International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Bhavana G et al. Int J Reprod Contracept Obstet Gynecol. 2016 Jun;5(6):2011-2016
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20161708

Research Article

Efficacy of prophylactic tranexamic acid in reducing blood loss during and after caesarean section

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Received: 22 April 2016
Accepted: 16 May 2016

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ABSTRACT

Background: In India, caesarean section rate is rising, so the impact of prophylactic injection of tranexamic acid in decreasing blood loss during caesarean section would be more beneficial in terms of having minimal blood loss intra operatively and post operatively and thereby decreasing maternal morbidity. The objective of the study was to evaluate the efficacy of prophylactic tranexamic acid in reducing blood loss during and after caesarean section.
Methods: A randomized controlled trial among 200 term women with singleton pregnancy for a period of 2 years was carried out. They were randomized by computer generated numbers into two groups: study group-100 women receiving prophylactic tranexamic acid women and control group-100 women receiving placebo.
Results: The blood loss during caesarean section was less in the tranexamic acid group compared to the placebo group. Similarly blood loss measured 6hrs after caesarean section was less in the tranexamic acid group compared to placebo group. 20-40min before the time of incision was the ideal time gap for administering the injection tranexamic acid for its optimum efficacy. Tranexamic acid group had lesser requirement of uterotonic when compared to placebo, but need for blood transfusion was similar in both the groups. Greater fall in the hemoglobin and haematocrit occurred in placebo group compared to tranexamic acid group. No changes in the post-operative vitals or side effects were seen in the tranexamic acid group. Even no change in birth weight and Apgar scores was seen in neonates of tranexamic acid group.
Conclusions: Injection tranexamic acid is the, antifibrinolytic agent that can be used for prophylactic administration before caesarean section for decreasing blood loss during surgery.

Keywords: Tranexamic acid, Blood loss, Caesarean section

INTRODUCTION

Each year, worldwide, about 530,000 women die from causes related to pregnancy and childbirth. Nearly all (99%) of these deaths are in low and middle income countries.[1] Post-partum hemorrhage (PPH) remains a leading cause of early maternal death, accounting for about 300,000 deaths worldwide every year and of morbidity related to anemia, blood transfusion and hemorrhage-related ischemic complications.[2] Detailed guidelines have been issued for optimal use of obstetric interventions and uterotonic drugs.[3] In contrast, haemostatic abnormalities in this setting have long been considered a consequence of uncontrolled bleeding, not deserving of early specific treatment. Thus haemostatic drugs are not routinely used as the first-line intervention in Post-partum hemorrhage.[3,4] This concept was recently challenged by the demonstration of a relationship between decrease in fibrinogen levels and blood loss.[4] At the same time, it was recognized that extensive tissue injury can shift the haemostatic equilibrium toward increased fibrinolysis, contributing to coagulopathy and bleeding.[5] Antifibrinolytic agents, mainly tranexamic acid and aprotinin, have been demonstrated to reduce blood

loss and transfusion requirements in various elective surgeries.[6]

Tranexamic Acid is a synthetic derivative of the amino acid lysine that exerts its anti-fibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules.[7] Tranexamic acids also inhibit conversion of plasminogen to plasmin by plasminogen activators.[8] It has been routinely used for many years to reduce hemorrhage during and after surgical procedures, such as coronary artery bypass, scoliosis surgery and knee arthroplasty, dentistry etc. It has been shown to be very useful for reducing blood loss and the need for blood transfusion.[9]

In India, caesarean section rate is rising, so the impact of prophylactic injection of tranexamic acid in decreasing blood loss during caesarean section would be more beneficial in terms of having minimal blood loss intra operatively and post operatively and thereby decreasing maternal morbidity. Hence present study is an attempt to study the efficacy of prophylactic injection tranexamic acid in decreasing blood loss during and 6hrs after caesarean section.

METHODS

A randomized controlled trial among 200 term women with singleton pregnancy for a period of 2 years was carried out at Department of Obstetrics and Gynecology, AIIMS, New Delhi, India.

