The Effect of Mefenamic Acid on Controlling Irregular Uterine Bleeding Second to Implanon Use

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Objective : *The aim of this double-blind, placebo-controlled study was to evaluate the effect of mefenamic acid and placebo on controlling irregular uterine bleeding secondary to Implanon use.*
Design : *Randomized placebo controlled trial.*
Setting : *Family Planning Clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*
Materials and methods: *A total number of 50 Implanon users with irregular bleeding who attended the Family Planning Clinic at Chulalongkorn Memorial Hospital. These subjects were randomly allocated into two groups. Twenty-five users received mefenemic acid, 500 mg per oral three times a day for 5 days, and placebos were given to the rest of studied subjects in the similar manner. During the follow-up periods, the participants were requested to maintain their daily record of bleeding, spotting, and adverse effects. The days of bleeding and spotting and the percentage of bleeding stopped women were analyzed in week 1 and 4.*
Results : *The percentage of subjects in whom bleeding was stopped during week 1 after initial treatment was significantly higher in the mefenamic acid group than that of the placebo group (65.20%, 21.70%;$p < 0.05$). During the follow–up period (4 weeks after initial treatment), a bleeding free-interval of > 20 days was found in 56.50% of the subjects treated with mefenamic acid and 21.70% of those treated with placebo; The mean number of bleeding/spotting days was lower in the group of patients with mefenamic acid treatment (10.52 and 16.78 days; $p< 0.05$). The difference is statistically significant.*
Conclusion : *Mefenamic acid was more effective than placebo in short–term treatment of irregular bleeding and spotting associated with Implanon use.*

Keywords : *Bleeding- irregularities, Implanon implant , Mefenamic acid.*

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Implanon is a long acting progestin contraceptive implant. It is efficacious, convenient and presents few compliance problems to the users. However, this device has the propensity to produce bleeding disturbances that can heavily affect the rate of discontinuation[1,2]. Counseling and reassurance are required when irregular or prolonged bleeding takes place. This symptom is most often encountered during the first year of use. Afterwards it becomes less frequent. The treatment that could reduce the bleeding problem should improve the continuation rate.The exact pathophysiological mechanisms of the irregular bleeding still remain unclear. Several studies were performed on endometrial morphology, histology, vascularity microstructure, biochemistry such as, lipid peroxide, vitamin E, tissue factor, progesterone receptors and the prostaglandins (PG), PGE_2, $PGF_{2\alpha}$[3-5]. Prostaglandins PGE_2 and $PGF_{2\alpha}$ markedly increase during the secretory phase and reach a maximum at the time of menstruation[5]. In the endometrium of progestogen users, arachidonic acid metabolism appears to be disturbed, as demonstrated by a significant increase in $PGF_{2\alpha}$ and epoxide metabolites[14,15]. The bleeding can be treated with exogenous estrogen, 1.25 mg conjugated estrogens or 2 mg estradiol,

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administered daily for 7 days[6]. A nonsteroidal anti-inflammatory drug given for a week is also effective[6]. Other treatment is oral contraceptive for 1-3 months[6].

Mefenamic acid is an antiprostaglandin that is usually used in gynecological practice for relief of dysmenorrhea and menorrhagia[7-10]. Mefenamic acid inhibits cyclooxygenase (COX), an enzyme responsible for the conversion of arachidonic acid into prostaglandin[16]. It supported the hypothesis that the mechanism of this disorder was alteration of prostaglandin product. The menstrual hemostasis may be affected by improvement of degranulation, platelet aggregation, and increased vasoconstriction[8]. The treatment of 1000 mg per day mefenamic acid for 5 days was proved to decrease vaginal bleeding and spotting from Norplant[11]. The advantages of mefenamic acid treatment are negligible side effects, a short course of treatment, and relief of pelvic pain[17,18]. One reason for choosing Implanon for women who came to the family planning clinic was personal or medical reasons for discontinuing use of the oral contraceptive pills. The estrogenic compound would not be appropriate to treat this side effect. The objectives of the present study were to evaluate the effectiveness and side effects of mefenamic acid in the treatment of irregular uterine bleeding secondary to the use of Implanon.

