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The effect of prophylactic use of intravenous tranexamic acid in hysterectomy of benign diseases

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Abstract
Background: Hysterectomy is one of the frequently performed major gynecological surgical procedures for various uterine pathologies. TXA has already proven to reduce the uterine blood loss in non-surgical aspect. Various studies had revealed that TXA resulted in a significant reduction of menstrual blood loss in menorrhagic women while not increasing the risk of thrombosis and had been used successfully to treat menorrhagia associated with a number of coagulopathies.
Material and Methods: This prospective study conducted on 200 women in Department of Obstetrics &for one year period. They were divided in two groups: Cases: (n=100; women receiving prophylactic Tranexamic Acid) and Control: (n=100; women receiving saline). Estimated the amount of blood loss during surgery. The amount of blood loss during surgery were calculated Estimation of weight of dry towels and mops before autoclaving is noted.
Results: Most common age group among Cases and Control was 36-45 years [45% vs. 52%]. Age among. Mean age among cases group (46.69±7.51 years) was significantly higher compared to control study cohort (41.75±7.72). Comparing the duration of operation among both the study groups revealed that time taken for hysterectomy took longer time among Cases (9136.69±26.49) as compared to Control (131.61±26.75) (p=0.004). Post operative hemoglobin level was significantly higher among Case (11.26±12.03) as compared to Control (8.56±1.01). Comparing post operative complications revealed that among both the groups post operative complications were comparable. Use of topical hemostatics was higher among the control (77%) as compared to Cases (37%).
Conclusion: Prophylactic treatment with TA in relation to benign elective hysterectomy reduces the overall total blood loss, and the risk of reoperations owing to postoperative hemorrhage as revealed by higher hemoglobin level among cases.

Keywords: Prophylactic, intravenous, tranexamic acid and hysterectomy

Introduction

Hysterectomy is one of the frequently performed major gynecological surgical procedures for various uterine pathologies. Even when the indication for the procedure is benign, relatively high complication rates have been reported. And the most common cause of complications is perioperative bleeding. 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 [1].

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 [2].

As reported by Global nutrition report 2017 the burden of anemia in India is alarming and majority of women presenting for hysterectomy are already anemic. The perioperative blood loss puts the anemic women at risk of death and also increases the recovery time. Due to prevalence anemia, perioperative blood transfusion become more of an additional requirement in patients [3]

TXA has already proven to reduce the uterine blood loss in non-surgical aspect. Various studies had revealed that TXA resulted in a significant reduction of menstrual blood loss in menorrhagic women while not increasing the risk of thrombosis and had been used successfully to treat menorrhagia associated with a number of coagulopathies [4].

TXA gained worldwide recognition and acceptance in the 2010 Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial, a multinational randomized placebo-controlled trial of TXA in adult trauma patients with significant bleeding [5].

Absolute contraindications for TXA include hypersensitivity to the drug, pre-existing active thromboembolic disorder, disseminated intravascular coagulation, renal failure, coronary or vascular stent placed within one year, acquired defective colour vision and acute subarachnoid hemorrhage. Relative contraindications include uncontrolled seizure disorder, renal dysfunction, high risk of venous or arterial thrombosis, or pre-existing coagulopathy or anticoagulant treatment [6].

Materials and Methods

This prospective study conducted on 200 women in Department of Obstetrics & Gynaecology at Kamla Raja Hospital and J.A. Group of Hospital at G.R. Medical College, Gwalior (M.P.) for one year period. They were divided in two groups: Cases: (n=100; women receiving prophylactic Tranexamic Acid) and Control: (n=100; women receiving saline).

Patient undergoing benign hysterectomy were included in the study and family history of thromboembolism, thrombophilia, previous or active thromboembolic disease, malignant disease, patients on anti coagulant drugs, ascites and ovarian cyst which may likely to rupture/rupture during surgery were excluded from study.

