Role of Intravenous Tranexamic acid (TXA) in reducing perioperative blood loss in hysterectomy for benign gynecological conditions.

Sukriti Bhutani[1], Roopa Malik[2], and Nirmala Duhan[1]

[1]Affiliation not available
[2]Pt B D Sharma University of Health Sciences

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Abstract

Objective Investigate the antihemorrhagic effect of intravenous perioperative tranexamic acid in hysterectomy for benign gynecological diseases. Study Design A prospective randomized case-control study was carried out in the Department of Obstetrics and Gynaecology, PGIMS, Rohtak, on 150 patients planned for hysterectomy for benign conditions. The women were randomized into two groups- Group I and Group II, with 75 subjects in each group. Group I was not be given any drug, while Group II was given TXA as intravenous bolus injection of 10mg/kg (maximum 1g) for 10 min about 30 min before incision. Unpaired 't' test and ANOVA test were used to calculate the difference of means of quantitative variables. An association was significant if the p-value < 0.05. Results Intraoperative blood loss was reduced in the group given tranexamic acid preoperatively (mean loss 489.07± 279.248 ml) v/s the control group (mean loss 539.93 ± 211.08ml) ($p<0.05$). This result was particularly significant in the subjects who underwent vaginal hysterectomy (mean loss 364.58 ± 108.53ml in Group II v/s 278.91 ± 118.34ml in Group I; $p<0.05$). The incidence of transfusion of blood or blood products intraoperative to postoperative day seven was significantly reduced in the tranexamic acid group (0.47 vs. 0.23, P = .02). Conclusion The results show that preoperative intravenous tranexamic acid reduces the total blood loss irrespective of the route of hysterectomy and the number of perioperative transfusions. No incidences of serious adverse events occurred. Thus, tranexamic acid should be considered as a prophylactic treatment before benign hysterectomy.

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Sukriti Bhutani, Resident, Department of Obstetrics and Gynaecology, PGIMS Rohtak, Roopa Malik, Professor, Department of Obstetrics and Gynaecology, PGIMS Rohtak, Nirmala Duhan, Professor, , Department of Obstetrics and Gynaecology, PGIMS Rohtak.

Background

What is already known about this subject: Hysterectomy is one of the most common gynecological surgery. Perioperative bleeding is shown to be the most common cause of complications during hysterectomy.. Anti-fibrinolytic agents, Tranexamic acid, has shown to reduce bleeding complications in other surgical and medical areas. However, knowledge about the drug's effectiveness concerning benign hysterectomy is still unknown.

What this study adds: Tranexamic acid can be given during preoperative period to reduce the blood loss during hysterectomy for benign diseases.

Abstract

Objective

Investigate the antihemorrhagic effect of intravenous perioperative tranexamic acid in hysterectomy for benign gynecological diseases.

Study Design

A prospective randomized case-control study was carried out in the Department of Obstetrics and Gynaecology, PGIMS, Rohtak, on 150 patients planned for hysterectomy for benign conditions. The women were randomized into two groups- Group I and Group II, with 75 subjects in each group. Group I was not be given any drug, while Group II was given TXA as intravenous bolus injection of 10mg/kg (maximum 1g) for 10 min about 30 min before incision. Unpaired 't' test and ANOVA test were used to calculate the difference of means of quantitative variables. An association was significant if the p-value < 0.05.

Results

Intraoperative blood loss was reduced in the group given tranexamic acid preoperatively (mean loss 489.07± 279.248 ml) v/s the control group (mean loss 539.93 ± 211.08ml) ($p<0.05$). This result was particularly significant in the subjects who underwent vaginal hysterectomy (mean loss 364.58 ± 108.53ml in Group II v/s 278.91 ± 118.34ml in Group I; $p<0.05$). The incidence of transfusion of blood or blood products intraoperative to postoperative day seven was significantly reduced in the tranexamic acid group (0.47 vs. 0.23,$P = .02$).

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The results show that preoperative intravenous tranexamic acid reduces the total blood loss irrespective of the route of hysterectomy and the number of perioperative transfusions. No incidences of serious adverse events occurred. Thus, tranexamic acid should be considered as a prophylactic treatment before benign hysterectomy.

