Original Research Article

Efficacy of intravenous tranexamic acid at reducing blood loss during elective caesarean section in a tertiary care hospital in North Kerala

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Abstract

Increasing caesarean section rate is a source of concern to obstetricians due to the attendant increased health risk, its commonest complication is bleeding, which occasionally may be life threatening. Tranexamic acid has recently been investigated as a potentially useful adjunct for the prevention of maternal morbidity. The research aimed to evaluate the efficacy of tranexamic acid at reducing blood loss during elective caesarean section. The method used was a Randomized, Double blind, Interventional study among women who had elective caesarean section at KMCT Medical College, Kozhikode, Kerala. Data analysis was done using statistical Package for Social Science (IBM SPSS). Mean blood loss in study arm was 352.4 ml, whereas in control arm it was 521.65 ml, which was statistically significant. Only 9.1 %of study population had >10% of fall in perioperative haemoglobin, whereas 43.2 % of control population had >10% fall, which was significant. Statistically significant difference between the two groups was noted with respect to duration of surgery. Intravenous tranexamic acid significantly reduced blood loss at elective caesarean sections. It also reduced the risk of blood loss greater than 1000 ml without increasing maternal risks.

Key words: Tranexamic acid, blood loss, elective caesarean section.

Introduction

PPH accounts for **major part** of this issue, accounts **nearly 30 % of maternal mortality**, one of the leading causes of maternal mortality and morbidity worldwide.Post-Partum Haemorrhage (PPH) is more after Caesarean section (4% vs. 0.6%) than vaginal delivery[1] and among these, 6% require blood transfusion[2-3] and 11% suffers from severe post-partum anemia[4]. Recently, Caesarean Section (CS) rates have increased to as high as 25–30 % in many countries of the world like China and India[5], which would cause more PPH rates than normal vaginal delivery. Maternal mortality ratio is 200 in India[6] and PPH still is a leading cause. Obstetric accounts for nearly 20-25% of all maternal deaths worldwide.

The sustainable devlopment goals-3 and maternal mortality

Ambitious Target: - Reducing the global maternal mortality rate to less than 70 per 100000 births [by 2030]

Annual rate of reduction based on estimated MMR (%) (2000-2017): - 5.5[4.2,7.6].

Kerala with lowest MMR of 43(2014-2016) followed by **Maharashtra** at 46 followed by **Tamil Nadu** at 60, **Telangana** at 63 and **Andhra Pradesh** at 65.

Tranexamic acid is biochemically Trans-4-(aminomethyl) cyclohexanecarboxylic acid (C8H15NO2). Tranexamic acid was first reported by Okamoto in 1962. Tranexamic acid (TXA) 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 the plasminogen molecules (Product monograph prCyclokapron, 2018)[7].

ITXA decreases the blood loss in patients with both normal and exaggerated fibrinolytic responses without increasing the risk of post-operative complications[8]. History shows that Utako Okamoto discovered Tranexamic acid in 1962, with her husband. After the 2nd Sino-Japanese war, her research group started work on anti -Plasmin. Intravenous administration of the tranexamic acid has been shown to reduce the need for transfusion and risk of maternal death[9]. Its efficacy in the treatment of postpartum haemorrhage has been validated in a large global multicentre randomized control trial Now, after CRASH-2 trial, TXA is being widely used for trauma and those at risk of increased blood loss

Onset of action: 5-15minutes.Duration of action: 3hours.It to be substantially excreted by kidneys: - Urine (> 95% as unchanged drug) about half of the drug excreted in the urine during first 3-4 hours, 90-95% within 24 hours and 95 -99% within 48-72 hours. Oral- 40% of a dose is excreted within 24 hours.

Dosing

TXA (Cyklokapron) -1gm in 100ml NS [10-15 mg/kg body weight] is given as slow intravenous dose, if necessary maintenance dose can be kept for eight hours. TXA crosses the human placenta. Following administration of 10mg/kg to pregnant women, 30mcg/ml of TXA measured in fetal serum. No adverse fetal effects were noted in studies on mice, rabbits.