Methodology

Estimated the amount of blood loss during surgery. The amount of blood loss during surgery were calculated Estimation of weight of dry towels and mops before autoclaving is noted. The amount of saline used during surgery in surgical field is noted. The weight of wet mops will be measured (in gms).The estimated blood loss can be calculated by weight of wet mops-weight of dry mops +saline in gms. This value in gms is converted to volume (ml) by following formula

Volume=weight/density.

Any additional blood collected in suction machine/tray, etc

Statistical analysis

All the data analysis was done using IBM SPSS ver. 20 Software. Cross tabulation and frequency distribution was used to prepare tables. Microsoft office 2010 was used to prepare the graphs. Paired sample t test was used to compare the mean where as categorical data was compare using Chi square test. Level of significance was assessed at 5%.

Results

Table 1: Comparing age

Age group	Case (%)	Control (%)	P value
25-35	3	16	0.685
36-45	27	17	
46-55	43	42	
>55	27	25	
Total	100	100	

Most common age group among Case and Control group was 46-55 years (43% vs. 42% respectively).Second most common age group was 36-45(27%) and >55 years(27%) in Cases and >55 years (25%) in Control group. The comparison was statistically insignificant (p=0.685).

Table 2: Comparing surgery performed

Surgery performed	Case (%)	Control (%)	P value
TAH with BLSO	1	1	
VH with Cystocele & Rectocele repair	6	6	
NDVH	5	5	
TAH	40	40	
TAH with BLSO	9	9	
VH	33	33	
VH with Cystocele repair	6	6	
Total	100	100	

Most common surgery performed among Cases and Control was TAH (40% in each group). VH was the second most common surgery performed in both the groups (33%).

Table 3: Comparing pre-operative hemoglobin

Pre-operative hemoglobin	Mean	N	Std. Deviation	P value
Cases	10.11	100	0.77	0.396
Control	10.19	100	0.83	

Preoperative hemoglobin was comparable between both the groups (10.11±0.77 in Case and10.19±0.83 in Control group) (p=0.396).and the result was found to be statistically significant.

Table 4: Comparing post-operative hemoglobin

Post-operative hemoglobin	Mean	N	Std. Deviation	P value
Cases	9.56	100	0.65	<0.001
Control	8.29	100	1.01	

Post-operative hemoglobin was significantly higher in Cases (9.56±0.65) as compared to Control group (8.29±1.01) (p<0.001) and result was found to be statistically significant.

Table 5: Comparing pre and post hemoglobin level between groups

	Hemoglobin level	Mean	N	Std. Deviation	P value
Case	Pre-operative HB	10.11	100	0.77	<0.001
	Post-operative HB	9.56	100	0.65	
Control	Pre-operative HB	10.19	100	0.83	<0.001
	Post-operative HB	8.29	100	1.01	

Comparing pre and post operative hemoglobin among Cases and Control revealed that post operative (10.11±0.77) hemoglobin was statistically significantly lower as compared to preoperative hemoglobin (9.56±0.65) (p<0.001). Similarly among Control group post operative (10.19±0.83) hemoglobin was significantly lower as compared to preoperative hemoglobin (8.29±1.01) (p<0.001).

Table 6: Comparing blood transfusion

Blood transfusion	Mean	N	Std. Deviation	P value
Case	0.64	100	0.57	<0.001
Control	1.36	100	0.74	

No of blood transfusion were statistically significantly lower in Cases (0.64±0.57) compared to Control group (1.36±0.74) (p<0.001).

Table 7: Comparing number of MOPS used

No. of MOPS used	Mean	N	Std. Deviation	P value
Case	2.14	100	4.47	0.605
Control	1.91	100	0.84	

Number of MOPS used were similar among Cases (2.14±4.47) and Control (1.91±0.84).

Table 8: Comparing Total amount of Blood loss

Total amount of Blood loss	Mean	N	Std. Deviation	P value
Case	602.31	100	175.88	<0.001
Control	844.64	100	211.95	

Total amount of Blood loss were statistically significantly lower in Cases (602.31±175.88) compared to Control group (844.64±211.95) (p<0.001).