They were randomized by computer generated numbers into two groups: study group-100 women receiving prophylactic tranexamic acid women and control group-100 women receiving placebo.

The following criteria were fulfilled before being selected in the present study:

Selection criteria

- Term singleton pregnancy delivered by CS.

Exclusion criteria

- Severe medical and surgical complications.
- History of allergy to tranexamic acid.
- History of thrombi-embolic disorders.
- Antenatal complications like, abnormal placenta (placenta-previa, placenta abruption, adherent placenta) severe preeclampsia.
- Multiple pregnancies, macrosomia, polyhydramnios, Fibroid uterus, previous caesarean section.

The protocol was submitted and approved in the Department of Obstetrics and Gynecology, AIIMS and by the hospital ethics committee and permission was obtained from DCGI, FDA Bhawan, Kotla, and New Delhi.

As soon as the decision for the caesarean section was taken, patient was assessed for the selection criteria. Informed consent was taken. Patient clinical history and investigations was noted and women were allocated to study group or control group according to randomized computer numbers.

- Drapes (4), sponges (20), pads (three pads, were used post operatively for six hours) were weighed beforehand.
- Hemogram, Prothrombin time, Kidney function tests were sent from labour room.
- Just before the induction of anesthesia 1gm of tranexamic acid in 20 ml of 5% glucose was given over 10 minutes in study group and 20ml of NS was infused in control group.
- Time from administration of injection tranexamic acid to the time of skin incision was noted.
- Two suction containers were used, one for the amniotic fluid and one for the blood.
- 10 units oxytocin was given after the delivery of anterior shoulder in all the patients.
- At the end of the surgery the drapes, sponges, gauze were weighed. Patient was provided with the sterile pads (three) post operatively for 6 hours. Patient was shifted on the bed with the plastic sheet.
- Calculation of the blood loss: Blood loss at caesarean delivery was calculated by measuring the blood collected in the suction apparatus and by weighing lap pads, towels, and drapes.
- Total blood loss=weight of all the drapes, sponges, {gauzes, pads} after the surgery -weight of drapes, gauzes, sponges ,pads before surgery plus volume of blood collected in the suction container
- Post operatively pulse rate, blood pressure, urine output, uterine contractility; side effects were charted hourly for six hours.
- Hemogram, prothrombin time, Kidney function tests were repeated48 hours after the surgery.
- If excessive bleeding was assessed by the operating surgeon, additional uterotonics were given.

Outcome

Primary outcome measures

1. Difference in blood loss between the two groups
- In women receiving tranexamic acid
- In women receiving placebo

Post operatively up to 6 hours in the same two groups

2. Side effects related to drug used.

Secondary outcome measures

The difference in following parameters in the two groups

1. Hemoglobin/haematocrit
2. Need for additional uterotonics
3. Need for blood transfusion

Statistical analysis

Data from all patients were used in the analysis using SPSS 15.0 software.

The data was expressed as mean or median (range) as applicable. Qualitative or quantitative data was compared by Chi Square (t test) for qualitative data and or ANOVA for comparing continuous data as appropriate. Post hoc (multiple) comparison was done in order to identify the contributory factors for the test of significance. P-value <0.05 was considered significant statistically.

RESULTS

Table 1: Blood loss during caesarean section.

	Study (n=100) Mean ±SD (ml)	Control (n=100) Mean ±SD (ml)	Difference between two groups (95% CI)	p value
Blood loss during caesarean	511.3±164.45	637.9 ±429.77	-126.6 {-217.34 ,35.85}	0.0065

There was mean blood loss of 511.3±164.456 ml in study group vs. 637.9±429.77ml in control group. There was a decrease in blood loss of 126.6ml with use of injection tranexamic acid 1 g in study group. This difference was statistically significant 95%CI (Table 1).

Table 2: Blood loss after caesarean section (first 6hrs).

