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The effect of routine intraoperative tranexamic acid in elective cesarean section

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Abstract
Objective: To find the role of routine intraoperative tranexamic acid infusion at elective cesarean section.
Study Design: Randomized case control study
Study Setting: AlKarkh Maternity Hospital, Baghdad Iraq.
Methodology: A total of 110 term pregnant women presenting in to our obstetric unit during the period between May, 2019 and January, 2020 and who were offered elective cesarean section, were randomly assigned to either receiving intraoperative tranexamic acid 1 gram in 100 milliliter saline infusion or saline infusion. Demographic characteristics were collected for all participants. Ten cases (1 in the tranexamic and 9 in the control group) were excluded as there were associated extensions of uterine incision in order to reduce confounders. A comparison of the outcomes of the two groups was done, it included an intraoperative blood loss determinator, a postoperative blood loss determinator, and an overall loss risk assessment. The corresponding parameters were the intraoperative surgical soaked packs count, average reduction in packed red blood cell volume 24 hour postoperatively, occurrance of postpartum hemorrhage and the overall need to receive blood transfusion. In term of associated side effects of receiving tranexamic acid, we sought whether there was any significant change in the blood pressure as well as the incidence of developing fever. Exclusion criterias were the contraindication to receive tranexamic acid assessed by referral to internist physician specialist review.
Results: Confounding factors including patient's age, parity and gestation length were taken into consideration and found to be similar between the two groups studied.
There was a significant difference between the postpartum decline of packed red blood cell volume (PCV) (pvalue 0.001), with mean postpartum PCV in tranexamic group 35.2% versus 33.3% in the saline infusion group. 21.9% of women in the control group had decline of PCV exceeding 10% of preoperative value, versus only 3.3% in studied group. We found that the number of cesareans where additional packs got required was significantly less in tranexamic group (15.3% vs.22%, p=0.001), no cases in the tranexamic group did receive a blood transfusion vs. 7.3% in the saline group (pvalue 0.03).Slightly higher incidence of hypotensive episodes in the tranexamic group (27.1% vs. 12.2%, pvalue 0.07).Fever was found to be more likely following cesarean in the control group (34.1% vs. 18.6%, pvalue 0.06).
Conclusion: The use of tranexamic infusion with inducton of anaesthesia at time of elective cesarean section is associated with less risk of intraoperative blood loss improving postoperative packed red blood cell volume decline significantly.

Keywords: Routine intraoperative tranexamic cesarean section Randomized case control study

Introduction

About one quarter of women in the UK have cesarean sections, increasing from 19.7% of births in 2000 to 26.2% in 2015. In at least 15 other countries, cesarean rates exceed 40% (Turkey, Egypt and Brazil) [1].

With the lack of accurate data from Iraq about cesarean section rates, one can only compare with its neighboring countries, as well as observe day to day hospital operative list and maternity dashboards to draw a similar conclusion.

That being said, it would be such an imperative thing to make this very commonly performed major operation a safe one.

Although a planned elective cesarean can be the safest option, especially to women who have had cesarean section in the past, yet excessive bleeding is a leading cause of maternal morbidity and mortality worldwide, with elective cesarean being associated with blood loss exceeding 500ml and 1000ml in 14.9% and 2.1% of cases respectively in one study [2].

Many had been recommending a careful risk assessment prior surgery, with the most skilled obstetric staff to carry on the surgery where there are known risk factors.
The challenge is rising when no risk factors are found, which would necessitate some regular prophylactic measures.
It has been recommended by NICE guidance to consider the addition of intravenous tranexamic acid at cesarean section when there was an increased risk of postpartum hemorrhage, but recommended further studies [3].
Our main concern is about making elective cesarean section a very safe option for women, reducing the risk of blood loss when it the risk factors for a major PPH are absent.
Tranexamic acid stabilizes the clots preventing them from breaking down. It is a well-known drug used in the treatment of PPH provided it is given within 2 to 3 hours after birth. The drug is a competitive inhibitor of plasminogen activation and can reduce blood loss by inhibiting the enzymatic breakdown of fibrinogen and fibrin clots [4].

