Thai Journal of Obstetrics and Gynaecology
May 2021, Vol. 29, No. 3, pp. 151-158

GYNAECOLOGY

Single Dose of Intravenous Tranexamic Acid for Reduce Blood Loss from Surgical Staging in Endometrial Cancer: A randomized controlled trial

Thanittha Sirithunyalak, M.D.*,
Kitiya Wuttibenjarussamee, M.D.*,
Maleechat Sripipattanakul, M.D.*,
Thumwadee Tangsiriwatthana, M.D.*

** Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand*

ABSTRACT

Objectives: To study the efficacy of single dose of intravenous tranexamic acid administration in reducing of intraoperative blood loss during surgical staging in endometrial cancer.

Materials and Methods: A randomized double-blinded, placebo-controlled trial was conducted. Thirty-four women who were diagnosed of endometrial cancer by tissue pathology and scheduled for surgical staging by gynecologic oncologists at Khon Kaen Hospital from November 2018 to May 2019 were randomized into two groups; 17 were allocated to receive intravenous tranexamic acid and 17 received placebo. Intraoperative measurement blood loss was recorded and analyzed.

Results: Both groups had similar baseline characteristics. The result of study presented that the measurement intraoperative blood loss in intravenous tranexamic acid group was significantly lower than control group (295.88 (256.01-335.87) vs. 613.94 (535.9-691.98) ml, $p < 0.001$) with mean difference was 318.05 ± 87.63 ml (95% confidence interval (CI) 139.54-496.56). There had 2 and 10 cases of intraoperative blood loss ≥ 500 ml in intravenous tranexamic acid and control group, respectively (number need to treat = 12.5 and relative risk 0.24; 95%CI 0.06-0.89, $p = 0.004$).

Conclusion: Single dose of intravenous tranexamic acid given 15 minutes before surgery could significantly reduce measurement blood loss in surgical staging for endometrial cancer without serious adverse side effect.

Keywords: endometrial cancer, surgical staging, tranexamic acid, intraoperative blood loss.

Correspondence to: *Thanittha Sirithunyalak, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen 40000, Thailand. Email: gowngown13@gmail.com*

Received: 29 September 2019, **Revised:** 17 December 2019, **Accepted:** 24 December 2019

ยาฉีดทรานเนคซามิคเพื่อลดการเสียเลือดขณะผ่าตัดกำหนดระยะโรคมะเร็งเยื่อบุโพรงมดลูก การทดลองแบบสุ่ม

ธนิษฐา ศิริธัญญาลักษณ์, กิติยา วุฒิเบญจรัศมี, มาลีชาติ ศรีพิพัฒนกุล, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษายาฉีดทรานเนคซามิคเพื่อลดการเสียเลือดขณะผ่าตัดกำหนดระยะโรคมะเร็งเยื่อบุโพรงมดลูก*

วัสดุและวิธีการ: *การทำวิจัยแบบสุ่มในผู้ป่วยหญิงที่ได้รับการวินิจฉัยเป็นโรคมะเร็งเยื่อบุโพรงมดลูกจากผลชิ้นเนื้อจำนวน 34 คน ที่เข้ารับการผ่าตัดกำหนดระยะที่โรงพยาบาลขอนแก่น ระหว่างเดือนพฤศจิกายน 2561 ถึง เดือนพฤษภาคม 2562 โดยอาจารย์ผู้เชี่ยวชาญทางด้านมะเร็งนรีเวชวิทยา ได้รับการสุ่มแบ่งเป็นสองกลุ่มคือ กลุ่มที่ได้รับยาทรานเนคซามิค และกลุ่มที่ได้รับยาหลอก โดยวัดปริมาณการเสียเลือดระหว่างผ่าตัดในกลุ่มที่ได้รับยาทรานเนคซามิคและยาหลอก*

ผลการศึกษา: *ลักษณะทางประชากรทั้งสองกลุ่มไม่แตกต่างกัน โดยกลุ่มที่ได้รับยาทรานเนคซามิคมีการเสียเลือดระหว่างการผ่าตัด 295.88 (256.01-335.87) มิลลิลิตร ส่วนในกลุ่มที่ได้รับยาหลอกมีการเสียเลือดระหว่างผ่าตัด 613.94 (535.9-691.98) มิลลิลิตร ซึ่งมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ค่าเฉลี่ยของความแตกต่างเท่ากับ 318.05 ± 87.63 มิลลิลิตร (95% confidence interval (CI) 139.54-496.56, $p < 0.001$) และการเสียเลือดขณะผ่าตัดที่มีปริมาณมากกว่าหรือเท่ากับ 500 มิลลิลิตร (number need to treat = 12.5 และ relative risk 0.24; 95%CI 0.06-0.89, $p = 0.004$).*