	Study (n=100) Mean±sd (ml)	Control (n=100) Mean ±sd (ml)	Difference between two groups (95%CI)	p value
Blood loss 6hrs after caesarean section	45.9 ±12.316	51.6 ±12.690	-5.7 (-9.18 - 2.212)	0.0015

The mean blood loss measured for 6 hrs after caesarean section in study group was 45.9±12.316ml compared to 51.6 ±12.690ml in control group with p value was 0.0015. This difference was statistically significant 95%CI (Table 2).

The need for additional uterotonics in the form of Syntocin, carboprost and methergin was statistically very less in study group compared to control group (p = 0.0001) (Table 3).

Table 3: Use of additional uterotonic during caesarean section.

Additional uterotonics {Syntocin (IU)}	Study (n=100)	Control (n=100)	p-value
<20	84%	33%	0.0001
21-40	16%	54%	
>40	0	13%	

Table 4: Difference in preoperative and post-operative hemoglobin.

	Study group		Control group	
	Pre-operative	Post-operative	Pre-operative	Post-operative
Hemoglobin (g/dl)	11.2± 1.28	10.5± 1.25	11.1± 1.24	9.9± 1.14
P value	0.66		0.0023	

The drop in hemoglobin after caesarean section in study group was not significant where as in control group was significant (Table 4).

Table 5: Post-operative vital monitoring.

	Study (n=100) Mean±sd	Control (n=100) Mean±sd	p-value
Heart rate (per min)	88.51±7.387	88.78±8.175	0.80
B.P (mm of HG) Systolic	123.26±12.95	123.07±12.25	0.91
Diastolic	68.2 ±7.32	71.1±7.62	0.98
Urine output(ml/hr)	78.9±26.39	74.3±+23.98	0.196

The patients were monitored for changes in heart rate, blood pressure, urine output during post-operative period for 6hrs. Table 5 showed that there were no statistically significant changes in vitals between the study group and placebo group.

The routine Hemogram and renal parameters were sent immediately when the decision for the caesarean section was taken and 48hrs after surgery. The above table16showed that the administration of tranexamic acid had no effect on altering the blood counts, renal parameters and prothrombin time (Table 6).

This table showed that with the time lag of 20min in administering the injection was observed in 6% among tranexamic acid group and 11% among placebo group. There was no statistical difference in blood loss during caesarean section and after caesarean section between both the groups with such lag in administration (Table 7A).

Table 6: Effect of tranexamic acid on platelet count prothrombin time, kidney function tests.

	Study preoperative	Group post-operative	Control pre-operative	Group post-operative	p-value
PLT* count (/mm3)	200452	176511.6	223753	198214.3	0.237
TLC**(/mm3)	7700	8600	7690	8900	0.478
PT***(sec)	11.7	12.3	11.6	12.2	0.091
UR/ CR****	31.03/0.69	32.6/0.72	31.3/0.7	32.7/0.72	0.5/0.7

*Platelet; **Total leukocyte count, ***Prothrombin time; ****Urea/creatinine.

Table 7A: Relation of time lag of 20min in administration of injection and amount of blood loss.

	Study n=6	Control n=11	p-value
Blood loss during surgery (ml)	500	500	0.06
Min-max(ml)	250-750	100-4500	
Blood loss after surgery(ml)	40	50	0.7
Min-max(ml)	30-50	0-60	

Table 7B: Relation of time lag of 20-40min in administration of injection and amount of blood loss.

	Study(n=91)	Control(n=85)	P value
Blood loss during surgery (ml)	500	600	0.0014
Min-max(ml)	300-1000	300-1100	
Blood loss after surgery (ml)	40	50	0.0001
Min-max(ml)	20-80	40-80	

Table 7B showed that the time lag of 20min-40min in administering the injection was observed in 91% among tranexamic acid group and 85% among placebo group. There was difference in blood loss of 100ml during caesarean section and, 10ml for 6hrs after caesarean section; between both the groups with such lag in administration. The result was statistically significant.

Table 7C: Relation of time lag of >40min in administration of injection and amount of blood loss.