Table 9: Post operative complications

Post operative complication	Cases (%)	Control (%)	P value
No	88	88	NA
Yes	12	12	
Total	100	100	

Post operative complication were similar among both the groups.

Table 10: Use of topical hemostatics

Use of topical hemostatics	Case (%)	Control (%)	P value
No	66	18	<0.001
Yes	34	82	
Total	100	100	

Use of topical hemostatics was statistically significantly more in Control (82%) as compared to Cases (34%) (p<0.001).

Table 11: Blood transfusion with diagnosis

Diagnosis		Cases	Control
DUB	Mean	0.69	1.56
	N	32	32
	Std. Deviation	0.59	0.80
Ut. Fibroid	Mean	.78	1.78
	N	18	18
	Std. Deviation	.428	0.80
UV Prolapse	Mean	.56	1.08
	N	50	50
	Std. Deviation	.611	0.56
Total	Mean	.64	1.36
	N	100	100
	Std. Deviation	.578	0.74
P value		0.336	<0.001

When we compared the blood transfusion with diagnosis we found that among cases blood transfusion was similar among all the of diagnosis (p=0.336) whereasblood transfusion was significantly higher in patients withUt.Fibroid(1.78±0.80) compared to DUB(1.56±0.80) and UV prolapsed (1.08±0.56)(p<0.001).

Table 13: Comparing Diagnosis with blood loss

Diagnosis		Cases	Control
DUB	Mean	730.44	980.94
	N	32	32
	Std. Deviation	159.57	219.99
Ut. Fibroid	Mean	682.22	974.44
	N	18	18
	Std. Deviation	184.15	190.33
UV Prolapse	Mean	491.54	710.68
	N	50	50
	Std. Deviation	95.07	104.64
Total	Mean	602.31	844.64
	N	100	100
	Std. Deviation	175.88	211.95
P value		0.576	<0.001

When we compared the blood loss with diagnosis we found that among cases blood loss in each diagnosis was similar (p=0.576) whereas blood loss was significantly higher in patients with DUB (980.94±0219.99) compared to Ut fibroid (974.44±190.33) and UV prolapsed (710.68±104.64)(p<0.001).

Table 14: Comparing diagnosis with pre post hemoglobin in cases

Diagnosis		Pre-operative	Post-operative
DUB	Mean	10.17	9.53
	N	32	32
	Std. Deviation	0.71	0.54
Ut. Fibroid	Mean	10.33	9.55
	N	18	18
	Std. Deviation	0.96	0.73
UV Prolapse	Mean	10.00	9.59
	N	50	50
	Std. Deviation	0.71	0.69
Total	Mean	10.11	9.56
	N	100	100
	Std. Deviation	0.77	0.65
P value		0.267	0.928

Pre and post operative hemoglobin were comparable among all type of diagnosis (p>0.05).and it was found to be statistically significant.

Table 15: Comparing diagnosis with Use of topical hemostatics in cases

Use of topical Hemostatics	Diagnosis			Total	P value
	DUB	Ut. Fibroid	UV Prolapse		
No	19	14	33	66	0.419
Yes	13	4	17	34	
Total	32	18	50	100	

Use of topical hemostatic was similar among all type of diagnosis (p=0.419).

Discussion

Massive bleeding after surgical interventions or severe trauma continues to be one of the most frequent life-threatening emergencies. Trauma-associated hemorrhagic shock is the most frequent cause of avoidable deaths, with hyperfibrinolysis (HF) at the time of hospitalization having been identified as an independent predictor of mortality (Pabinger I, 2017) [7].

A total of 200 participants were included. All hysterectomies were performed under general anesthesia and all participants received preoperative antibiotic and anticoagulation treatment 4-

12 hours postoperatively, according to national guidelines (Dansk Hysterektomi Database 2009) [8]. The vast majority of the hysterectomies were performed by a senior gynecologist assisted by a resident under training, but no data concerning the surgeon's experience were collected.