Keywords: Anti-fibrinolytic therapy, Benign hysterectomy, Bleeding complication, Hysterectomy, Tranexamic acid

INTRODUCTION

Hysterectomy, despite a decline in the rates of effective conservative management of benign uterine disease, is the most frequent gynecological surgery and overall, second to the cesarean section in many parts of the world [1] [2]. The choice of the approach depends on the surgeon's preference, nature of the disease, the indication of the surgery, and patient characteristics [3]. Common medical indications of hysterectomy include gynecological ailments such as fibroids, dysfunctional uterine bleeding, uterine prolapse [4], endometriosis, or chronic pelvic pain. It may also be required for cases of acute menorrhagia refractory to medical or conservative surgical treatment [5]. In the United States, among women aged 15 years and above who underwent hysterectomy during 2000–04, uterine leiomyoma was the most common hysterectomy indication accounting for nearly 41% of all hysterectomies [1].

Hysterectomy can be a part of staging laparotomy or radical hysterectomy. Rates of various complications with hysterectomy have been reported from 0.5% to 43% [6].

Tranexamic acid (TXA) is a synthetic lysine analog that competitively blocks the lysine-binding sites of plasminogen, plasmin, and tissue plasminogen activator, thereby retarding fibrinolysis and blood clot degradation. It may be administered orally, intravenously, or topically, with a rapid onset of action (tmax = appx 3 hours) and 11-hour half-life [7]. It is 6 to 10 times more potent than aminocaproic acid, another commonly used synthetic anti-fibrinolytic agent. Typical IV dosing is 10 mg/kg followed by infusion of 1mg/kg/hour [8]. A dosage of 10 to 15m/kg administered over 5 to 10 minutes before skin incision can also be given [9]. Intravenous TXA can cause hypotension (with rapid IV injection), dizziness, allergic dermatitis, diarrhea, nausea, vomiting, and blurred vision [10]. The CRASH-2 trial collaborators randomized 20,211 adult trauma patients with significant bleeding or at risk of significant bleeding within 8 hours of injury to IV

tranexamic acid or placebo [11]. Mortality was significantly reduced with tranexamic acid (RR .91; p=.0035). Systematic reviews were done in 2011, and 2012, of patients undergoing elective surgery, showed that TXA administration reduced the risk of transfusion perioperatively(RR.61).[12,13]

The use of oral TXA in the management of acute and abnormal uterine bleeding has been reported and is FDA-approved for the treatment of menorrhagia [11] [12]. One randomized study of oral TXA in the treatment of ovulatory menorrhagia reported a 45% decrease in mean menstrual blood loss using TXA compared with placebo [14]. Oral administration of TXA in cases undergoing conization of the cervix with the open surgical technique has also been reported [15]. In patients undergoing primary debulking surgery for gynecologic cancers, the administration of IV TXA has been shown to decrease intraoperative blood loss by 30% and reduce the need for intraoperative blood transfusion [16,17]. However, the role of IV tranexamic acid has not been effectively evaluated in reducing blood loss during hysterectomies for benign gynecological conditions, hence the need for this study.

MATERIALS AND METHODS

This study aimed to evaluate the role of intravenous tranexamic acid in reducing the perioperative blood loss in hysterectomy for benign conditions. The prospective randomized case-control study was carried out in the Department of Obstetrics and Gynaecology of Pt. B.D. Sharma PGIMS, Rohtak, on 150 patients planned for hysterectomy for benign conditions. Informed written consent was taken from every patient before the surgery. The required sample size was calculated based on the power of the 80% study and an α error of .05.

Patients were presenting for hysterectomy for any benign indication including abnormal uterine bleeding, menorrhagia, uterine fibroids, adenomyosis, pelvic pain, dysmenorrhea, pelvic organ prolapse or endometriosis, with age [?] 18 years and willing to consent for the study and to receive IV tranexamic acid before hysterectomy were included in the study. The patients with known or suspected endometrial/ovarian/cervical cancer or dysplasia, those with known bleeding/clotting disorders or a history of thromboembolism, those with history of allergic reactions to tranexamic acid, those with uncontrolled current illness (cardiac, hepatic, renal, etc.) or defective color vision or those previously on tranexamic acid before surgery were all excluded from the study.

The women were randomized into two groups- Group I and Group II, according to the computer-generated randomization number sequence for two-arm study with 75 subjects in each group. Group I was not be given any drug, while Group II was given TXA in an intravenous bolus injection of 10mg/kg (maximum 1g) for 10 min about 30 min before incision. The total volume of blood loss (m) during the operation was measured by the gravimetric method by adding the volume of contents of the suction container (excluding the volume of the fluid used for irrigation in laparoscopic hysterectomy) (a) to the difference in weight (where 1.06g is equivalent to 1ml) between the dry (b) and wet (c) mops used during the surgery m=a+(c-b).

