

ROLE OF PERIOPERATIVE TRANEXAMIC ACID IN REDUCING INTRAOPERATIVE BLOOD LOSS DURING ABDOMINAL HYSTERECTOMY

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Abstract

Background: Prophylactic use of Intravenous Tranexamic acid to reduce intra-operative blood loss during abdominal hysterectomy. **Materials and Methods:** A Prospective Randomized Controlled study was conducted among patients posted for abdominal hysterectomy with or without salpingo-oophorectomy in the department of Obstetrics and Gynaecology. All the cases were randomly divided into two groups. Group 1 cases had receive placebo normal saline while Group 2 cases received 1gram IV tranexemic acid just half an hour before the incision. **Result:** The mean age of subjects in group 1 was 45.8 ± 5.1 yrs and in group 2 was 44.5 ± 6.6 yrs. In group 1, 26% cases had diabetes mellitus, 24% had hypertension and 8% had hypothyroidism while in group 2, 14% cases had diabetes mellitus, 10% had hypertension and 4% had hypothyroidism. In the present study AUB + Fibroid uterus was the most common indication of abdominal hysterectomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy or total abdominal hysterectomy with bilateral salpingectomy was the most common surgical procedure conducted in both the groups. The mean Intraoperative Blood loss in group 1 was 244.40 ± 41.11 ml and in group 2 it was 171.40 ± 21.38 ml with statistical significant mean difference between two groups. Post operatively the mean change in hemoglobin was high in group 1 (1.38 ± 0.37) when compared to group 2 (0.75 ± 0.19) with a statistical significant mean difference between two groups. In group 1, 26% of the cases required blood transfusion while in group 2 only one case (2%) required blood transfusion. The mean duration of hospital stay (days) in group 1 was 4.10 ± 0.76 and in group 2 was 3.96 ± 0.90 with no statistical significant mean difference between two groups. **Conclusion:** Tranexamic acid should be considered as prophylactic treatment in abdominal hysterectomy in order to reduce the risk of substantial bleeding and reoperations.

INTRODUCTION

Hysterectomy is the second most frequently performed major surgical procedures on women all over the world, next only to cesarean section. It is the most common non-obstetric gynaecological procedure with an incidence of 3.6 per 1000 person-years in Germany in 2006; 4.8 per 1000 woman-years in Australia in 2003 and 5.1 per 1000 person-years in the US in 2004.^[1] Hysterectomy remains the gold standard for the treatment of benign uterine pathologies and part of the surgical treatment of gynaecological malignancies.^[2]

In India a study conducted in a northern state of India (Haryana) states that incidence of hysterectomy was

7% among married women above 15 years of age. Another study from a western state (Gujarat) pointed out that 7-8% of rural women and 5% of urban women had already undergone hysterectomy at an average age of 37 years.^[3]

Indications of hysterectomy vary from benign condition to malignancies of genital tract. Term "hysterectomy" though means removal of uterus, in practice it has a much wider classification depending upon the indication. At times it is done without removal of the cervix (supracervical hysterectomy) or with removal of adnexa (hysterectomy with salpingo-oophorectomy). It can also be a part of staging laparotomy or radical hysterectomy. Hysterectomy can be performed abdominally,

vaginally or through abdominal ports with help of a laparoscope. Approach depends on surgeon's preference, indication for surgery, nature of disease, and patient characteristics.^[4]

Worldwide most of the hysterectomies are performed abdominally. One in nine women will undergo a hysterectomy in their lifetime. Surgical blood loss of more than 1000 ml or blood loss that requires a blood transfusion usually defines intraoperative hemorrhage. Intraoperative hemorrhage has been reported in 1–2% of hysterectomy studies.^[5]

As with any surgical treatment, complications affect the outcomes of hysterectomy. Hemorrhage, which is the most frequent and critical complication, often occurs during surgery. Data from The Danish Hysterectomy and Hysteroscopy Database (DHDD) have revealed a relatively high complication rate of 16–18% from 1998 to 2006, of which perioperative bleeding complications represent the most common cause. From 2004 to 2006, 6–8% of all women undergoing benign hysterectomy experienced a bleeding complication.^[6]

Therefore, adequate haemostatic techniques are essential during abdominal hysterectomy. Currently, surgical haemostasis can be secured by a variety of methods, including mechanical sutures (or clamping), electric coagulation, ultrasonically activated scalpel, or drugs. Moreover, haemostatic medications are also used. Misoprostol and vasopressin are used to decrease blood loss during hysterectomy. Recently, attention has focused on the use of tranexamic acid (TA) to reduce blood loss if given prophylactically at hysterectomy.