สรุป: *การให้ยาทรานเนคซามิคก่อนเริ่มผ่าตัด 15 นาทีสามารถลดปริมาณการเสียเลือดในการผ่าตัดกำหนดระยะในโรคมะเร็งเยื่อบุโพรงมดลูกได้อย่างมีนัยสำคัญทางสถิติและไม่พบผลข้างเคียงที่รุนแรง*

คำสำคัญ: *มะเร็งเยื่อบุโพรงมดลูก, การจัดเตรียมการผ่าตัด, กรด tranexamic, การสูญเสียเลือดระหว่างการผ่าตัด*

Introduction

Endometrial cancer is the third most common malignancy of female genital gynecological cancers. In general, 2-3% of women can develop endometrial cancer during lifetime[1]. The percentage of 5-year survival rate in endometrial cancer is approximately 75%[1]. Surgical staging is a part of standard treatment including hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, peritoneal cytology and omentectomy[1, 2]. Surgical staging usually causes intraoperative bleeding and half of women who undergoing this operation require blood transfusion[1, 2].

Tranexamic acid is an antifibrinolytic drug. It works by preventing blood clots from breaking down and decreases activity of complement and consumption of C1esterase inhibitor. One of the components of this acid is a synthetic compound derived from amino acid, lysine and it can be activated by attach to the lysine-binding sites on plasminogen. Consequently, plasmin formation is inhibited, and the plasminogen is displaced from the fibrin surface to prevent fibrinogeolysis leading to protect exiting blood clots destruction[3].

Tranexamic acid also exerting an anti-inflammatory and improve platelet function. When it is administered intravenously, plasma concentration time curve shows a triexponential decay with a half-life 2 hours for the terminal elimination phase. The main route for excretion is via the urinary system about 90% at 24 hours after intravenous administration of 15 mg/kg body weight. The concentration of tranexamic acid remains in different tissues around 17 hours and remains in serum 7-8 hours[3].

Side effects of tranexamic acid are rare, some common side effects include gastrointestinal tract; nausea, vomiting, diarrhea, the skin and subcutaneous tissue; allergic skin reactions, thromboembolic events, impaired color vision and other visual disturbances. Tranexamic acid is not increase risk of serious thrombosis including pulmonary embolism and deep vein thrombosis[3, 4].

However, the aspect of gynecological cancer surgery, particularly endometrial cancer, the effect of tranexamic acid on blood loss and blood transfusion requirements is unclear and neovascularization occurs only in malignancy and lead to accelerate excessive bleeding in surgery. Surgical staging usually causes intraoperative bleeding and half of women who undergoing this operation require blood transfusion as mentioned above. Therefore, the authors would like to conduct this study to determine the efficacy of tranexamic acid in reducing intraoperative blood loss during surgical staging in endometrial cancer patients.

Materials and Methods

A randomized double-blind, placebo-controlled study comparing a single dose of tranexamic acid with placebo given intravenously 15 minutes before the operation in patients who were diagnosed of endometrial cancer by tissue pathology and scheduled for surgical staging surgery at Khon Kaen Hospital from November 2018 to May 2019 by gynecologic oncologists. This study was approved by Khon Kaen Hospital Institute Review Board in Human Research and individual informed consent was obtained.

The participants were randomly allocated into two groups: study and control group by computer-generated in 1:1 ratio. Study group received 15mg/kg of tranexamic acid in bottle of normal saline 100 ml given intravenously 15 minutes before operation. Control group received 15 mg/kg of normal saline solution in bottle of normal saline 100 ml with identical in appearance. Study drug and placebo were prepared by nurse at gynecologic ward. The randomization list was kept in a sealed opaque envelope. Study drugs and placebo were administered by anesthesiologic nurses or anesthesiologists at operative room. All participants in this study did not routinely receive antifibrinolytic agent for venous thromboembolism prophylaxis.

Inclusion criteria were women aged 18 years old or more who were diagnosed of endometrial cancer by tissue pathology and scheduled for surgical staging. Exclusion criteria were allergy to tranexamic acid, treatment with anticoagulants within seven days before surgery, history of venous thromboembolism from

history taking and physical examination, history of myocardial infarction or unstable angina or coronary heart disease within one year, previous prostatic valve replacement, reduced renal function with plasma creatinine levels above 250 umol/l or 2.8 mg/dl or glomerular filtration rate (GFR) < 30 ml/min, history of neoadjuvant chemotherapy, radiation therapy and history of bleeding disorders.