FDA Pregnancy Category -B .Hence it was decided to study and assess the role of prophylactic Tranexamic acid in reducing the blood loss during elective caesarean section.

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Aims and objectives

Aims

To study and assess the role of prophylactic Tranexamic acid in reducing the blood loss during elective caesarean section.

Objectives

- To evaluate blood loss intraoperatively after prophylactic Tranexamic acid
- To compare intraoperative blood loss of study group with control group.
- To determine whether Tranexamic acid is effective in reducing blood loss during caesarean section and bring down morbidity and mortality associated with caesarean section

Materials & methods

This is a randomized, placebo controlled interventional, prospective study and was initiated after obtaining clearance form Institutional Human Ethics Committee (IHEC), KMCT Medical College Hospital.

Study design

Randomized, Double blind, Interventional study

Study place

KMCT Medical College Hospital

Study population

Antepartum patients getting admitted in Obstetric ward, KMCT Medical College Hospital for undergoing Elective Lower segment caesarean section.

Study period

One Year from March 2019 to December 2019

Inclusion criteria

1. Singleton pregnancy 2. Elective LSCS

Exclusion criteria

1.Emergency LSCS 2.Increased risk for thrombosis 3. Past H/O Thromboembolism 4.Past H/O postpartum haemorrhage 5.H/O Gestational hypertension 6.H/O Chronic Hypertension 7.Patients with Renal disease 8.Heart Disease Complicating Pregnancy 9.Patients with Bleeding disorders 10.Abnormal Placentation 11.Multiple pregnancies 28 12.Polyhydramnios 13.Those requiring Blood Transfusion due to Anaemia.

Sample size

150

75 cases and 75 controls after a pooled mean sample size of following articles (From PubMed): 1.S. Sampath kumari et al[10] sample size: 100. 2. Movafegh et al[11] sample size :100 3. Gohel et al[12], sample size :100, 4. Shahid A[13] sample size: 74 5. Xu et al[14], sample size: 174 6. Gungorkuk et al[15], sample size:100 7. Gai et al[16], sample size: 180.

Mean sample size

1+2+3+4+5+6+7 =828/7 =118.285.

Following informed consent, patients were allotted to either of the 2 groups as per randomization. Preoperative haemoglobin estimated in both groups. TXA injection was prepared by diluting 1g (10ml) TXA with 100ml of normal saline. TXA was administered at least 20 minutes prior to skin incision, to those in study group. No drug was given to the control group. After delivery of the neonate, routine care was given to both groups: 10 units of oxytocin added to ringer lactate and allowed flow at rate of 60ml/hour for 3 hours after surgery. The blood loss was measured following placental delivery to the end of the surgery. Blood collected from the suction container was noted and soaked mops and operation table perineal sheet were weighed by electronic scale before and after the surgery. The quantity of blood loss (mL) was determined as the weight of the used materials in both the periods subtracted weight of the materials prior to the surgery and added the volume sucked in the suction bottle after placental delivery measured in ml. Amniotic fluid and the amount of blood lost before placental delivery were thus not included in measuring blood loss in the study. Postoperative hemoglobin was estimated 24hours after the surgery. This study was approved by The Institutional Human Ethics Committee [IHEC], KMCT Medical College Hospital.

Blood loss calculation

Adopted Gravimetric method in this study for calculating blood loss during surgery, materials used during surgery are mop, perineal sheet. Suction apparatus is used to collect blood in operating field

1] Blood absorbed by soaked mops =Weight of soaked mop – dry weight [1mg approximately = 1ml of blood]

2] Blood adsorbed by perineal sheet = weight of soaked sheet – dry weight

3] Blood in suction apparatus = fluid collected in suction apparatus (after placental delivery)- volume of wash saline given

- Dry weight of mop (10”X10”) = 30gm
- Dry weight of perineal sheet = 70gm

Total perioperative blood loss = 1+2+3

Data analysis

Primary Outcome Measure was the estimated blood loss at elective caesarean section.

