The Effect of Tranexamic Acid for Treatment Irregular Uterine Bleeding Secondary to DMPA Use

A-jaree Senthong MD*,
Surasak Taneepanichskul MD*

** Deapartment of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Objective: *Evaluate the efficacy of tranexamic acid and placebo for controlling irregular uterine bleeding in depot-medroxyprogesterone acetate (DMPA) users.*
Material and Method: *A double-blind, placebo-controlled study was conducted on 100 DMPA users attending the Family Planning Clinic King Chulalongkorn Memorial Hospital. All users had abnormal bleeding. They were randomly divided in two groups; a group of 50 received tranexamic acid, 250 mg four times a day for 5 days and another group of 49 received placebo in the same manner. One subject dropped out from the study. Total day of bleeding/spotting and percentage of women in whom bleeding was stopped were analyzed at the end of weeks 1 and 4.*
Results: *The percentage of subjects in whom bleeding was stopped during the first week after initial treatment was significantly higher in the tranexamic acid group than the placebo group (88% vs. 8.2%, $p < 0.001$). During the follow-up period (4 weeks after initial treatment), a bleeding-free interval of > 20 days was found in 68% of subjects treated with tranexamic acid and 0% treated with placebo($p < 0.001$). The mean number of bleeding/spotting days were also significantly different between the groups (5.7 ± 2.5 vs. 17.5 ± 7.2 days, $p < 0.05$).*
Conclusion: *Tranexamic acid was more effective than placebo in short-term treatment of irregular uterine bleeding/spotting associated with DMPA use.*

Keywords: *Medroxyprogesterone 17-acetate, Tranexamic acid, Uterine hemorrhage*

J Med Assoc Thai 2009; 92 (4): 461-5
Full text. e-Journal: *http://www.mat.or.th/journal*

Depot-medroxyprogesterone acetate (DMPA) is a long acting progestin contraceptive method. This agent is effective and convenient and presents only a few acceptor compliance problems. However, DMPA has the propensity to produce bleeding disturbances that can greatly increase discontinuation rates. A study in Thai women above the age of 35 demonstrated a 1-year continuation rate of only 20% with DMPA, and irregular bleeding was the major cause of the termination[1]. Another study in Thai adolescents demonstrated a 6-month continuation rate of 69.4%, 9 months of 42.6%, and 12 months of 30.6%. The most common side effect that caused discontinuation within 1-year time was irregular bleeding[2]. Counseling and reassurance are required as these vaginal bleeding disturbances are known as side effects and are not harmful. Thus, any intervention that effectively controlled vaginal bleeding disturbances will improve the continuation rate.

The exact patho-physiological mechanisms of irregular bleeding have remained unclear. Several studies have been performed on endometrial morphology, histology, vascular microstructure and biochemistry, such as tissue factor, lipid peroxide, vitamin E, progesterone receptors, matrix metallo-proteinases, prostaglandins PGE2 and PGF2a[3-7]. The bleeding can be treated with exogenous estrogen, either 1.25-mg conjugated estrogens or 2-mg estradiol, given daily for a period of seven days. A non-steroidal anti-inflammatory drug (NSAID) given for a period of one week is also effective. Another option is to administer an oral contraceptive for 1-3 months[8].

Correspondence to: Senthong A, Deapartment of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: ajaree_s @hotmail.com

There have been a number of studies that investigated medical treatments of irregular bleeding in DMPA users in a prospective randomized trial. In one study, DMPA users with bleeding complaints were allocated to use mefenamic acid, 500 mg, twice a day for five days or placebo. The result of one study concluded that mefenamic acid was effective in very short-erm control of bleeding[9]. Another study, compared the efficacy between selective COX-2 inhibitor (Valdecoxib) 40 mg, once a day for five days, and placebo were used. Result was also effective in control of bleeding[10]. However, at present, there is no effective standard treatment for bleeding complaints in DMPA users.

Tranexamic acid is a synthetic lysine derivative that exerts antifibrinolytic effect by reversibly blocking the lysine binding sites on plasminogen and thus preventing fibrin degradation[11,12]. It was effective in reducing intraoperative blood loss in cardiac surgery with pulmonary bypass, total Knee arthroplasty. It has been used to treat menorrhagia with a significant reduction of menstrual blood loss by 45-54%[13,14].