Tranexamic acid (TA) is an antifibrinolytic agent approved for treatment of various types of hemorrhage. It inhibits fibrin degradation, thereby promoting the blood's ability to form stable blood clots. In several countries, the drug is used as prophylactic treatment prior to major surgery. 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. Similar results have been found within traumatology. The antihemorrhagic effect of TA regarding gynecological surgery has been investigated in only a limited number of clinical trials. In contrast, a substantial number of studies have been conducted on the effect of TA as treatment for women with menorrhagia.^[7] Women undergoing hysterectomy might benefit from prophylactic TA during surgery. On this basis the present study was conducted to investigate the antihemorrhagic effect of prophylactic TA in abdominal hysterectomy.

MATERIALS AND METHODS

This is Prospective Randomized Controlled study was carried out over a period of 24 months from December 2019 to November 2021 in Women undergoing abdominal hysterectomy with or without salpingo-oophorectomy. It was carried out at

Department of Obstetrics and Gynaecology, Kamineni academy of medical sciences and research center, LB Nagar, Hyderabad.

Based on previous study conducted by Gupta K et al.,⁸ on the prophylactic role of tranexamic acid to reduce blood loss during surgery, the post-op hemoglobin in placebo group was 9.8 ± 1.3 and Group TXA was 10.6 ± 1.5 .

Sample size was calculated using the formula, Confidence Interval (2-sided) at 95% $[Z_{1-\alpha/2}] = 1.96$ Power at 80% $[Z_{1-\beta}] = 0.84$

Ratio of sample size (Group 2/Group 1) = 1
Minimum Sample size calculated in each group $n = (1.96 + 0.84)^2 \times [(1.3)^2 + (1.5)^2] / (9.8 - 10.6)^2 = 7.84 \times (3.94) / 0.64 = 30.89/0.64 = 48.2$

For, the present study the sample size in each group was rounded to 50 in each group and the total sample was 100 cases.

Inclusion Criteria

Women undergoing abdominal hysterectomy ± salpingo-oophorectomy for the indications (Myoma, AUB, Chronic pelvic pain, Endometrial hyperplasia, Adenomyosis and endometriosis and post-menopausal bleeding).

Exclusion Criteria

Women with cardiac, hepatic and renal and thromboembolic diseases, Hysterectomy for gynecological malignancies and Obstetric hysterectomies.

Patients were randomized into two groups based on random allocation from computer generated tables

The Two Groups would be Divided as 1:1 ratio

- Group 1: received placebo normal saline.
- Group 2: received 1gram IV tranexemic acid in 100ml normal saline just half an hour before the incision

Method of Collection of Data

Institutional ethical committee clearance was obtained from Kamineni Academy of Medical Sciences and Research Center, LB Nagar, Hyderabad prior to the start of study. A written and informed consent was taken from patients who were participated in the present study.

All women satisfying the inclusion criteria and consenting to participate in the study was randomized into two groups based on random allocation from computed generated tables. Demographic data was collected, relevant findings pertaining to history and clinical examination & diagnosis was documented. The clinical history and the relevant investigations were noted. To achieve a minimum hemoglobin of 10 g/dL before surgery, Packed red blood cell concentrate (PRBC) was transfused 48 hours preoperatively in needed patients. Hemoglobin measurements were repeated on the previous day of surgery in the hospital laboratory. Prior to the day of surgery, anesthesiologists had evaluated all the patients. The patients were advised fasting as per ASA (American society of anesthesiologist's) guidelines.

On arrival in the theatre, twelve-lead ECG (leads II and V5) for heart rate (HR) and ST segment changes,

Pulse oximetry (SpO₂), and non-invasive blood pressure monitors were attached, and baseline readings were recorded. All the patients were administered combined spinal and epidural anesthesia through standard institutional protocol. An anesthesiologist, who was not involved in the study prepared the study solution. The volume of TXA (1 gram) or the same volume of placebo (0.9% NaCl) was added to a 100-mL Normal saline bag. The patients then received the study solution as an intravenous infusion given over 10 minutes.