	Study n=3	Control n=4	
Blood loss during surgery(ml)	550	600	0.76
Min-max(ml)	300-600	400-700	
Blood loss after surgery(ml)	50	60	0.68
Min-max(ml)	40-60	30-60	

Table 7C shows that the blood loss during and after caesarean section in the study group was lesser when they received the injection tranexamic acid with the time lag of >40min, but the blood loss measured was not statistically significant.

Effects on neonate

All the neonates of patients who received injection tranexamic acid had similar course as was seen in neonates of patients who received placebo in the form of similar Apgar scores at birth and birth weight and no other side effects. This shows injection tranexamic acid had no side effects on neonates.

DISCUSSION

In the present study caesarean section was performed in 46.7±5.6min both in the tranexamic acid group and the placebo group. In the studies by Gohel et al, Shekavat et al the mean duration of surgery was within the range of 20 min - 40 min which was less than the present study.[10,11]

In the present study the time gap was noted from time of administration of injection tranexamic acid and time of incision. But in study by Gungorduck et al times gap of 10 min was taken for administration of drug, whereas in study by Gohel et al and Movafegh et al the time gap of 20 min was taken for administration of drug.[10,13,14]

The outcome clearly showed that the blood loss was decreased by the usage of prophylactic 1g IV tranexamic acid before caesarean section. The blood loss decreased during postoperative period for 6 hrs with injection tranexamic acid was only 5.7 ml with 95% CI of-9.18ml - 2.212ml. This showed prophylactic administration of injection tranexamic acid 1g IV in 20ml of NS slowly over 5-10 min decreases blood loss during caesarean section and also 6 hrs post-operatively when compared to placebo.

In the study conducted by Gohel et al, a randomized case controlled prospective study, showed that tranexamic acid significantly reduced bleeding from time of placental delivery to 2 hours postpartum in LSCS (P=0.001).[10] In the study conducted by Gungorduck et al a prospective, randomized, double-blind, placebo-controlled study showed the mean estimated blood loss was significantly lower in women treated with TA compared with women in the placebo group.[13]

The mean blood loss in the present study was similar to the study Gungorduck et al but more than the studies Gai

et al, Gohel et al, Shekavat et al.[10,11,13,14] But in all the studies as ours the use of tranexamic acid in the study group statistically decreased the amount of blood loss during caesarean section.

In the present study we found that ideal time lag of administering the tranexamic acid was 20-40 min. In contrast to study conducted by Gai et al, Gohel et al, Shekavat et al the present study determined the role of time lag in administering drug and its significance in decreasing blood loss, which showed statistically significant decrease in blood loss when the injection tranexamic acid was administered with time gap of 20 min-40 min.[10,11,14] But when the drug administered in time gap of <20min the blood loss in tranexamic acid group was similar to placebo group and when the drug administered with the time gap of >40 min the blood loss was less in tranexamic acid group than the placebo group which was not statistically significant.

There were no major side effects in the form of deep venous thrombosis, hypotension etc, in patients who received prophylactic tranexamic acid. Only 3 patients developed minimal side effects in the form of nausea and vomiting which was relieved with antiemetics.

In the study conducted by Gai et al, Gohel et al, Shekavat et al, the adverse effects of injection tranexamic acid were monitored and no side effects of the drug were found.[10,11,14] The result of the present study was in accordance with the above mentioned studies.

In the immediate post-operative period, vitals were monitored and it was found that there was no difference in tranexamic acid group and placebo group. Similarly, post operatively 48hrs later; the renal parameters, liver function parameters, prothrombin time; Hemogram was done to know the effect of the injection tranexamic acid, but there was no demonstrable difference between the tranexamic acid group and placebo group.

In the study conducted by Gai et al, Gohel et al, Shekavat et al, heart rate, blood pressure, urine output were checked and noted before the surgery, immediately after placental delivery and 1 and 2 hours after birth, respectively.[10,11,14] There was no statistically significant difference between two groups. There was also no significant difference in the Hemogram, renal and liver function tests between two groups, there was no episode of thrombosis in the study.