All participants had routine preoperative evaluation. Surgery was performed under standard general anesthesia. All operations were performed by gynecological oncologists. Intraoperative blood loss was measured by adding blood volume in suction bottles to the difference in weight between the dry and wet swabs and gauzes before and after operation (1 gm is equivalent to 1 ml). Any intraoperative and postoperative transfusion were recorded. Hemoglobin level was determined by preoperative evaluation and 24 hours after surgery. Postoperative diagnosis was confirmed by pathological report.

The sample size was calculated based on the data from pilot study. We used 90% power to detect the difference of the primary outcome and p value less than 0.05 was statistically significant and 15% drop out was added. The totally of 34 participants (17 in each group) were enrolled into the study.

Primary outcome was measurement blood loss by adding blood volume in suction bottles to the difference in weight between the dry and wet swabs and gauzes before and after operation and incidence of intraoperative blood loss ≥ 500 ml.

Secondary outcomes were incidence of blood transfusions, operative time, side effects, difference of hemoglobin level, length of hospital stay and complications.

Statistical analysis was performed using STATA version 14.1. Selection bias was controlled by using a computer-generated randomization in 1:1 ratio. Confounding bias controlled by restriction in inclusion-exclusion criteria and randomization process to make these factors balance between two groups. Categorical variables were analyzed by chi-square test. Differences in continuous variables were analyzed with Mann-Whitney U test and student-t test due to characteristics of data distribution and were presented as mean ± standard deviation, median and interquartile range (IQR).

Results

There were 38 women who were diagnosed of endometrial cancer by tissue pathology and scheduled for surgical staging. The sample size was calculated based on the data from pilot study with 90% power at the 5% level of significance. Four women did not meet the criteria, one due to history of radiation therapy and three dues to baseline creatinine above 2.8 mg/dl. Therefore, 34 women were recruited into the study, 17 in each group (Fig. 1).

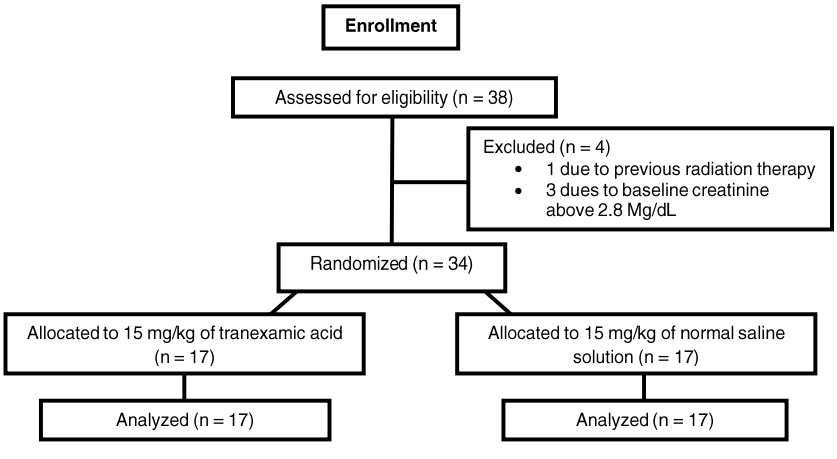

Fig. 1. Flow chart of participants in the study.

Both groups had similar baseline characteristics including age, body mass index, history of previous surgery, preoperative hemoglobin level, underlying disease such as diabetes mellitus and essential hypertension and International Federation of Gynecology and Obstetrics (FIGO) staging of endometrial cancer[1] (Table 1).

Table 1. Baseline characteristics of participants.

Characteristic	Tranexamic acid (n=17)	Placebo (n=17)	p value
Age (years) Mean ± SD	60.65 ± 10.96	56.82 ± 6.09	0.47
BMI (kg/m^2) Mean ± SD	23.77 ± 3.47	24.58 ± 3.93	0.62
Previous surgery (n, %)	8 (47.06)	9 (52.94)	0.73
Preoperative Hb level (g/dl)	11.64 (10.31-12.97)	11.87 (10.39-13.35)	0.63
Diabetes mellitus (n, %)	7 (41.18)	5 (29.41)	0.47
Essential hypertension (n, %)	7 (41.18)	8 (47.06)	0.73
Stage FIGO staging (n, %)			
- I	8 (47.06)	9 (52.94)	0.73
- II	2 (11.76)	2 (11.76)	1.00
- III	7 (41.18)	6 (35.29)	0.72
- IV	0	0	-
Cell type (n, %)			
- Endometrioid	15 (88.24)	14 (82.35)	0.43
- Non endometroid	2 (11.76)	3 (17.65)	0.31