Method
This study is a randomized case control study, carried at AlKarkh Maternity Hospital, a hospital situated at the west bank of the Tigris river, that offers wide range of services to resident of the Iraqi capital, Baghdad. Our studied sample consisted of 100 pregnant women carrying a term pregnancy and who underwent an elective cesarean section during the period between August, the first 2019 and April, the first 2020.
The inclusion criterias were as following:
- Age 18-35-year-old
- Term gestation
- Singleton pregnancy due for elective cesarean for obstetric reasons

The exclusion criteria were
- Any risk for developing PPH (grand multipara, multiple pregnancy, high blood pressure, diabetes, placenta previa and known anemia, obesity with bmi over 29).
- Contraindications to the use of tranexamic acid (like past deep vein thrombosis and bleeding disorders, based on a careful medical assessment and with collaboration of internist physician specialist).

The decision for cesarean was made by the specialist obstetrician on call that day.
Patients were informed about the drug and their consent was documented in patient's note and operative notes. Randomization was secured and patients were either being part of the tested group receiving a tranexamic infusion of 1gram in 100ml saline right after general anesthesia induction, or assigned to join control group and were given a saline infusion.

Data collection
Data collection involved completion of paper forms by a competent resident attending the operative ward directly through specialist obstetrician observation and maternal medical examination as well as to follow postoperative charts and blood tests.
Ten cases were excluded, one case in the tranexamic and nine cases in the control group, due to extensions in the uterine incision which would increase blood loss and affects comparison.

Items collected
- Woman's age
- Woman's parity
- Mode of last delivery
- Gestational age
- Additional Oxytocin use
- Operative time was the time from skin incision to skin closure.
- Use of additional surgical packs
- PCV before and 24 hours after surgery
- Transfusion of blood
- Hypotensive episodes intraoperatively
- Fever

A regular oxytocin infusion of 10 units was given to all women after the baby delivery, any additional requirement for uterotonic was taken into consideration and noted as an element of excessive blood loss. The surgical tray was supplied with a set of five equally sized surgical gauze pack, and when operating specialist suggest them all soaked, additional sets required were provided and recorded as an element of excessive blood loss as well. No suction machines were allowed to maintain integrity.

Statistical analysis
Analysis of data was carried out using the available statistical package of SPSS-17 (Statistical Packages for Social Sciences- version 17).
Statistical analysis involved descriptive statistics such as frequency, percentages, averages, ranges (minimum-maximum values), and standard deviation for both groups.
The significance of difference between the variables was estimated by using independent student-t-test for difference between two means or averages, while different percentages were tested using chi-square test (χ^2-test).
Analysis of variance (1way ANOVA) were performed with $p < 0.001$.
Statistical significance was considered whenever the P value was less than 0.05.

Results
Comparing the two groups, avariables including the patient's age, parity and gestational age were not statistically different.
We found that the tranexamic acid did not affect the duration of cesarean section (mean duration in minutes 26.6± 3.6 vs.25.9± 2.4 for control). (Table 1)

Table 1: confounders including age, parity and GA with cesarean section mean duration in minutes

	Controls group (n=41)	Tranexamic group (n=59)	P value
Age	24± 4	26.6± 4.3	0.08
Parity	0.98±0.7	1.1±0.7	0.3
Gestational age	38.4±1.3	37.9±1.02	0.06
C/S duration	25.9± 2.4	26.6± 3.6	0.27

Results are expressed as mean± SD

Statistically significant difference in reduction of PCV postoperatively compared to preoperatively in favor of the Tranexamic group with mean PCV postoperative of 35.2± 3.3 versus 33.3± 3.1 in the control group. (table 2) (figure 1), additionally, 21.9% of women in the saline only group had a decline of 10% and more in PCV versus only 3.3% in the tranexamic group.