The difference in preoperative hemoglobin between the groups was not statistically significant but the postoperative difference in hemoglobin between the groups was statistically significant. So, by administration of injection tranexamic acid preoperatively in the patients might decrease drop in hemoglobin level by 0.526 g/dl and haematocrit 1.2%. The above mentioned difference in fall between two groups might have greater importance in developing countries like India where anemia constitute about 57.9% of prevalence in the pregnant population.[15]

In the study conducted by Gohel et al showed hemoglobin decreased slightly after birth in both the groups, but there was no statistical difference between the two groups.[10]

In the studies conducted by Shekavat et al, Gungorduck et al the result was similar to the present study where tranexamic acid group had greater mean hemoglobin and haematocrit 24 hrs after surgery.[11,13]

In the present study need for additional uterotonic requirement of 21-40 U and >40 U Syntocin was seen in placebo group compared to tranexamic acid group. The result showed that the usage of injection tranexamic acid among study group had significantly decreased need for additional uterotonics.

In the study conducted by Gungorduck et al showed significantly more women in the placebo group 48 (14.5%) needed additional uterotonic agents than those in the Tranexamic acid group 28 (8.5%); RR 1.7; 95% CI 1.1 to 2.6; p¼0.02).[13] No patient needed surgical procedure, such as a B-lynch suture, uterine artery ligation, or caesarean hysterectomy. The result thus obtained was similar to the present study but we obtained exactly the amount of the Syntocin required in addition to tranexamic acid (1g).

Present study showed the need for transfusion was not affected by tranexamic acid. Among the patients who received prophylactic injection Tranexamic acid before caesarean section 2 patients received blood transfusion but among patients who received placebo before caesarean section one patient received 5 whole red blood cell transfusion and underwent per partum hysterectomy for uncontrolled blood loss and other two received 2 whole RBC.

In the study conducted by Gungorduck et al seven (2.1%) patients in the placebo group received a packed red blood cell transfusion (four patients received 1 U, two patients received 2 U, and one patient received 3 U), whereas two (0.6%) patients in the Tranexamic acid group did so (one patient received 1 U and one patient received2 U).[13] No significant between-group difference was found in the requirement for blood transfusion (p¼0.28).

No side effects were observed in the neonates .No difference in the Apgar score, birth weight was seen between tranexamic acid group and placebo group. The result was similar to that of the study conducted by Gohel et al, Gai et al, Shekavat et al.[10,11,14]

The estimation of blood loss from the time of incision to the end of the caesarean section was done in the present study. But there were various studies which studied the role of tranexamic acid in decreasing the incidence of

Post-partum hemorrhage after caesarean section. In the study Conducted by Gai et al the incidence of post-partum Hemorrhage was lower in the study group than in the control (P <0:05).[14] There was no statistical difference in the incidence of post-partum hemorrhage from the end of Caesarean section to 2 h postpartum between the two groups. In the study blood loss >400 ml within 2 hrs after birth was taken as Post-partum hemorrhage. In the study conducted by Gohel et al showed significant decrease in the incidence of >500 ml blood loss in the study group compared to control group) in caesarean section.[10] Yang et al showed post-partum hemorrhage was decreased by usage of tranexamic acid in vaginal delivery.[16]

CONCLUSION

Injection tranexamic acid is the, antifibrinolytic agent that can be used for prophylactic administration before caesarean section for decreasing blood loss during surgery. It has also the extended efficacy for 6 hrs in the post-operative period which helps in decreasing blood loss even in the post-operative period. Irrespective of age, BMI of the patient, injection tranexamic acid can be administered in the dose of 1g IV for optimum efficacy because it has least side effects. Tranexamic acid also can decrease the need for additional uterotonics during Caesarean Section. Tranexamic acid has no side effects in the neonate.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Bhavana G, Abhishek MV, Mittal S. Efficacy of prophylactic tranexamic acid in reducing blood loss during and after caesarean section. Int J Reprod Contracept Obstet Gynecol 2016;5:2011-6.