After 30 minutes, the skin incision was commenced. Perioperative bleeding was managed according to clinical practice. If patients developed signs of hemodynamic instability due to blood loss (heart rate >120 beats/min or a systolic blood pressure <20% of baseline value) despite adequate volume replacement, PRBC was transfused. The mean arterial blood pressure was maintained during surgery. The placement of drains was allowed but not encouraged. Following surgery, the patients were transferred to post-anesthesia care unit for further observation. Postoperative hemoglobin was ascertained at 24 hours. All the patients were closely observed for signs and symptoms of thromboembolic phenomena and other adverse events.

Intra-operative blood loss was estimated by gravimetric method. Drapes, sponges, abdominal pads were weighed beforehand. At the end of the surgery, the drapes, sponges, gauze were weighed again in an electronic weighing machine. Difference

in weight was noted. One mg weight was taken as equivalent to 1ml of blood. Blood loss during surgery was measured as follows. Amount of blood loss (ml) = (weight of sponges, pads and drapes after surgery – weight of sponges, pads and drapes prior to surgery) + amount of blood collected in suction container.

Data Analysis

Data collected was entered into MS-Excel 2013 spreadsheet. The collected data was analyzed using IBM statistical package for social sciences (IBM SPSS) version 23 software (trial version). Continuous variables was reported as mean ± standard deviation (SD) while categorical variables was expressed as absolute values and percentages. Chi-square test and paired t-test was applied to find the significant difference between two groups. P-value less than 0.05 was considered statistically significant.

RESULTS

In group 1, 64% of the study population belongs to 41 – 50 years followed by 20% in 51 – 60 years age group. In group 2, 56% of the study population belongs to 41 – 50 years followed by 30% in 31 – 40 years age group. There was no statistical significant difference of age between two groups. The mean age of subjects in group 1 was 45.8 ± 5.1 yrs and in group 2 was 44.5 ± 6.6 yrs.

Table 1: Age comparison between two groups

Age group	Group 1	Group 2
31 – 40 years	8 (16%)	15 (30%)
41 – 50 years	32 (64%)	28 (56%)
51 – 60 years	10 (20%)	5 (10%)
> 60 years	0	2 (4%)
T total	50 (100%)	50 (100%)
Mean age	45.8 ± 5.1 yrs	44.5 ± 6.6 yrs
Chi-square test = 6.064, df = 3, p-value = 0.109 (Not significant)		

Table 2: Comparison of weight, height and BMI between two groups

	Group 1	Group 2	p-value (un-paired t-test)
Weight (kgs)	54.76 ± 5.09	54.96 ± 4.97	0.843 (NS)
Height (cms)	155.78 ± 2.60	155.98 ± 2.64	0.704 (NS)
BMI (kg/sq.mt)	22.55 ± 1.84	22.58 ± 1.82	0.942 (NS)

The mean weight, height and BMI was comparable between the two groups.

Table 3: Comparison of comorbidities between two groups

Comorbidities	Group 1	Group 2
HTN	12 (24%)	5 (10%)
DM	13 (26%)	7 (14%)
Hypothyroid	4 (8%)	2 (4%)
Others	1 (6%)	3 (6%)

In group 1, 26% cases had diabetes mellitus, 24% had hypertension and 8% had hypothyroidism. In group 2, 14% cases had diabetes mellitus, 10% had hypertension and 4% had hypothyroidism.

Table 4: Comparison of Indications for surgery between two groups

	Group 1	Group 2
AUB	9(18%)	6(12%)
AUB +Adenomyosis	1(2%)	1(2%)
AUB + Dermoid cyst	1(2%)	0
AUB + Fibroid uterus	20(40%)	28(56%)
AUB + Left ovarian cyst	1(2%)	0

Endometrial hyperplasia	4(8%)	1(2%)
Endometriosis	1(2%)	1(2%)
Fibroid uterus	2(4%)	1(2%)
Fibroid uterus +Endometrial polyp	1(2%)	0
Fibroid uterus +Right ovarian cyst	1(2%)	1(2%)
Left ovarian cyst	1(2%)	1(2%)
Multiple fibroids	6(12%)	7(14%)
PMB +Lt Ovarian Cyst	1(2%)	0
Right ovarian cyst	1(2%)	2(4%)
Right ovarian cyst+ Fibroid uterus	1(2%)	0

In both the groups AUB + Fibroid uterus was the most common indication of abdominal hysterectomy. Other common causes in both the groups were AUB and multiple fibroids.