Table 2: Comparing reduction in PCV postoperatively

Controls group (n=41)		Tranexamic group (n=59)	
PCV before	PCV after	PCV before	PCV after
36.01± 2.9	33.3± 3.1*	36.7± 3.2**	35.2± 3.3**†

Results are expressed as mean± SD
Statistical test: ANOVA
*. Statistically significant from Control PCV before, *P*<0.001
** Statistically significant from Control PCV after, *P*<0.001
† Statistically significant from Tranexamic group PCV before, *P*<0.05

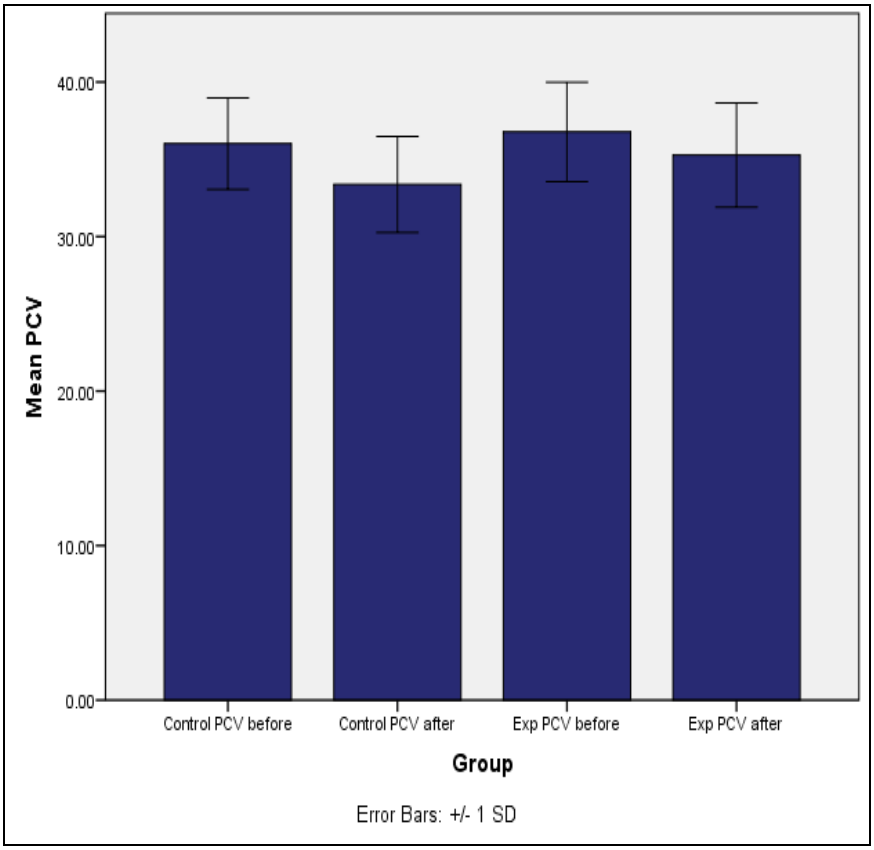

Fig 1: Comparing reduction in PCV postoperatively

Additional surgical gauze pack use, a measure of intraoperative blood loss was significantly less required in tranexamic group with 15.3% vs.53.7%, pvalue 0.001. (Table 3)

Table 3: RR calculated according to Altman, 1991

Additional Packs	Controls group		Tranexamic group		
	No.	%	No.	%	
Yes	22	53.7	9	15.3	X^2=16.6, P=0.001 RR= 0.28
No	19	46.3	50	84.7	

Statistical test: Chi-square

Similarly, statistically significant difference shown through table 4, regarding the use of additional uterotonics in 92.7% of cases in control group compared to 78% in the tranexamic acid group. (*p* value 0.001)

Table 4: Comparing additional intraoperative uterotonic use.

Utertonic	Controls group		Tranexamic group		
	No.	%	No.	%	
Yes	38	92.7	46	78	X^2=48.3, P=0.001 RR=0.84
No	3	7.3	13	22	

Statistical test: Chi-square
RR calculated according to Altman, 1991

Blood transfusion was not required during and after cesarean section in the tranexamic acid group, whereas in the control group 3 cases did receive a blood transfusion within 2 hours of the cesarean section (7.3%, pvalue 0.03), implying a difference of statistic relevance. (Table 5)

Table 5: Blood transfusion need comparison

Transfusion	Controls group		Tranexamic group		
	No.	%	No.	%	
Yes	3	7.3	0	0	X^2=4.4, P=0.03 RR=0.1
No	38	92.7	59	100	

Statistical test: Chi-square
RR calculated according to Altman, 1991

None of the cases that received tranexamic acid had developed PPH in the first 24 hours after operation, while only 2 cases in the control group did developped PPH, the difference between the two groups found to be of no statistic significance (table 6).