Material and Method

The study was undertaken at the Family Planning Clinic, Department of Obstetrics and Gynecology, Chulalongkorn Memorial Hospital, Bangkok, Thailand from June 2003 till April 2004. The subjects were women who used Implanon and came to the clinic with a complaint of bleeding disturbances. The following inclusion criteria were applied: 1) Implanon use at least 2 months before enrollment; 2) bleeding disturbances: prolonged bleeding defined as $\geq$ 8 continuous days of bleeding or spotting, or irregular bleeding defined as a current bleeding episode initiated after a bleeding free-interval of < 15 days (for both situations, the women displayed bleeding or spotting on the day of admission); 3) reproductive age between 15 and 45 years old; 4) normal pelvic examination and normal transvaginal ultrasonography; 5) body mass index (BMI) between 19 and 30 kg/m^2.

The following exclusion criteria were applied:1) gynecological or medical disease that may cause abnormal uterine bleeding; 2) contraindication to nonsteroidal antiinflammatory drugs [NSAIDs]; 3) chronic use of NSAIDs (more than two tablets three a times week); 4) previous treatment for Implanon-related bleeding within 3 months before recruitment; 5) unwillingness to participate in a placebo-controlled study; 6) having anemic symptom.

Being recruited into the study, all subjects were requested to record any episode of bleeding, spotting or no bleeding on their daily menstrual record card. According to the current definition of the World Health Organization, every person recruited into the trial is mandate to have fully informed consent. The study was approved by the Ethics Committee for Research in Humans of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

During their recruitment, a gynecological examination and vaginal ultrasound were performed to rule out any possibility of confounding cause for bleeding or spotting. A vaginal ultrasound was also performed using a real-time sector scanner (Toshiba, SSA-220A, Capasee II, Japan) with a 6.0 MHz vaginal transducer. The endometrial thickness, the maximum diameter of the endometrium, was measured along its longitudinal axis from myometrium to myometrium. The investigators performed all observations to avoid bias.

Fifty subjects were recruited into the study. They were randomly assigned by a random number table into two treatment groups. In one group, each of the 25 subjects, was given mefenamic acid (Mednil® Pharmaland, Thailand), two capsules (250 mg/capsule) three times a day for 5 days, and in the other group, the placebo was administered in the same manner. Phamaland also provided the placebo capsules that appeared similar to the mefenamic acid capsules. The assignment of both groups was double blinded. The treatments were not identified on any clinical form, they were coded numbers that were broken only at the end of the study.

During the follow-up periods, the participants were requested to maintain their daily record of bleeding, spotting, or no bleeding and any adverse effects. They were instructed to return to the clinic at the end of weeks 1 and 4 after initial treatment. Days of treatment required for stopping the bleeding episode, total number of bleeding or spotting days, and length of the bleeding-free interval after the initial treatment were recorded and analyzed.

All data were collected, coded, and analyzed using SPSS software (SPSS, Chicago, IL). Comparison of the mean values was preformed by independent t-test. The p value < 0.05 was considered significant.

Results

Fifty women were recruited into the study. However, there were 46 women who actually completed the trial. Twenty-three subjects received mefenamic acid and the other took placebo. Four women did not complete the trail because they were lost to follow-up. Two were in the placebo group and the others were in the treatment group.

There were no significant differences between the groups regarding their age, parity, duration of Implanon use, BMI (body mass index), and endometrial thickness (Table 1). All subjects had regular menstrual periods before using the hormonal contraception.

The ultrasound examination of endometrial thickness showed that most women had either very thin or thin endometrium (< 3 mm, 23.91%; 3-6 mm, 67.39%). Only four cases(8.69%) had > 6 mm in thickness of endometrium (Table 2).