Table 5: Comparison of surgical procedure between two groups

	Group 1	Group 2
TAH + BS	16 (32%)	17 (34%)
TAH + BS + LO	2 (4%)	1 (2%)
TAH + BS + RO	2 (4%)	3 (6%)
TAH + BSO	24 (48%)	20 (40%)
TAH + BSO + B/L DJ Stenting	6 (12%)	9 (18%)
T total	50 (100%)	50 (100%)

Chi-square test = 1.527, df = 4, p-value = 0.822 (Not significant)

Total abdominal hysterectomy with Bilateral salpingo-oophorectomy or total abdominal hysterectomy with Bilateral salpingectomy was the most common surgical procedure conducted in both the groups. In group 1 TAH + BSO + B/L DJ Stenting was done in 12% and in group 2 it was conducted in 18% cases.

The mean Intraoperative Blood loss in group 1 was 244.40 ± 41.11 ml and in group 2 it was 171.40 ± 21.38 ml. There was statistical significant mean difference two groups with less blood loss in group 2.

Table 6: Comparison of pre-op and post-op Hemoglobin between two groups

	Group 1	Group 2	p-value (un-paired t-test)
Pre-op Hb (gm/dl)	10.69 ± 1.04	11.02 ± 0.98	0.108 (NS)
Post-op Hb (gm/dl)	9.31 ± 1.26	10.27 ± 1.01	0.000 (Sig.)
Mean change Hb	1.38 ± 0.37	0.75 ± 0.19	0.000 (Sig.)

Table 7: Duration of surgery and hospital stay

Duration of surgery (minutes)			
	Mean	SD	
Group 1	156.10	23.82	t = -0.240 & p-value = 0.811 (NS) [unpaired t-test]
Group 2	157.20	21.90	
Duration of hospital stay			
	Mean	SD	
Group 1	4.10	0.76	t = 0.838 & p-value = 0.404 (NS) [unpaired t-test]
Group 2	3.96	0.90	

The mean pre-op Hb in group 1 was 10.69 ± 1.04 gm/dl and in group 2 was 11.02 ± 0.98 gm/dl with no statistical significant mean difference between two groups.

The mean post-op Hb in group 1 was 9.31 ± 1.26 gm/dl and in group 2 was 10.27 ± 1.01 gm/dl with a statistical significant mean difference between two groups.

The mean change in hemoglobin was high in group 1 (1.38 ± 0.37) when compared to group 2 (0.75 ± 0.19) with a statistical significant mean difference between two groups.

In group 1, 26% of the cases required blood transfusion while in group 2 only one case (2%) required blood transfusion. There was statistical significant association found between requirement of blood transfusion and TXA with less requirement in TXA group.

The mean duration of surgery (minutes) in group 1 was 156.10 ± 23.82 and in group 2 was 157.20 ± 21.90 with no statistical significant mean difference between two groups. The mean duration of hospital

stay (days) in group 1 was 4.10 ± 0.76 and in group 2 was 3.96 ± 0.90 with no statistical significant mean difference between two groups.

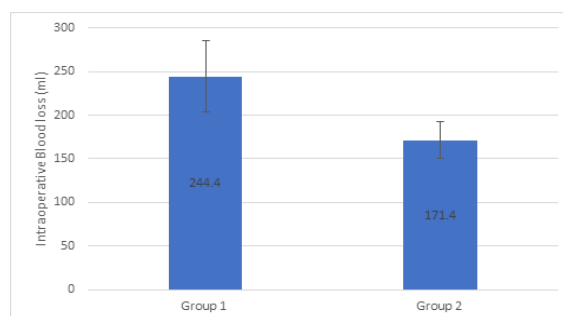


Figure 1: Comparison Intraoperative blood loss between two groups

t = 11.139 & p-value < 0.0001 (Sig.) [unpaired t-test]