Table 6: Comparing postpartum hemorrhage PPH between groups

PPH	Controls group		Tranexamic group		
	No.	%	No.	%	
Yes	2	4.9	0	0	X^2=2.9, P=0.08
No	39	95.1	59	100	

Statistical test: Chi-square

In term of tranexamic acid side effects encountered intraoperatively, there was a small association with hypotension, yet of no statistic significance, as 27% of patients in the tranexamic group developing hypotensive episode versus 12.2% in the control group, pvalue 0.07. (table 7)

Table 7: Hypotensive episodes comparison

Hypotension	Controls group		Tranexamic group		
	No.	%	No.	%	
Yes	5	12.2	16	27.1	X^2=3.2, P=0.07
No	36	87.8	43	72.9	

Statistical test: Chi-square

We noticed that 34.1% of women in the control group had developed fever in the first 24 hours after surgery, versus only 18.6% in the group that received tranexamic acid, and although this was an important observation, it was of no statistic relevance. (Table 8)

Table 8: Fever comaparison between the two groups

Fever	Controls group		Tranexamic group		
	No.	%	No.	%	
Yes	14	34.1	11	18.6	X^2=3.1, P=0.06
No	27	65.9	48	81.4	

Statistical test: Chi-square

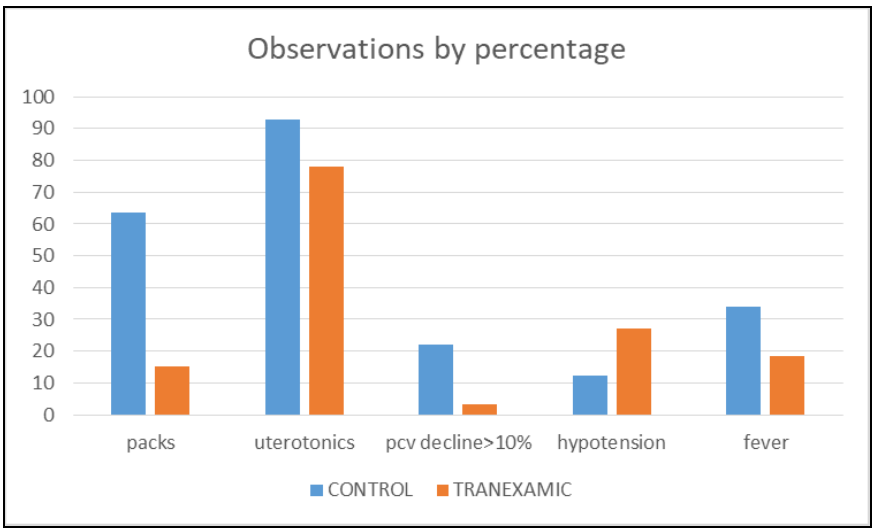

Fig 2: Significant observations as percentages

Figure is a graph description of all significant observations this study found.

Discussion

Tranexamic acid is a competitive inhibitor of plasminogen activation and thus prevents enzymes from breaking down the thrombus impairing fibrinolysis and one of the drugs on the WHO list of essential medicines [5].

It is a cheap and widely available drug that is distributed as oral 500 mg tablets (commonly used to reduce heavy menstrual blood loss), topical for epistaxis or intravenous solution (500mg in 5ml and 1000mg in 10 ml) injection to reduce hemorrhage associated with surgical procedures in hemophiliac patients. It is commonly described as a safe drug, including in pregnancy and lactation, with only very few contraindications; in patients with subarachnoid hemorrhage, defective color vision, active intravascular clotting and hypersensitivity to tranexamic acid or any of its ingredients [6].