Endometrial fibrinolysis might be the mechanism of bleeding complaints in DMPA users[15]. Tranexamic acid was appeared to effective treatment for irregular uterine bleeding secondary to Norplant users[16]. Thus, the objective of the present study was to evaluate the effectiveness of tranexamic acid in the treatment of irregular uterine bleeding as a result of DMPA use.

Material and Method

The present study was undertaken in the Family Planning Clinic, Department of Obstetrics and Gynecology, Chulalongkorn Hospital, Bangkok, Thailand. Participants were recruited from women using DMPA who voluntarily came to the clinic with complaints of bleeding disturbances. To qualify for the present study, the participants were required to meet all of the inclusion criteria and to possess none of the exclusion criteria. Bleeding disturbances were defined as bleeding or spotting for eight or more continuous days or a current bleeding episode initiated after a bleeding-free interval of 14 days or less.

The following inclusion criteria were applied, (a) being DMPA users for a period of 1-18 months before enrolling in the present study, (b) possessing body mass index between 18-30 kg/m2, (c) Willingness to participate in a placebo-controlled study and ability to keep an accurate daily menstrual record card, (d) having 8 days or more of a bleeding or spotting prior to obvious bleeding on the day of admission, (e) being 20-45 years old, and (f) having a normal pelvic examination.

The following exclusion criteria were applied, (a) having any gynecological disease that could cause abnormal uterine bleeding, (b) having any medical disease that would cause bleeding tendency, (c) contraindication to tranexamic acid, (d) having a history of hepatic impairment or renal insufficiency, and (e) having previous treatment for DMPA-related bleeding for a period of three months prior to recruitment.

The present study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University. The eligible subjects were required to sign informed consent forms before enrolling in the present study. After being recruited into the present study, all participants were requested to record the pattern of bleeding upon admission, the episodes of bleeding, and the time when the bleeding stopped on their menstrual calendar. Upon admission, a gynecological examination and a vaginal ultrasound were performed to rule out any other possible confounding causes for the bleeding. A vaginal ultrasound was performed using a real-time sector scanner (Toshiba, SSA-250A, Tochigi-ken, Japan) with a 5-MHz vaginal transducer. The results were summarized with frequency and percentage for categorical data and mean $\pm$ SD for continuous data.

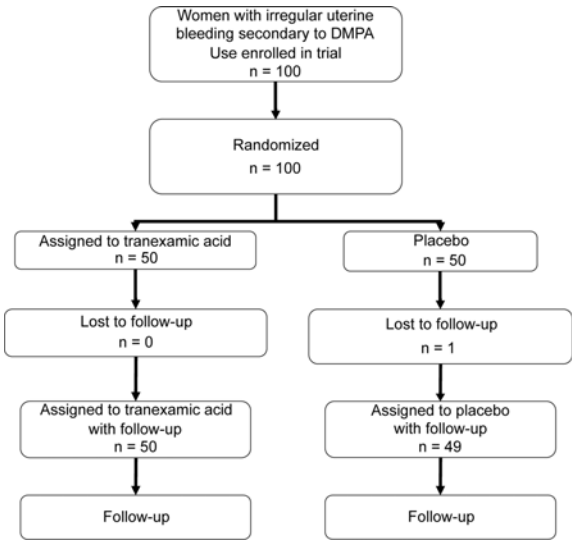

Fig. 1 Summary of patients randomized to tranexamic acid or placebo

Student unpaired t-test were used to compare between mean ± SD of the two groups, Chi-square test were used to compare the categorical data. A p-value of less than 0.05 was considered as statistically significant.

Results

One hundred women were enrolled. One was dropped from the study because she was lost to follow-up. The remaining 99 subjects were included in the present analysis. Fifty subjects were given tranexamic acid and 49 were given placebo. There were not significant differences between the groups regarding age, parity, BMI, number of DMPA injection, and endometrial thickness (Table 1). All subjects had a regular menstrual period before using the hormonal contraception. Of the subjects, 88% treated with tranexamic acid stopped bleeding, whereas 8.2% in the placebo group stopped bleeding within seven days after initiation of the treatment thus, a significant difference ($p < 0.05$). The mean bleeding free interval during 28 days for the tranexamic acid and placebo were 20.6 and 7.5 days respectively. This was also a significant difference between the two groups ($p < 0.05$).

Discussion

DMPA is a progestin-only contraceptive method well accepted worldwide. The most common problem for DMPA users is the change in menstrual bleeding with continuing use, the occurrence of bleeding can be reduced dramatically. One-year continuation rate of DMPA in adolescents and women aged above 35 year were 30.6%, and 20% respectively[1,2]. The main factor associated with discontinuation in a previous study was irregular uterine bleeding. Importantly, pretreatment counseling and successfully treated abnormal bleeding could improve the continuation rate.