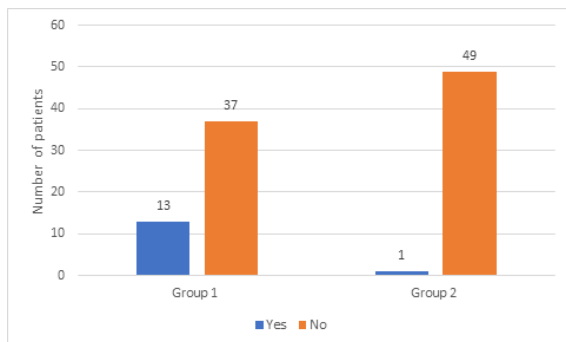


Figure 2: Comparison between groups based on Requirement of blood transfusion

DISCUSSION

Hysterectomy is one of the most frequently performed major gynaecological surgical procedures. Even when the surgery is performed for benign indications, relatively high complication rates have been reported because of perioperative bleeding. With such a high prevalence of anemia in India, majority women present themselves with borderline hemoglobin status and does not tolerate even small volume blood loss as occurring during surgery, necessitating perioperative blood transfusion. Blood is a scarce and costly resource and blood transfusion is not without risks. It has several rare but serious adverse effects. Worldwide, most people do not have access to safe blood. Transfusion can also have potential of adverse immune consequences and end organ effects. A popular conservative approach is to minimize perioperative bleeding through the prophylactic use of antifibrinolytic agents.

TXA, a 4-aminomethyl cyclohexane carboxylic acid exerts an antifibrinolytic effect through the reversible blockade of the lysine-binding sites on the plasminogen molecule, thereby inhibiting clot degradation. It is a competitive inhibitor of plasminogen activation. Compared to other synthetic lysine analogues, TXA has a higher antifibrinolytic efficacy in peripheral tissue and a longer half-life of 3.1 hours.

The mean age of subjects in group 1 was 45.8 ± 5.1 yrs and in group 2 was 44.5 ± 6.6 yrs with no statistical significant difference between two groups. Majority of the cases in both the groups belongs to 41 – 50 years. Topsoee MF et al,^[9] study on anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy, had also reported that the mean age in TA group was 47.9 ± 8.9 yrs and in placebo group was 49.1 ± 9.9 yrs. Anandhan SY et al,^[10] had also reported the mean age in Control Group was 43.64 ± 3.33 yrs while in study group was 42.4 ± 5.7 yrs which was similar to the present study. Similar to the study findings Arthi PN et al,^[11] study had reported that the mean age in TA group was 39.88 yrs and in placebo group was 40.28 yrs. Prasad R et al,^[12] study had reported that the mean age in TA group was 45.9 yrs and in placebo group was 49.3 yrs which was similar to the present study.

The mean weight, height and BMI was comparable between the two groups. The anthropometric measurements was comparable to study conducted by Anandhan SY et al,^[10] Topsoee MF et al,^[9] had also reported that the mean BMI in placebo group was 25.9 and in TA group was 25.0 kg/sq.mt which was similar to the present study. Prasad R et al,^[12] had also reported similar weight distribution in both the groups. Similar to the study findings Arthi PN et al,^[11] study had reported that the mean height and weight was comparable between two groups with no significant difference.

In group 1, 26% cases had diabetes mellitus, 24% had hypertension and 8% had hypothyroidism. In group 2, 14% cases had diabetes mellitus, 10% had hypertension and 4% had hypothyroidism. Overall Topsoee MF et al,^[9] had also reported that 18.85 in TA group and 21.6% in placebo group had comorbidities.

In both the groups AUB + Fibroid uterus was the most common indication of abdominal hysterectomy. Other common causes in both the groups were AUB and multiple fibroids. Arthi PN et al,^[11] study had also reported that fibromyoma followed by Dysfunctional uterine bleeding was the most common indication for abdominal hysterectomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy or total abdominal hysterectomy with bilateral salpingectomy was the most common surgical procedure conducted in both the groups. In group 1 TAH + BSO + B/L DJ Stenting was done in 12% and in group 2 it was conducted in 18% cases.