Common side effects reported are nausea, vomiting, diarrhea, and to a lesser extent abdominal pain, headache, lightheadedness and fever.

According to B.J. Hunt, it has been shown to reduce mortality due to traumatic bleeding by a third, with no adverse effects affecting patient's safety, and that using a dose of 1gram intravenously would ensure efficacy [7].

This study was conducted to reveal in simple steps whether routine intraoperative dose of tranexamic acid equivalent to 1000mg in 100ml normal saline can be recommended in low risk patients undergoing elective cesarean section to make the procedure safer.

It involved randomization to either receiving tranexamic acid or a normal saline infusion, comparing blood loss in the two groups assessed through various parameters.

The most important finding in this study was the packed cell volume (PCV) fall reduction in the tranexamic acid group, with the mean postoperative PCV of 35.2± 3.3 versus 33.3± 3.1 in the control group, and fewer cases with PCV decline >10% of their preoperative value in the tranexamic arm (3.3% vs.21.9%), a result correlating to a study by Dr. S. Sampathkumari involving 100 patients randomized to either 1gm infusion of tranexamic or saline infusion, showing a significant reduction in blood loss, and better 24hour postoperative hemoglobins (11.83 ± 1.1) vs.(10.34 ± 1.03) with p value 0.0001.

Similarly, less uterotonic drugs were required in the tranexamic acid arm (8), a result that matched our findings, as we noticed a reduction in the additional use of uterotonic drugs of 0.84 with 95% CI (0.7-0.98).

In addition, this study found a reduction in additional gauze packs used in the tranexamic acid group, shown by risk reduction of 0.28 with 95% CI (0.14-0.5), comparable to a study of tranexamic versus sublingual misoprostol by Pakniat et.al finding lesser amount of gauze used with tranexamic compared to sublingual misoprostol [9].

Furthermore, this study has shown a significant reduction in blood transfusion requirement, as none of the patient received a blood transfusion in tranexamic arm versus 3 patients in the control group, with a relative risk of 0.1, 95%CI (0.005-1.8). This finding is comparable to a systematic review done by Franchini M. *et al*., who searched the effect of tranexamic acid on postpartum blood loss, finding a relative risk of 0.3, 95% CI (0.18-0.49) [10]

No effect on the duration of sugery was found of significance, unlike the study of Dr. S. Sampathkumari, who stated lesser duration in the tranexamic arm (33minutes vs.42minutes, pvalue0.0001) [8]. This might be explained by the tendancy of having a specialist obstetrician conducting most cesarean section complying with the shortage of residents in our hospital at the time this study was conducted.

In term of adverse events related to the tranexamic acid arm, although hypotensive episodes occured more frequently 27.1% vs. 12.2 this was of no statistical significance (p value-=0.7). These episodes were managed promptly.

Postpartum hemorrhage was reduced in most studies [8], but we did not find that tranexamic acid to reduce PPH to a significant level, this could be explained by the fact that only 2 patients overall suffered PPH in the first 24 hours postpartum and both were in the control group, and it is likely to be better investigated by increasing the sample size.

Fever is reported as a side effect of tranexamic [11] by manufacturer, but this study found higher occurence of fever (but not statistically significant) in the control group (34.1% vs. 18.6%, pvalue 0.06).

This could possibly be explained by a masking effect of general aneasthetics related vasodilation and resultant relative hypothermia during the intraoperative period, as well as the higher blood loss in the control group contributing to fever postoperatively.

Additionaly, no patient had any hypersensitivity reaction to the drug during surgery and when followed up to 2 hours after including: (itching, oedema, urticaria, rash or breathing difficulty) although it was found to be associated with macular rash and hypersensitivity reaction in a case series described by Calpai G. *et al.* [12]

None of the patients developed thromboembolic event as they were followed up by the internal medicine specialist for the next 6 weeks after surgery similar to a study by Sentilhes L. *et al.* [13]

Conclusion

The routine uses of tranexamic acid intraoperatively in low risk women undergoing elective cesarean section has a beneficial effect on the associated blood loss improving postoperative packed cell volume without significant adverse effects.

Conflict of Interest: The authors declare no conflict of interest

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