The mop used for skin and surface bleeding was discarded on opening the peritoneal cavity. The type of anesthesia given was noted. The weight of the hysterectomy specimen was measured. The total duration of surgery from skin incision to skin closure was noted. Requirements of blood transfusion intraoperatively and postoperatively up to 7 days of surgery were recorded. Complications in the postoperative period were recorded. Postoperative hemoglobin was measured on postoperative day 2. If hemoglobin was found to be <7g/dl, blood transfusion was done.

The primary outcome was intraoperative blood loss. The secondary outcome was the requirement of blood transfusion, the changes in hemoglobin after the operation, and the duration of hospital stay.

Statistical Analysis

At the end of the study, the collected data were analyzed through SPSS (Statistical Package for Social Studies) Version 25.0 and the online Graph Pad for Windows (Prism 7). Clear values for various outcomes

were determined before running frequency tests. Pearson's chi-square test was used to evaluate differences between groups for categorized variables.

Unpaired 't' test and ANOVA test were used to calculate the difference of means of quantitative variables. All tests were performed at a 5% level of significance. Thus an association was significant if the p-value less than 0.05.

RESULTS

A total of 150 patients planned for hysterectomy for benign conditions were made a part of this prospective case-control study. Both the groups were matching with regard to demographic data (table 1) like blood pressure, pulse rate, and BMI. Heavy menstrual bleeding was seen as the most common complaint amongst the subjects undergoing hysterectomy, followed by the feeling of something coming out per vaginum while AUB-L was seen as the most common indication of hysterectomy followed by 3° cervical descent with rectocele and enterocele. Preoperative hemoglobin levels were shown to be higher in the control group, but an inverse correlation was found to be statistically significant ($p<0.019$). Similarly, postoperative hemoglobin values were found to be higher in the case group, which was statistically significant ($p<0.031$). There were a variety of routes followed for hysterectomy, out of which TAH with salpingectomy was the most common, followed by VH with anterior colporrhaphy and posterior colpoperineorrhaphy.As shown in table table 2, the mean intraoperative blood loss in the case group was seen to be 489 ml, while in the control group, it was 540ml, which was seen to be statistically significant. The intraoperative blood loss was overall decreased in the case group irrespective of the route of hysterectomy (table 3). This was found to be statistically significant only for vaginal hysterectomy with anterior colporrhaphy and posterior colpoperineorrhaphy. The difference in intraoperative blood loss between the case and the control groups was also found to be statistically significant ($p<0.02$). The weight of the hysterectomy sample obtained postoperatively was also found to be higher in the group, which received tranexamic acid, and this difference was found to be statistically significant as well ($p<0.05$). On the contrary, the requirement for blood or blood product transfusions (intraoperative to postoperative day 7) was seen to be higher in the case group, which was also statistically significant ($p<0.02$). Also, the mean duration of hospital stay post-hysterectomy was shown to be higher in the case group, but the difference was not found to be statistically significant ($p<0.09$).

Intraoperative blood loss was directly proportional and significant for the weight of the hysterectomy sample obtained and was independent of the use of tranexamic acid, $p<0.01$. Also, the intraoperative blood loss was seen to be more in the cases operated in general anesthesia than spinal anesthesia. These values were also found to be statistically significant, $p<0.04$. A correlation was also found between the intraoperative blood loss and the size of the uterus, $p<0.01$. It was seen that as the size increased, the blood loss increased proportionally, irrespective of the use of TXA.

With respect to the side effects of tranexamic acid, it was shown that the incidence of nausea and vomiting in the case and the control group (7 v/s 0 respectively) and diarrhea (2 and 1 respectively). There was no evidence found of serious adverse effects of tranexamic acid-like visual disturbances, hypotension, or venous thromboembolism.

