 ± 207	0.18
Duration of surgery (mn)	40 ± 5	37 ± 9	0.21
Preoperative hemoglobin (g/dL)	11.5 ± 0.9	11.7 ± 1	0.31
Preoperative hematocrit (%)	34.6 ± 2.5	35.2 ± 2.6	0.37

Table 2. Postoperative outcomes.

	TXA1	TXA2	P
Mean blood loss (ml)	375.5 ± 202	253.3 ± 150	0.017
Postoperative hemoglobin (g/dl)	10.5 ± 0.9	11.1 ± 0.9	0.022
Postoperative hematocrit (%)	31.2 ± 6	33.6 ± 2	0.081
Total dose of oxytocin (IU)	30.7 ± 9	25.3 ± 1	0.05

Discussion

We found that giving 15 mg/kg of tranexamic acid intravenously, 5 minutes before CS is more effective than giving 10 mg/kg to reduce blood loss due to CS as well as the oxytocin consumption.

Tranexamic acid is known to reduce bleeding in many procedures [4]. Its anti-fibrinolytic effect is due to inhibiting the activation of plasminogen by plasminogen activator and blocking the lysine-binding sites of plasminogen to fibrin [6-10]. This results clinically in lower blood loss. However, the effect of TXA on blood loss in obstetric procedures is still not enough studied [4,11-13].

Sekhavat, *et al.* [12] assessed only postoperative bleeding 2 hours after surgery; they found TXA to reduce 24% of postoperative blood loss in the active group. In our study, blood loss reduction was of about 33% in the 15 mg/kg-group.

A standard dose of 1 gr of TXA was tested in a placebo-controlled study [13], a reduction of 37% in postoperative bleeding was found in the intervention group. In fact most of the studies used a standard dose of TXA regardless to the patient's weight. The exact efficient dose of TXA is still controversial which the reason for our study is. In addition we're still not able to know whether side-effects related to the use of TXA, such as acute renal failure, are dose-related.

Weighted doses of TXA were used by Movafegh, *et al.* [14], they found that intravenous administration of 10 mg/kg of TXA 20 minutes before CS reduces intra and postoperative blood loss, as well as intraoperative oxytocin use compared to placebo.

Assessing blood loss during and after CS or vaginal delivery has for long been a matter of controversy. Accurate collection is actually not easy because blood is mixed with amniotic fluid during CS. After CS, blood loss is estimated by inspecting vaginal towels and sheets. Actually, visual estimation of bleeding during and after CS or vaginal delivery is not accurate; it tends to overestimate at lower blood loss or underestimate at higher blood loss. Calibrated blood collection drapes are a simple and accurate means to measure blood loss when available.

Pritchard, *et al.* [15] used a technique involving chromium labeled red blood cells in order to measure blood loss during CS; they found it to be about 930 ml. Such techniques may be too complex to use in current clinical practice.

Stafford *et al.* [16] calculated blood loss using a formula which involved hematocrit changes before and after caesarean section, maternal weight and height. They compared calculated blood loss to that estimated visually. They found visual estimation to significantly underestimate blood loss, especially when it exceeds 1000 ml and 1500 ml.

In our study, the total blood loss volume during and after CS was estimated using the Gross's *formula* [5] for estimation of blood loss: "*Total blood loss=(Estimated blood volume)/ [(Hct start - Hct final)/Hct average]".*

This formula is an approximation to the original formula described in 1974 [17]. The original theoretical equation, which has been verified in several clinical studies [5,17,18] involved the solution of a differential equation that resulted in a formula requiring the computation of natural logarithms: "***Blood loss=(Estimated blood volume) × [ln(Hctstart/ Hctfinal)]".***

Administration of TXA in pregnant women may raise concerns about thromboembolism. Previous studies have shown the safety of

this drug for use in both pregnant and non-pregnant patients [7,18-20]. Acute renal failure is a life-threatening complication that may be related to the use of TXA. We did not test renal function after surgery. In fact, cases of acute renal failure associated with the use of TXA in postpartum hemorrhage may raise concerns about the possible side-effects of this drug, knowing that optimal doses are still not determined. Further studies are needed to assess safeness of Tranexamic acid on parturients' renal function in both curative and preventive indications.

Conclusion

The 15 mg/kg-dose of Tranexamic acid was found to be more efficient on blood loss during and after cesarean section than the 10 mg/kg-dose, with higher postoperative hemoglobin rates and less recourse to oxytocin.

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