Data are presented as Mean ± SD, median (interquartile range) or n (%)
SD: Standard deviation,
BMI: Body Mass Index,
Hb: Hemoglobin,
FIGO: International Federation of Gynecology and Obstetrics

Measurement intraoperative blood loss in intravenous tranexamic acid group was significantly lower than control group 295.88 (256.01-335.87) versus 613.94 (535.9-691.98) ml ($p < 0.001$) with mean difference was 318.05 ± 87.63 ml (95% confidence interval (CI) 139.54-496.56). There had 2 and 10 cases of participants who had intraoperative blood loss over 500 ml in tranexamic acid group and control group, respectively (number need to treat (NNT) = 12.5, relative risk (RR) 0.24; 95%CI 0.06-0.89, $p = 0.004$) (Table 2).

Other surgical outcomes including difference of hemoglobin level, blood transfusion, duration of surgery, duration of hospital stay were not significantly different between groups (Table 2). One of the participants in control group had undergone re-operation due to rebleeding. The most common adverse effect found in both groups was nausea vomiting (23.53% vs. 11.76%) but without significant difference ($p = 0.36$) (Table 2).

Table 2. Primary and secondary outcomes.

Characteristic	Tranexamic acid (n=17)	Placebo (n=17)	p value
Measurement blood loss (ml), median (IQR)	295.88 (256.01-335.87)	613.94 (535.9-691.98)	0.001
Total blood loss ≥ 500 ml (n, %)	2 (11.76)	10 (58.82)	0.004
Difference of hemoglobin level (g/dl), median (IQR)	0.15 (-0.85-1.15)	0.61 (0.33 - 1.55)	0.12
Blood transfusion (n, %)	0	2 (11.76)	-
Operative times (min), median (IQR)	162.88 (129.42-196.34)	166.59 (113.66-219.52)	0.90
Length of hospital stay(day), median (IQR)	6.52 (4.07-8.97)	6.76 (4.94-8.58)	0.45
Complications			
Re-operations due to bleeding (n, %)	0	1 (5.88)	0.31
Infections (n, %)	2 (11.76)	1 (5.88)	0.54
Side effect			
Nausea and vomiting (n, %)	2 (11.76)	4 (23.53)	0.36

Data are presented as median (interquartile range, IQR) or n (%)

Discussion

The current study is the first randomized controlled trial that investigating the efficacy of tranexamic acid in reducing intraoperative blood loss during surgical staging in endometrial cancer and the results showed that a single dose of tranexamic acid given 15 minutes before surgery significantly decreases intraoperative blood loss when compared with placebo. Our finding was consistent with Lundin, et al[4] who conducted a randomized double-blind, placebo-controlled, multicenter study about single-dose tranexamic acid in advanced ovarian cancer surgery and revealed that it could reduce blood loss and transfusions. The estimated blood loss and blood transfusion were significantly lower in the intervention group compared with the placebo group. Median total blood loss was 520 and 730 mL, respectively (p = 0.03), and 30% and 44%, respectively received transfusions (odds ratio 0.44; upper 95% CI 0.97; p = 0.02) and there was no serious adverse side effect found. Topsoee, et al[5] conducted anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy founded that intraoperative estimated blood loss was lower 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 = 0.006, p = 0.006 and 100.0 mL vs 166.0 mL, p = 0.004) and neither serious events nor mortality were observed in both groups. When intraoperative blood loss ≥ 500 ml was taking into consideration, we founded that tranexamic acid can significantly reduce massive blood loss better than placebo. The number needed to treat (NNT) was 12.5, which means that we can prevent one patient from massive intraoperative blood loos in every 13 patients. This finding was more effective than the results of Topsoee, et al[5] who studied the efficacy of tranexamic acid in benign hysterectomy and founded that tranexamic acid could reduce blood loss with NNT of 24 when compared to placebo. This might be explained by the radicality of surgical procedures between benign and malignancy surgeries which surgical staging in malignant surgery tends to have more amount of blood loss. Therefore, in our study, the difference in total blood

loss among groups was obviously detected.