Secondary Outcome Measures were; excessive blood at caesarean section loss defined as blood loss > 500 ml, duration of surgery ,change in haemoglobin after caesarean section, the need for blood transfusion during or after the surgery and maternal side effects (nausea, vomiting, headache, skin rash, thromboembolism, and maternal death.

Statistical method

All statistical procedures were performed using Statistical Package for Social Sciences (SPSS) 20.0. Calculations for power (80%) of study will be performed before commencement of the study. All quantitative variables expressed in mean and standard Deviation. Qualitative variables will be expressed in percentages. Shapiro-Wilk test was used for testing the normality assumption of the data. Independent t test and chi square test was used for association. Probability value

Results

FIGURE 1: There is no statistically significant difference between the two groups with respect to gestational AGE.

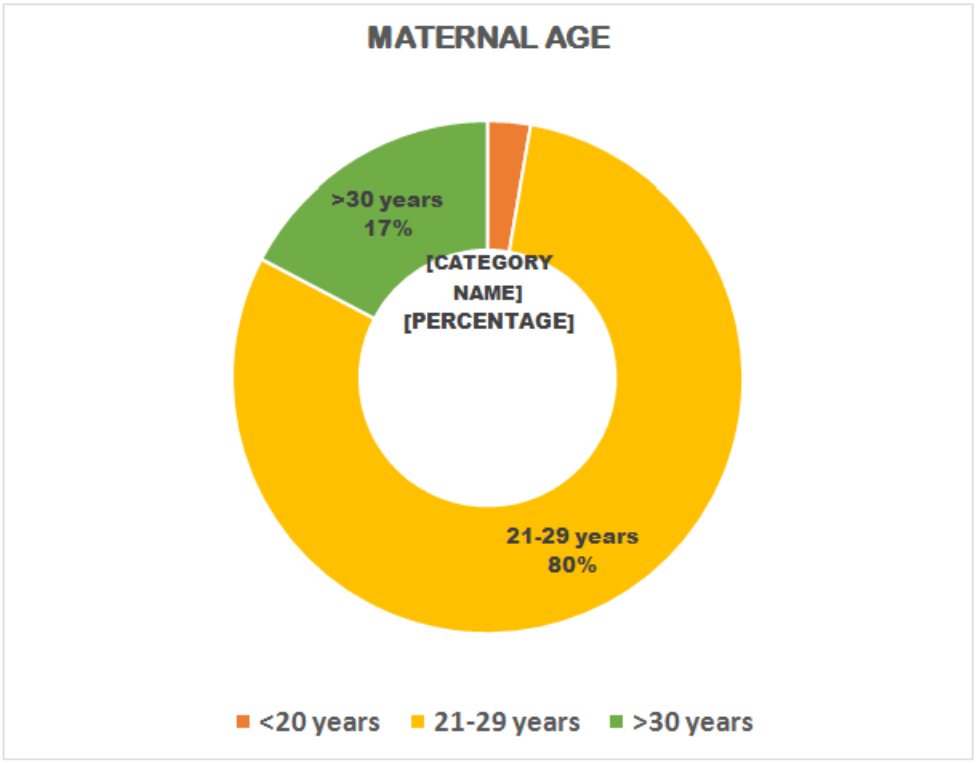

Figure 1-Maternal Age

FIGURE 2 shows distribution with respect to Gestational age

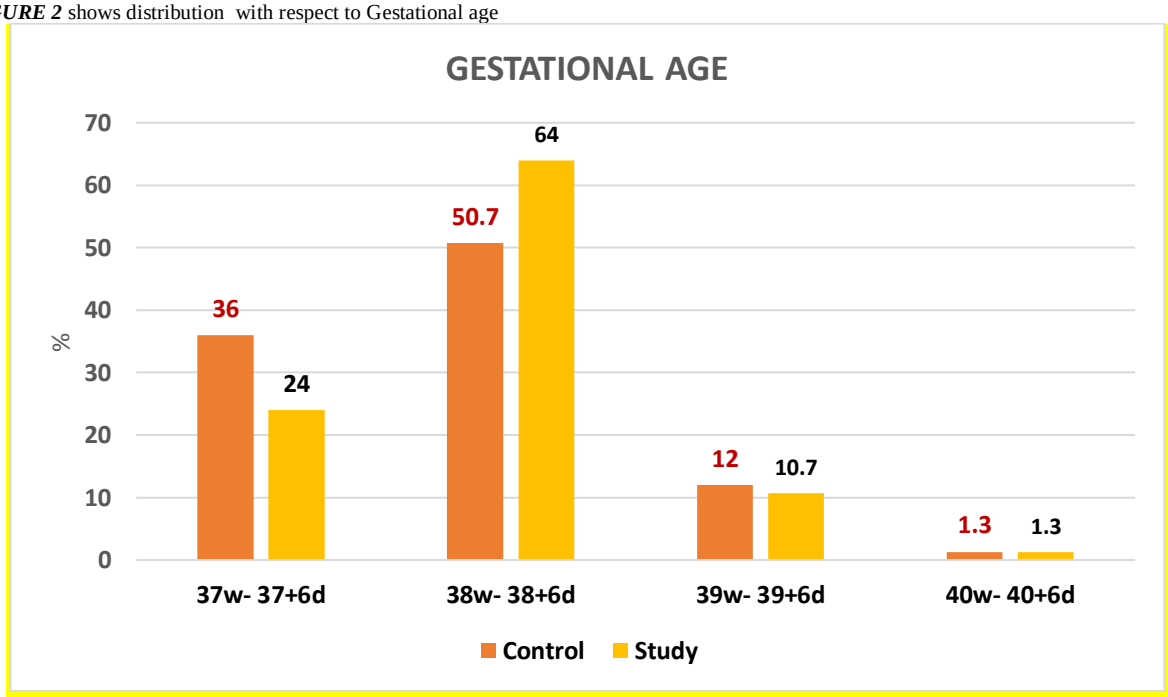

Figure2-Gestational Age

FIGURE 3 shows mean duration of surgery in study arm is 56 ± 11.03 min, whereas in control arm it is 71.2 ± 11.53 min, which is statistically significant (p value <0.05)