Irregular bleeding resulting from DMPA use can be treated with either exogenous estrogen or NSAIDS for one week[7]. Potential risk and disadvantages of long-acting contraception such as DMPA, some women cannot, however, tolerate the side effects of estrogen, while others may have a reaction to it. Long-term administration of conventional NSIADS for treatment of irregular bleeding may also increase the risk of dyspepsia and gastric ulcer.

The mechanism to reduce endometrial bleeding attributed to tranexamic acid is believed to be the antifibrinolytic effect. The mechanism of action is reversibly block the lysine binding site on plasminogen and thus prevents fibrin degradation. In a previous study, tranexamic acid was effective treatment for irregular uterine bleeding associate in Norplant use.

The result of the present study demonstrated that the percentage of women who stopped bleeding within seven days after initial treatment was significantly higher after tranexamic acid treatment 88% of the tranexamic acid group vs. 8.2% of the placebo group. The mean value of the bleeding-free days in a period of 28 days was 20.6 days in the tranexamic acid group vs. 7.5 days in the placebo group. The present study also demonstrated the effectiveness of tranexamic acid treatment, which verifies the hypothesis that mechanism of tranexamin acid with antifibrinolytic effect to reduce irregular bleeding secondary to DMPA use. The present study also demonstrated that mild degree of nausea/vomiting was the only adverse effect in the present study. The limitation of the present study was the short follow-up period. Long-term adverse effects of tranexamic acid and long-term administration of tranexamic acid to treat irregular bleeding in DMPA users should be closely monitored. Clinically controlled trials using a low-dose contraceptive pill, low-dose estrogen, selective COX-2 inhibitor, and tranexamic acid during a long follow-up duration are suggested for future studies. In conclusion, tranexamic acid is effective in short-term control of irregular bleeding in DMPA users.

Table 1. Baseline characteristics of participants

Baseline characteristics	Tranexamic group n = 50	Placebo group n = 49	p-value*
Age	29.64 ± 7.096	28.69 ± 7.671	NS
BMI	23.11 ± 2.76	22.57 ± 2.07	NS
Endometrial thickness (mm)	4.08 ± 1.44	4.51 ± 1.74	NS
Parity	1.32 ± 0.74	1.12 ± 0.60	NS
No. of DMPA injections	1.38 ± 0.49	1.27 ± 0.45	NS

NS = no statistically significant difference

References

1. Taneepanichskul S, Reinprayoon D, Phaosavadi S. DMPA use above the age of 35 in Thai women. Contraception 2000; 61: 281-2.
2. Chotnopparatpattara P, Taneepanichskul S. Use of depot medroxyprogesterone acetate in Thai adolescents. Contraception 2000; 62: 137-40.
3. Vincent AJ, Zhang J, Ostor A, Rogers PA, Affandi B, Kovacs G, et al. Decreased tissue inhibitor of metalloproteinase in the endometrium of women using depot medroxyprogesterone acetate: a role for altered endometrial matrix metalloproteinase/ tissue inhibitor of metalloproteinase balance in the pathogenesis of abnormal uterine bleeding? Hum Reprod 2002; 17: 1189-98.
4. Lockwood CJ, Runic R, Wan L, Krikun G, Demopolous R, Schatz F. The role of tissue factor in regulating endometrial haemostasis: implications for progestin-only contraception. Hum Reprod 2000; 15 (Suppl 3): 144-51.
5. Subakir SB, Abdul MO, Sabariah S, Affandi B. Oxidative stress, vitamin E and progestin break-through bleeding. Hum Reprod 2000; 15 (Suppl 3): 18-23.
6. Fraser IS, Hickey M. Endometrial vascular changes and bleeding disturbances with long-acting progestins. Steroids 2000; 65: 665-70.
7. Mitchell MD. Reproductive roles of eicosamoids. In: Adashi EY, Rock JA, Rosenwaks Z, editors. Reproductive endocrinology, surgery and technology. Philadelphia: Lippincott-Raven; 1996: 841-58.
8. Speroff L, Fritz MA. Long-acting of contraception. In: Speroff L, Fritz MA, editors. Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005: 949-69.
9. Tantiwattanakul P, Taneepanichskul S. Effect of mefenamic acid on controlling irregular uterine bleeding in DMPA users. Contraception 2004; 70: 277-9.
10. Nathirojanakun P, Taneepanichskul S, Sappakit-kumjorn N. Efficacy of a selective COX-2 inhibitor for controlling irregular uterine bleeding in DMPA users. Contraception 2006; 73: 584-7.
11. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. Drugs 2003; 63: 1417-33.
12. Hambleton J. Drugs used in disorders of coagulation. In: Katzung BG, editor. Basic and clinical pharmacology. 9th ed. New York: McGraw Hill; 2004: 543-60.
13. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. BMJ 1996; 313: 579-82.
14. Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. Br J Obstet Gynaecol 1995; 102: 401-6.
15. Runic R, Schatz F, Krey L, Demopoulos R, Thung S, Wan L, et al. Alterations in endometrial stromal cell tissue factor protein and messenger ribonucleic acid expression in patients experiencing abnormal uterine bleeding while using norplant-2 contraception. J Clin Endocrinol Metab 1997; 82: 1983-8.
16. Phupong V, Sophonsritsuk A, Taneepanichskul S. The effect of tranexamic acid for treatment of irregular uterine bleeding secondary to Norplant use. Contraception 2006; 73: 253-6.