There was a previously published randomized trials of tranexamic acid deal with prostate cancer surgery that suggested their intraoperative treatment with low dose tranexamic acid was safe and effective in declining the rate of perioperative blood transfusions in patients undergoing radical retropubic prostatectomy. They found that patients who needed transfusion were 34% in the tranexamic acid group and 55% in the control group (absolute reduction in transfusion rate 21% (95% CI 7% to 34%); relative risk of receiving transfusions for patients treated with tranexamic acid 0.62 (0.45 to 0.85); number needed to treat 5 (3 to 14); p = 0.004)[6]. Cochrane review[7] on antifibrinolytics and surgeries showed that tranexamic acid significantly reduced the risk of blood transfusions with RR 0.61; 95% CI, 0.53-0.70.7 consistent with the results of Ker, et al[8] which conducted the systematic review of the same comparison with RR of 0.62; 95% CI, 0.58-0.65. Although we conducted this antifibrinolytic drug in gynecologic surgery, none of the participant who received tranexamic acid had blood transfusion compared with 2 of 17 in control group. This finding confirmed the effect of tranexamic acid in the aspect of reducing blood loss. In case of the incidence of reoperation Cochrane review showed no difference in re-operation in tranexamic acid and control group in another surgeries[8]. Our study also founded the incidence of re-operation due to bleeding at vaginal stump in one participant (5.88%) in control group, which consistent with previous study[5], however, vaginal stump bleeding caused from operative technique rather than drug effect. The serious adverse event such as thromboembolic events did not occur in this study but as we know the risk of venous thromboembolism was increased in gynecological cancer more than normal population, however we founded the clinical evidence shows no significant increase risk in venous thromboembolism in tranexamic acid use[3]. Our finding consistent with Lundin, et al[4] who conducted a randomized double-blind, placebo-controlled, multicenter study about single dose of tranexamic acid in advanced ovarian cancer surgery that showed no serious adverse effect included venous thromboembolism in the study. Current study shows only few cases of both groups experienced wound infection and nausea and/or vomiting but without statistically significance. The our study found that nausea and vomiting were the most common adverse effect but it cannot be clearly distinguish from anesthetic agents or other drugs such as morphine that we used for postoperative pain relief, however, there was no significant difference in incidence of nausea and/or vomiting between groups.

However, the power of this study did not serve to estimate these outcomes. The clinical meaningful of the efficacy of tranexamic acid in significantly reducing intraoperative blood loss, especially reduce total blood loss ≥ 500 ml, plays an important role in decreasing the need of blood transfusion, particularly in anemic patients. Our study founded that tranexamic acid can significantly reduce intraoperative blood loss ≥ 500 ml 76% (RR 0.24; 95%CI 0.06-0.89, p = 0.004).

The strength of this study was a randomized double blinded, placebo-controlled trial with the precise measurement of blood loss.

Conclusion

Single dose of intravenous tranexamic acid given 15 minutes before surgery significantly reduce intraoperative blood loss during surgical staging in endometrial cancer without serious adverse side effect.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Jonathan S. Berek, Lisa N.Abaid, Jean R. Anderson, Mira Aubuchon. Berek and Novak's Gynecology, 15th edition ed. Philadelphia: Wolters Kluwer 2014.
2. Di Saia P, Creasman W, Mannell R, McMeekin S, Mutch D. Clinical gynecologic oncology, 8th edition ed. Netherland: Elsevier 2012.
3. Medsafe.govt.nz.2018[cited27July2018]. Availablefrom:http://www.medsafe.govt.nz/profs/Datasheet/d/dbl-tranexamicacidinj.pdf
4. Lundin E, Johansson T, Zachrisson H, Leandersson U, Bäckman F, Falknäs L. Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions: double-blind placebo-controlled

randomized multicenter study. Acta Obstet Gynecol 2014;93:335-44.
5. Topsoee M, Bergholt T, Ravn P, Schouenborg L, Moeller C, Ottesen B. Anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy a double-blinded randomized placebo-controlled trial. Am J Obstet Gynecol 2016;215:72.e1-72.e8.
6. Crescenti A, Borghi G, Bignami E, Bertarelli G, Landoni G, Casiraghi GM. Intraoperative use of tranexamic acid to reduce transfusion rate in patients undergoing radical retropubic prostatectomy: double blind randomized placebo controlled trial. BMJ 2011;343:d5701.
7. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012;344:e3054.
8. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Antifibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011:16.
9. Biswas J, Chaudhuri P, Mandal A, Bandyopadhyay S, Dasgupta S, Pal A. Effect of a single preoperative dose of sublingual misoprostol on intraoperative blood loss during total abdominal hysterectomy. Int J Gynaecol Obstet 2013;122:244-7.