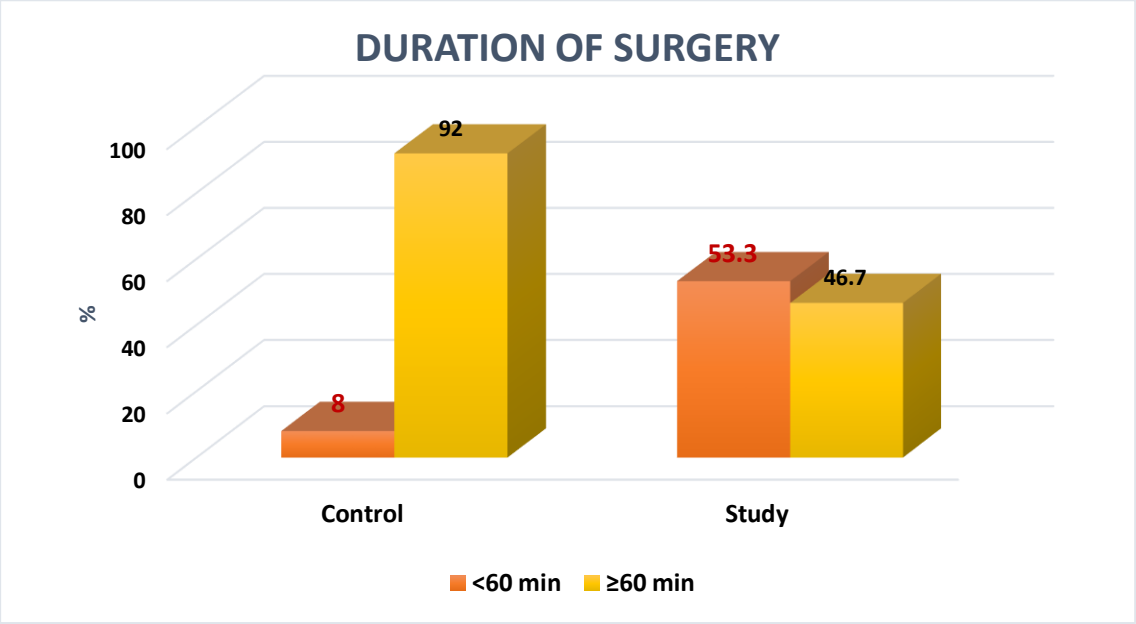

Figure 3-Duration Of Surgery

Table 1 There is no statistically significant difference between the two groups with respect to MATERNAL WEIGHT, as indicated by the p value (>0.05)

Table 1--Maternal Weight

CONTROL	71.94	6.12	1.01	0.13
STUDY	70.39	6.55		

- There is no statistically significant difference between the two groups with respect to Weight, as indicated by the p value (>0.05).

TABLE 2 shows, statistically significant difference between the two groups with respect to duration of surgery which is statistically significant (p value <0.05)

Table 2: Duration of surgery

<60 MIN	6 (8)	40(53.3)	36.24	<,0.001**
>60 MIN	69(92)	35(46.7)		

- p value <0.05 is statistically significant;

** <0.001 is statistically highly significant

TABLE 3- Pre-op hemoglobin status

TABLE 3--PREOP HB

CONTROL	11.91	1.00	0,81	0.42
STUDY	11.77	0.99		

- There is no statistically significant difference between the two groups with respect to , as indicated by the p value (>0.05).

TABLE 4 &5 shows Post -op Hb and mean blood loss respectively

TABLE 4--POST OP HB

CONTROL	10.74	1.28	4.03	<0.001**
STUBY	11.57	1.19		

- p value <0.05 is statistically significant;

** <0.001 is statistically highly significant

TABLE 5-Blood Loss

GROUP	CONTROL	STUDY	CHI-SQUARE	P-VALUE
<500 ML	27(36)	72(96)	60.16	<,0.001**
>500ML	48(64)	3(4)		

- p value <0.05 is statistically significant;

** <0.001 is statistically highly significant

In the study arm blood loss was 352.4± 104.47 ml, whereas in control arm it was 521.65± 140.84 ml, which was statistically significant (p value <0.05)

Only **9.1 %**of study population had >10% of fall in perioperative hemoglobin, whereas **43.2 %** of control population ha >10% fall, which was again statistically significant.