การประเมินประสิทธิภาพของยา tranexamic acid และยาหลอกในการควบคุมภาวะเลือดออกจากการฉีดยาคุมกำเนิด DMPA

อาจรีย์ เส้นทอง, สุรศักดิ์ ฐานีพานิชสกุล

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของยา Tranexamic acid และยาหลอกในการควบคุมภาวะเลือดออกจากการฉีดยาคุมกำเนิด depot-medroxyprogesterone acetate (DMPA)*

ชนิดของการศึกษา: *การวิจัยเชิงทดลอง*

สถานที่ทำการศึกษา: *หน่วยวางแผนครอบครัว โรงพยาบาลจุฬาลงกรณ์*

วัสดุและวิธีการศึกษา: *ผู้มารับบริการฉีดยาคุมกำเนิด DMPA ที่หน่วยวางแผนครอบครัวที่มีภาวะเลือดออกทั้งหมด 100 คน จะถูกแบ่งออกเป็น 2 กลุ่มโดยวิธีการสุ่ม, ผู้รับบริการจำนวน 50 รายที่ได้รับยา tranexamic acid 50 ขนาด 250 มิลลิกรัม เวลาเช้า กลางวัน เย็น และก่อนนอนเป็นเวลา 5 วัน และผู้รับบริการที่ได้รับยาหลอกเป็นจำนวนทั้งหมด 50 ราย แต่มีผู้ออกจากการศึกษา 1 ราย เนื่องจากไม่ได้มาตรวจติดตามการรักษา โดยได้รับยาหลอกลักษณะเดียวกัน, ช่วงระยะเวลาที่ติดตามผู้รับบริการทุกคนจะต้องบันทึกภาวะเลือดออกในแต่ละวันว่าหยุดหรือไม่หยุด จากนั้นนำผลที่ได้มาวิเคราะห์หาร้อยละของจำนวนผู้รับบริการที่มีภาวะเลือดหยุดในสัปดาห์แรกและมีระยะเวลาที่เลือดออกหยุดติดต่อกัน ตั้งแต่ 20 วันขึ้นไปและวิเคราะห์หาค่าเฉลี่ยจำนวนวันที่มีเลือดออกในระยะเวลา 4 สัปดาห์ โดยการเปรียบเทียบในระหว่าง 2 กลุ่ม*

ผลการศึกษา: *ร้อยละของผู้มารับบริการที่มีภาวะเลือดหยุดในสัปดาห์แรกหลังการรักษาและมีระยะเวลาที่เลือดหยุดติดต่อกันตั้งแต่ 20 วันขึ้นไปในกลุ่ม tranexamic acid สูงกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (88%, 8.2%; $p < 0.05$ และ68%, 0%; $p < 0.05$) และหลังจากการตรวจติดตามครบ 4 สัปดาห์หลังการรักษา ค่าเฉลี่ยจำนวนวันที่มีเลือดออก ในกลุ่ม tranexamic acid ต่ำกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (5.7 ± 2.5, 17.5 ± 7.2 $p < 0.05$)*

สรุป: *ยา tranexamic acid มีประสิทธิภาพในการควบคุมภาวะเลือดออกจากการฉีดยาคุมกำเนิด DMPA มากกว่ายาหลอก*