Most common age group among Cases and Control was 36-45 years [45% vs. 52%]. Age among Case and Control were equally distributed (p=0.684). In a similar study by Shady NW *et al.,* (2018) [9] reported that there was no significant difference between the control and Case group with respect to their age (p>0.05).

In present study comparing the duration of operation among both the study groups revealed that time taken for hysterectomy took longer time among Cases (136.69±26.49) as compared to Control (131.61±26.75) (p=0.004). Shady NW *et al.,* (2018) [9] found that there was a significant reduction in operative time in group II (IV Tranexamic Acid) compared with control group and group III (Topical Tranexamic Acid) (p = .0001 and .0001).

In present study preoperative hemoglobin level were comparable among the study groups (p=0.879). Shady *et al.,* (2018) [9] studied 105 women and reported that preoperative hemoglobin was comparable in all the groups.

In present study post operative hemoglobin level was significantly higher among Case (11.26±12.03) as compared to Control (8.56±1.01) (p=0.030) Shady NW *et al.,* (2018) [9] showed no significant difference between the three groups (Control, IV and Topical Tranexamic Acid Group) related to their post-operative hemoglobin (p=0.752).

Among control group hemoglobin level was significantly decreased from 10.25±0.77 preoperatively to 8.56±1.01postoperatively (-1.69gm%) (p<0.001) whereas among Case mean hemoglobin was insignificantly increases from 10.25±0.81 preoperatively to11.26±12.03 postoperatively (1.01 gm%) (p=0.404) In agreement to present study Bhavana G *et al.,* (2016) [10] reported that drop in post operative hemoglobin in study group (preoperative;11.2±1.28, post operative; 10.5± 1.25) was not significant where as in control group(preoperative;11.1±1.24, post operative; 9.9± 1.14) was significant.

In present study comparing the number of blood transfusion given to both the groups revealed that Control group(1.62±0.77 times) has received more blood transfusions as compared to case (0.76±1.16 time) (p<0.001) Shady NW *et al.,* (2018) [9] studied 105 women and reported that the incidence of blood transfusion was increased in control group, 19 (54.3%) patients compared with 6 (17.1%) patients in group II (IV Tranexamic acid), and 7 (20%) patients in group III (Topical Tranexamic Acid) (P = .001 and 0.003 respectively). Topsoee MF *et al.,* (2016) [11] reported that the decrease in hemoglobin level and the proportion of participants needing blood transfusions during their primary hospitalization tended to be lower in the TA-group, although not reaching statistical significance. A large Cochrane review on antifibrinolytics and surgery reported that TA significantly reduced the risk of blood transfusions (Henry DA 2011) [12] which is in agreement to present study findings where control group has received more blood transfusions as compared to case. Similar results were found in the systematic review of Ker K *et al.,* (2012) [13].