Table 1: Demographic Data

Parameters	Case Group (n=75)	Control Group (n=75)	P Value
Age (yrs)	50.88±7.661	51.01±9.658	0.1
Educational Level (% uneducated)	67	58	
Parity 0 1 2 3 4 5 6	1 3 31 20 10 8 2	1 5 22 22 17 4 4	
Pulse rate (bpm)	89.15± 8.9	89.57 ± 6.3	0.736
DBP (mmHg)	80.51± 6.8	80 ± 8.6	.507
SBP (mmHg)	122.68 ± 9.4	123.95 ± 10.4	.338
BMI (kg/m^2)	21.55± 0.85	21.6 ± 0.79	.724

Parameters	Case Group (n=75)	Control Group (n=75)	P Value
Comorbidity	43(57.3%)	32(42.7%)	
Indication – Meno/metrorrhagia	38	31	0.251
Indication-UV prolapse	23	25	0.726

Table 2: Individual surgical parameters in both groups

	Case(mean±S.D.)	**Case(mean±S.D.)**	**Control(mean±S.D.)**	**t-test**	**p- value**
HbPreOp (g/dl)	9.3 ± 0.68	9.3 ± 0.68	9.66 ± 1.14	-2.376	**0.019**
HbPostOp (g/dl)	9.57 ± 0.61	9.57 ± 0.61	9.26 ± 1.05	2.176	**0.031**
Intraoperative blood loss (ml)	489.07	± 279.248	539.93 ± 211.08	1.258	**0.02**
Weight of hysterectomy sample (g)	274.47	± 178.81	216.8 ± 185.44	1.939	**0.05**
Number of transfusions	0.47 ± 0.74	0.47 ± 0.74	0.23 ± 0.48	- 2.351	**0.02**
Days of Hospital stay	9.15 ± 2.73	9.15 ± 2.73	8.44 ± 2.32	1.706	0.09

Table 3: Correlation of intraoperative blood loss with the route of hysterectomy

Hysterectomy	**Case**	**Control**	**T** -test	**P-value**
Laparoscopic hysterectomy	50 ± 0.00	190 ± 0.00	0	0
TAH with Bursch colposuspension	0	450 ± 0.00	0	0
VH with ant colporrhaphy and post colpoperineorrhaphy	364.58 ± 108.53	278.91 ± 118.34	-2.635	0.011
TAH with salpingectomy (U/L, B/L)	615.91 ± 211.70	664.52 ± 212.23	0.823	0.414
TAH with BSO	607.5 ± 207.38	697.33 ± 257.27	1.074	0.292
NDVH with salpingectomy (U/L, B/L)	396.67 ± 108.62	594 ± 366.44	1.542	0.149

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DISCUSSION

The majority of hysterectomies, around 90%, are performed for benign conditions, such as fibroids causing abnormal uterine bleeding [1]. There is no universal agreement between gynecologists about the optimum method of hysterectomy, and many clinicians believe that different pathologies require different surgical approaches. [2] Depending on their location, size, and number, fibroids can be removed using hysteroscopic, laparoscopic, and laparoscopically assisted or (mini) laparotomy-based procedures. In the ACOG Committee Opinion No. 444, the Committee on Gynecologic Practice concluded, Vaginal hysterectomy is the approach of choice whenever feasible, based on its well-documented advantages and lower complication rates. [18] Johns et al. [19] reviewed 2,563 hysterectomies performed for non-malignant indications, and they concluded that