Figure4- hemoglobin difference between both the groups

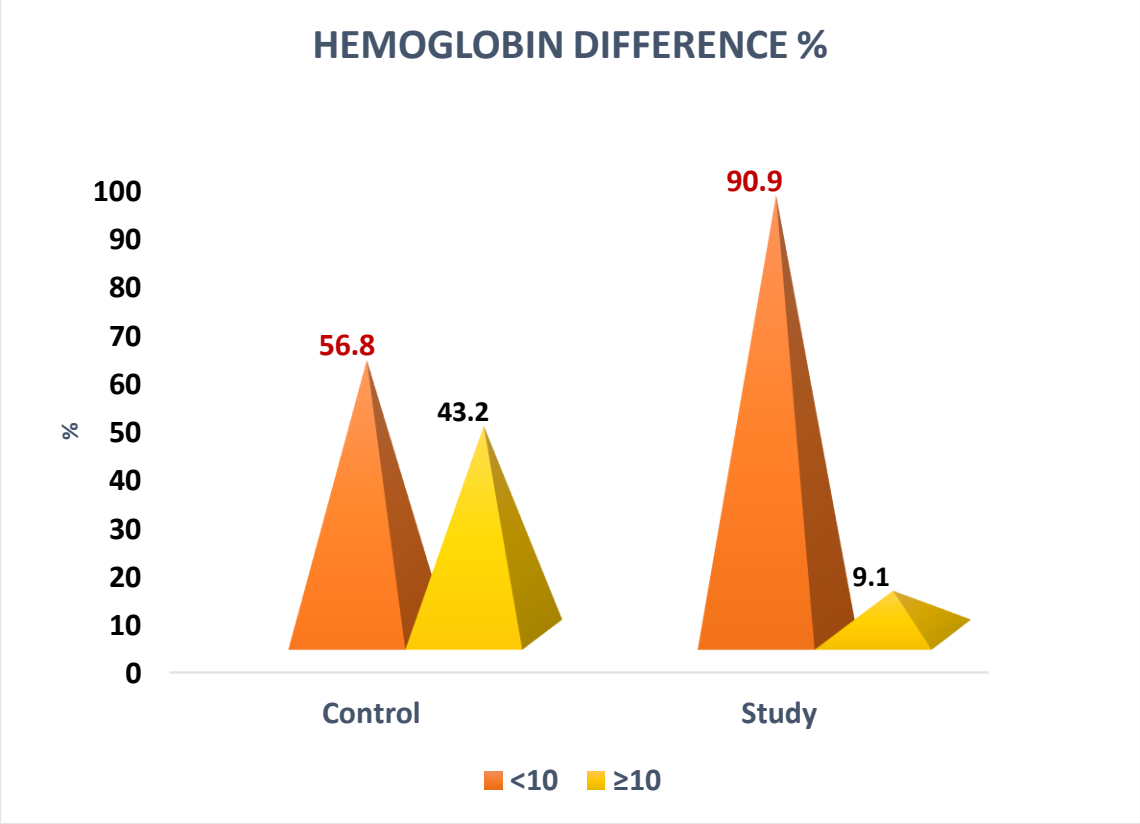

FIGURE-4 Hemoglobin Difference

- ** P<0.001 is statistically highly significant chi square test

Discussion

The study was conducted on 150 term, with singleton pregnancy being delivered by Elective LSCS. Two groups: 75-75 in each group; Study group - interventional arm where tranexamic acid was given; Control group – tranexamic acid was not given. The most common indication was previous LSCS and it contributed to 80% in study arm and 84% in control arm. Mean duration of surgery in study arm was 56 min, whereas in control arm it was 71.2 min, which was statistically significant. Mean blood loss in study arm was 352.4 ml, whereas in control arm it was 521.65 ml, which was statistically significant. Only 9.1 %of study population had >10% of fall in perioperative haemoglobin, whereas 43.2 % of control population had >10% fall, which is again statistically significant.

1 gm tranexamic acid significantly reduced the amount of blood loss during Elective Caesarean Section in my study. Thus, can be used effectively and safely in patients undergoing LSCS with no adverse effects and thus can prevent maternal mortality and morbidity

Comparative similar research studies for preventing pph after caesearen delivery

Study (Year)	Country	Sample(N)	Intervention	Result	P value	Adverse effects
Gai et al[16](2004)	China	180	Iv Infusion x 5 min, 10 min prior CS	360 ml Vs 439.3ml	**0.002**	No thromboembolic/ other side effects
Gohel et al[12](2007)	India	100	Iv Infusion x 5 min, 20 min prior CS	375ml Vs 473ml	**0.003**	No thromboembolic /other side effects
Sekhavat[17]et al (2009)	Iran	90	Iv infusion x 5 min, 10 min prior CS	280ml Vs 371ml	**0.001**	No thromboembolic /other side effects
Gungorkuk[15] et al (2011)	Turkey	100	Iv Infusion x 5 min, 10 min prior CS	500ml Vs 600.7ml	**<0.001**	No thromboembolic /other side effects
Movafegh[11]et al (2011)	Iran	100	Iv Infusion x 10 min, 20 min prior CS	263ml Vs 405ml	**<0.001**	No thromboembolic /other side effects