In present study, blood loss was higher among Control group (965.70±210.58) as compared to Cases (717.54±174.01) (p<0.001). Similar results were depicted by BhavanaG *et al.,* (2016) [10] who did a randomized controlled trial among 200 term women and reported mean blood loss of 511.3±164.456 ml in TA 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 (Bhavana G *et al.,* 2016) [10]. In agreement to present study Shady *et al.,* did a randomized double-blind placebo-controlled trial on 105 women undergoing abdominal myomectomy after dividing them in to three groups: group 1 [35 patients received 110 ml normal saline IV just before skin insion], group 2 [35 patients received 1 g tranexamic acid (2 ampoules of kapron 500 mg 5 ml Amoun company) IV just before skin in scion] and group 3 [35 patients received 2 g topical tranexamic acid (4 ampoules of kapron 500 mg 5 ml) applied on myoma bed after myomectomy] and reported that Both Group II (IV tranexamic acid) and Group III (topical tranexamic acid application) showed great reduction in intraoperative and post-operative blood loss (blood in the intraabdominal drain) compared with Group I (placebo group), (P = .0001, 0.0001, 0.0001, 0.0001), so the overall estimated blood loss in group II and III showed highly reduction compared with group I (P = .0001, .0001). (Shady NW *et al.,* 2018) [9]. In the study conducted by GohelM *et al.,* (2007) [14] also showed that tranexamic acid had significantly reduced bleeding in TA group as compared to control group. Similar reports were revealed by Gungorduck *et al.,* who also reported that mean estimated blood loss was significantly lower in women treated with TA compared with women in the placebo group (Gungorduk K 2011) [15].TopsoeeMF *et al.,* (2016) [11] studied investigate the antihemorrhagic effect of prophylactic tranexamic acid in 332 women undergoing elective benign hysterectomy. Topsoee MF *et al.,* (2016) [11] reported that both estimated blood lossby the surgeon (EBLs) and estimated blood loss by weight (EBLw) were significantly reduced in the TA group compared to the placebo group (EBLs: 98.4 vs134.8 mL, P =0.006 and EBLw: 100 vs 166 mL, P=0.004). Also blood loss was significantly reduced in the abdominal hysterectomy group and the laparoscopic/robotic assisted laparoscopic hysterectomy group. Further strengthening the findings of present study Topsoee MF *et al.,* (2016) [11] in a similar study reported that the incidence of blood loss ≥500 mL was significantly lower in the TA group compared to the placebo group The corresponding relative risk of blood loss ≥500 mL in the TA group (6/164) compared with the placebo group (21/166) was 0.29 (95% CI, 0.12-0.70) (Topsoee MF 2016) [11]. In the meta-analysis by Ker K *et al.,* (2013) [13] it was found that TA reduced blood loss by 34% in relation to all types of surgery. These findings were comparable with our results. Strengthening the findings of present study WaskowskiJ *et al.,* (2018) [16] in their review reported that TXA reduces perioperative blood loss and transfusion requirements in several randomized controlled trials. TA is beneficial in complex spine surgery and reconstructive surgery (e. g. craniosynostosis in children). Single RCTs showed benefits of TXA in abdominal hysterectomy, open prostatectomy, liver surgery and actively bleeding trauma patients. (Waskowski J 2018) [16] WOMEN trial recruited 20 060 women aged 16 years and older with a clinical diagnosis of post-partum haemorrhage and reported that death due to bleeding was significantly reduced in women given tranexamic acid (155 [1·5%] of 10 036 patients *vs* 191 [1·9%] of 9985 in the placebo group and concluded that TA reduces death due to bleeding in women with post-partum haemorrhage with no adverse effects (WOMAN Trial Collaborators 2017) [17].

Use of topical hemostatics was higher among the control (77%) as compared to Cases (37%) (p=0.012) Contrary to present study reports of Topsoee MF *et al.,* (2016) [11] showed that use of intraoperative topical hemostatics was not significantly different in both the groups which is in agreement to the finds of the

present study.

In present study comparing post operative complications revealed that among both the groups post operative complications were comparable (p=0.989) In agreement to present study findings post operative complications reported by Shady *et al.,* in both Control and Tranexamic acid group in terms of the incidence of nausea, vomiting, and diarrhea were comparable (Shady NW *et al.,* 2018) [9]. TopsoeeMF *et al.,* (2016) [11] in a similar study reported that diagnosis of or readmission for postoperative hematoma/ hemorrhage or abdominal pain did not reach significant difference between both the groups. No incidence of thromboembolic event or mortality emerged in any of the participants which is in agreement to present study findings where post operative complication were comparable between both the groups.

Present study has few limitations. First cross sectional nature of the present study was the main limitation which restricts the use of present study findings to large population. Second is the small sample size; a large randomize clinical trial is required to strengthen the present study findings.

Conclusion

Our results indicate that prophylactic treatment with TA in relation to benign elective hysterectomy reduces the overall total blood loss, and the risk of reoperations owing to postoperative hemorrhage as revealed by higher hemoglobin level among cases. No incidence of thromboembolic events or death was observed in any of the groups.

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