LAVH was safe with similar complication rates as abdominal or vaginal hysterectomy, and was superior to abdominal hysterectomy (AH). English et al. (2019) showed that in their study, there were 18,033 hysterectomies for benign indications from 61 hospitals. [20]The median estimated blood loss was 100 mL, and the 90th percentile estimated blood loss was 400 mL. It was shown that there were increased risks of transfusion, readmission, reoperation, length of stay, and major postoperative complications with estimated blood loss greater than 400 mL. The risk factors for estimated blood loss greater than 400 mL included abdominal surgery compared with laparoscopic hysterectomy (adjusted odds ratio [aOR] 2.8, CI 2.3-3.5), surgical time longer than 3 hours (aOR 3.9, CI 3.3-4.5), and specimen weight greater than 250 g compared with less than 100 g (aOR 4.8, CI 3.9-5.8). Adhesive disease, being younger than 40 years of age, having a body mass index greater than 35, and the need for a preoperative transfusion were also statistically significantly associated with estimated blood loss greater than 400 mL. [20] Peipert et al. [4] demonstrated that patients with excess blood loss >750 mL had a 3.7-fold increase in febrile morbidity after hysterectomy. Surgery affects the coagulation systems and consequent to the increased release of plasminogen activator inhibitor, the fibrinolytic system shuts down, thus leading to coagulopathy and bleeding. [3] A normal woman can tolerate a blood loss of up to 1000 mL with a minimal effect on their health status, whereas, in a woman with severe anemia or cardiovascular disease, a blood loss of as little as 200 mL may be life-threatening and require additional intervention. [6]. A number of pharmacological agents have been used to reduce perioperative blood loss, and these include the anti-fibrinolytic drugs aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA). A popular conservative approach is to minimize perioperative bleeding through the prophylactic use of anti-fibrinolytic agents. [4] Excessively rapid dissolution of hemostatic fibrin (hyperfibrinolysis) results in excessive or recurrent bleeding and can be prevented by anti-fibrinolytic drugs, which stabilize the fibrin clot. The two commercially available anti-fibrinolytic agents, tranexamic acid(TXA) and e-aminocaproic acid(EACA) are synthetic derivatives of the amino acid lysine and act by blocking the action of plasmin. [5] In a Cochrane review addressing TA's efficacy in all types of surgery, a significant reduction of bleeding was found corresponding to a mean of 414 ml. [21] In addition to inhibiting plasmin, tranexamic acid also competitively inhibits the activation of trypsinogen by enterokinase, noncompetitively inhibits trypsin, and weakly inhibits thrombin. Dunn et al. (1999) showed that perioperative treatment with tranexamic acid (most commonly as an intravenous loading dose of 10 mg/kg followed by an infusion of 1 mg/kg/hour) resulted in significant reductions in postoperative blood losses (mostly measured over 12 to 24 hours) in randomized, double-blind comparisons with placebo in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). [7] Maddali et al. (2007), Casati et al. (2002) showed that intravenous tranexamic acid was significantly ($p < 0.05$–0.0001) more effective than placebo in reducing postoperative blood loss and transfusion requirements in patients undergoing CPB. [8,9]. Tranexamic acid has also demonstrated efficacy in the treatment of bleeding during pregnancy, such as that associated with placental abruption. [7] The WOMAN trial showed that TXA reduces death due to bleeding in women with PPH by about one-fifth. When given within 3 hours of giving birth, it reduces maternal death due to bleeding by around one-third. [10] [11]. Kouides et al. (2009) conducted the trial to test the efficacy of tranexamic acid in the treatment of heavy menstrual bleeding. [12] Lukes et al. demonstrated that oral tranexamic acid treatment was well tolerated and significantly improved both menstrual blood loss and health-related quality of life in women with heavy menstrual bleeding. [13] The most frequently reported adverse events include headache, nausea, vomiting, diarrhea, dyspepsia, dysmenorrhoea, dizziness, back pain, numbness, and anemia. Where stated, most adverse events were of mild or moderate severity. [5].

Cumulative meta-analysis showed that reliable evidence that tranexamic acid reduces the need for transfusion has been available for over ten years. [14] Topsoee et al. (2016) showed that intraoperative total blood loss was reduced in the group treated with tranexamic acid compared to the placebo group when estimated both subjectively by the surgeon and objectively by weight (98.4 mL vs. 134.8 mL, P = .006 and 100.0 mL vs. 166.0 mL, P = .004). The incidence of blood loss [?]500 mL was also significantly reduced (6 vs. 21, P = .003), as well as the use of open-label tranexamic acid (7 vs. 18, P = .024). Furthermore, the risk of reoperations owing to postoperative hemorrhage was significantly reduced in the tranexamic acid group compared to the placebo group (2 vs. 9, P = .034). Celebi et al., randomized women with advanced-stage ovarian cancer patients to 15 mg/kg IV TXA or the same volume of placebo immediately before surgery.

Outcomes in the present study included a significantly lower mean estimated blood loss and decreased need for transfusion in the TXA group. [22] Goswami et al. had compared the efficacy of two different doses of TXA in their study and inferred that 15 mg/kg dose was more effective than 10 mg/kg dose without an increase in adverse effects. [15]

CONCLUSION:

The results obtained from our study on 150 subjects support the hypothesis that the use of perioperative treatment with intravenous tranexamic acid, 30 minutes before skin incision, reduces the overall total blood loss, especially if the route of hysterectomy was vaginal. It also reduces the duration of hospital stay and the need for postoperative blood transfusion. No incidences of serious adverse reactions occurred. Thus, tranexamic acid should be considered preoperatively prior to elective benign hysterectomy.

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