The mean Intraoperative Blood loss in group 1 was 244.40 ± 41.11 ml and in group 2 it was 171.40 ± 21.38 ml. There was statistical significant mean difference two groups with less blood loss in group 2. Similar to the study findings Anandhan SY et al,^[10] had also reported that the amount of blood loss was lower (283.71 ± 33.06 ml) among the Tranexamic acid group when compared to that of the Control group (579 ± 132.41 ml). They found that the risk of perioperative blood loss was reduced by 40% when the patients were treated with Tranexamic acid. Arthi PN et al,^[11] study had reported that the mean estimated blood loss in group TA and placebo group were 360.16 ± 107.1 ml and 540.22 ± 121.9 ml respectively, there was a significant reduction in mean blood loss in group TA when compared to placebo group and the difference was statistically significant.

The mean pre-op Hb in group 1 was 10.69 ± 1.04 gm/dl and in group 2 was 11.02 ± 0.98 gm/dl with no statistical significant mean difference between two groups. The mean post-op Hb in group 1 was 9.31 ± 1.26 gm/dl and in group 2 was 10.27 ± 1.01 gm/dl with a statistical significant mean difference between two groups. The mean change in hemoglobin was high in group 1 (1.38 ± 0.37) when compared to group 2 (0.75 ± 0.19) with a statistical significant mean difference between two groups. Similar to the study findings Anandhan SY et al,^[10] had reported

that the post-operative hemoglobin level was about 7 to 8.5 gm/dl in the control group which was substantially reduced when compared to the study group where the Post-operative Hemoglobin level was 9.5 to 11 gm/dl. Topsoee MF et al,^[9] had reported that the mean pre-op Hb in placebo group was 8.2 ± 0.7 gm/dl and in TA group was 8.3 ± 0.9 gm/dl which was low when compared to the present study. They also found that the mean drop in hemoglobin was 0.84 gm/dl in placebo and 0.75 gm/dl in TA group. Arthi PN et al,^[11] study had reported that the Pre-op Hemoglobin in placebo group was 11.06 ± 0.54 gm/dl and in TA group was 11.1 ± 0.56 gm/dl which was similar to the present study. They also reported that the postoperative hemoglobin measured at 24 hours postoperatively was significantly lower in placebo group (9.24 ± 0.42 g/dL) when compared to TA group (9.78 ± 0.44 g/dL) which was similar to the present study.

In group 1, 26% of the cases required blood transfusion while in group 2 only one case (2%) required blood transfusion. There was statistical significant association found between requirement of blood transfusion and TXA with less requirement in TXA group. Anandhan SY et al,^[10] had also reported that the blood transfusion done in the study group in the post-operative period was among 4% which was very less when compared the transfusion done in the control group i.e., 30%. Topsoee MF et al,^[9] had reported that 4.2% in placebo group and 1.2% in TA group required blood transfusion with no significant difference between two groups. Similar to the study findings Arthi PN et al,^[11] had reported that TA Group 12% patients required one unit of PRBC transfusion compared to 42% patients in placebo Group and it was statistically significant.

The mean duration of surgery (minutes) in group 1 was 156.10 ± 23.82 and in group 2 was 157.20 ± 21.90 with no statistical significant mean difference between two groups. Similar to the study findings Topsoee MF et al,^[9] had reported that the mean duration of surgery in placebo group was 118 ± 50.2 and in TA group was 114 ± 42.9 minutes with no difference between two groups. However, Arthi PN et al,^[11] had reported that TA group patients had a significantly shorter operating time when compared to placebo group (127.86 versus 148.64 minutes).

The mean duration of hospital stay (days) in group 1 was 4.10 ± 0.76 and in group 2 was 3.96 ± 0.90 with no statistical significant mean difference between two groups. However Topsoee MF et al,^[9] had reported that the mean duration of hospital stay was low in both the groups i.e., in placebo group it was 1.4 ± 1.1 days and in TA group was 1.4 ± 1.1 days. The complications noted with respect to tranexamic acid in the present study are nil.

CONCLUSION

Tranexamic acid has significantly reduced the amount of total blood loss and need of blood transfusion during abdominal hysterectomy with no apparent effect on blood coagulation parameters. A single prophylactic dose of TXA given immediately before surgery seems to be a cost-effective way of reducing the blood loss with adequate safe profile. Overall, our findings lead to the conclusion that TA should be considered as prophylactic treatment in abdominal hysterectomy in order to reduce the risk of substantial bleeding and reoperations.

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