Xu et al[14] (2013)	China	174	Iv Infusion x 5 min, 10 min prior CS	379ml Vs 441ml	0.02	GI side effects
Senturk et al[18] (2013)	Turkey	223	Iv Infusion x 5 min, 10 min prior CS	272ml Vs 347ml	**0.001**	No thromboembolic /other side effects
Shahid et al[13] (2013)	Pakistan	74	Iv Infusion x 10 min, 10 min prior CS	356ml Vs 710ml	**<0.001**	No thromboembolic /other side effects
Abdel et al[19] (2013)	Egypt	740	1gm iv x 10 min, 10 min prior to CS	242ml Vs 510ml	**<0.001**	GI side effects
Goswami[20] et al (2013)	India	90	Iv 10-15 mg/kg, 20min prior to CS	377mlVs 261ml Vs 527ml	-	No thromboembolic/other side effects
S.Sampathkumari[10] (2018)	India	100	Slow Iv infusion ,15 min prior to CS	406ml Vs 460ml	**0.0001**	No thromboembolic /other side effects
Present study (2019)	**Kerala, India**	**150**	**Iv Infusion x 10min, 20 min prior to CS**	**352ml Vs 521ml**	**<0.001**	**No thromboembolic /other side effects**

The above table is summary of twelve (along with the present study) randomized of controlled trials analyzing the effect of tranexamic acid in reducing postpartum hemorrhage.

These studies were conducted on women undergoing elective and emergency caesarean sections. Only two studies were conducted on only elective section. All these trials were almost uniform in their final conclusion that tranexamic acid effectively reduced the peri-operative blood loss, without any major alteration in the vital signs of the subjects. However they had certain limitations. Power to assess the adverse effects was not upto the mark. Almost all the studies were conducted in a single center and few were not fully randomized. There was no control arm in two of the studies. Blood loss estimation was the major drawback and the important limitation of this study. First, measurement was based on gravimetric method- which is not 100% accurate, next the measurement varied from one trial to another and finally this calculation was subjected to observer variation. The most reliable of these were two:

- One RCT conducted by Gundorkuk[15] and colleagues, they analyzed their study by intention to cure and treat. There was statistically significant in the blood loss between the study arm and control arm. [499ml Vs 600ml].
- Another RCT was conducted by. S. Sampathkumari[10] and colleagues noted t significant differences in blood loss (406ml Vs 460ml) and 24 hr postoperative hemoglobin was significant higher in study group (11.83 ±1.1) compared to control group (10.34 ±1.03).

Comparable to above specified studies, trials and meta-analysis present study proved that TXA significantly reduced bleeding from the time of placental delivery till end of surgery in LSCS. This study showed significant decrease in the bleeding volume in TXA group as compared with placebo group. There was significant reduction in duration of surgery. There was significant difference in Hemoglobin variation before and after surgery, between the two groups. Previous studies have shown the safety of this drug for use in both pregnant and non-pregnant patients. None of the women in my study showed any signs /symptoms of intermediate thrombo-embolic events.

Conclusion

- 1 gm tranexamic acid significantly reduced the amount of blood loss during Elective Caesarean Section in my study. Thus, can be used effectively and safely in patients undergoing LSCS with no adverse effects and thus can prevent maternal mortality and morbidity.
- There is statistically significant difference in the volume of blood loss from placental delivery till end of surgery, between the two groups.
- Only 4% of population in study arm had ≥ 500ml of blood loss; whereas 64% of population in control arm had ≥ 500ml of blood loss
- There is statistically significant difference in percentage of fall in hemoglobin value from the pre-operative value, between the two groups
- Age, weight, parity, indications for LSCS are standardized between the 2 groups, with no bias.

Pregnancy is a hypercoagulable state, hence the risk of thromboembolic events are more during pregnancy and till 6 weeks postpartum, when compared with normal population. Nevertheless it is important to notice that use of Tranexamic acid was not associated with any side effects and or complication like thrombosis.

Thus TXA is a promising drug, inexpensive and easy to administer, that could be added to the routine delivery management to all women worldwide..

Limitations

The limitation of the study include:

- Small sample size
- Blood loss was measured after placental delivery, and consequently, skin muscle and uterine bleeding prior to placental delivery could not be strictly avoided.
- Spillage of blood over the drapes could not be measured
- Amniotic fluid too contributed to mirror adjustments. But as this circumstance is common for both the study and control groups, there was no bias as such.
- Long-term effects of TXA on the patients and the neonates were not taken into account

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