Of the total number of subjects, 65.20% treated with mefenamic acid stopped bleeding, whereas 21.70% in the placebo group stopped bleeding within 7 days after initiation of treatment. During the follow-up (4 weeks after initiation of treatment), 56.50% in the mefenamic group and 21.70% in the placebo group stopped bleeding. Bleeding that stopped within 4 weeks of follow-up was defined as cessation of bleeding after initiation of treatment with a bleeding free-interval of > 20 days. There was a significant difference in the percentage of cessation between both treatment regimens in week 1 and 4 weeks of follow-up (Table 3).

The mean duration of bleeding and spotting days in the mefenamic group were 10.52 days which was significantly less comparing to 16.78 days in the placebo group during 28 days of follow-up.

Table 1. Baseline characteristics of the subjects (mean ± SD)

	Mefenamic acid (N=23)	Placebo (N=23)	P-value
Age (y)	31.26 ± 5.10	28.69 ± 5.41	NS
Parity	1.08 ±0.84	1.13 ± 0.69	NS
Duration of Implanon use (months)	3.52 ± 1.62	3.21 ± 1.31	NS
Body mass index (kg/M^2)	21.87 ± 2.19	21.89 ± 1.68	NS
Endometrial thickness (mm)	4.16 ± 1.67	3.59 ± 0.95	NS

NS = no significance

Table 2. Endometrial thickness

Endometrial thickness(mm)	N	%
< 3	11	23.91
3-6	31	67.39
> 6	4	8.69
Total	46	100

Table 3. Percentage of women who stopped bleeding within 7 days and 28 days after initiation of the treatment

	Mefenamic acid	Placebo	P- value
≤ 7 days to stop bleeding	65.20% (15/23)	21.70% (5/23)	< 0.05
Bleeding-free interval ≥ 20 days (within 28 days of follow)	56.50% (13/23)	21.70% (5/23)	< 0.05

Side effects

There were 7 cases who reported side effects. Four were in the mefenamic acid group and three in the placebo group. Three cases in the mefenamic acid group had abdominal discomfort and one had headache .In the placebo group, one case got headache and two had breast tenderness.

Discussion

Implanon , a sub-dermal implant, is a contraceptive method which already accepted throughout the world. Prolonged or irregular bleeding is the major adverse effect causing discontinuation of the implant [1,2]. Participants in the present trial were women admitted to the clinic because of their bleeding complaints during Implanon use. The results of this study showed that the percentage of women who stopped bleeding within 7 days after initiation of the treatment was significantly higher in the mefenamic acid group than the placebo group (65.20% in mefenamic acid group vs. 21.70% in placebo group). The similar results were obtained after 28 days of follow-up (56.50% in mefenamic acid vs. 21.70% in placebo group). The use of mefenamic acid significantly reduced the number of bleeding and spotting days over the placebo.

The ultrasound measurement of endometrial thickness showed that the Implanon users with irregular bleeding had wide distribution of the thickness (very thin 23.91%, thin 67.39% and thick

8.69%). The result did not correlate with that of a previous study which reported that endometrial tissue of women who used etonogestrel implant was mostly atrophic[12].

The great benefits of mefenamic acid are that it is rapidly absorbed, metabolized, and excreted. The use of mefenamic acid was associated with low incidence of side effects without serious complication[11].

The pathophysiology of irregular uterine bleeding is currently not known. However, few studies showed that some factors or substances might be associated with irregular bleeding in implant acceptors[3,4]. The blood concentration of lipid peroxide significantly increased while the blood concentration of vitamin E significantly decreased after 3 months exposure to Norplant[3]. One study presented that the concentrations of both PRB and PRA (progesterone receptor B and A) isoforms were lower at the bleeding site versus the non-bleeding site[3]. Hysteroscopic studies demonstrated major change in the extent of superficial endometrial vascularity disturbance in superficial vascular morphology and increased endometrial vascular and epithelial fragility only in progesterone use[4].

Irregular bleeding of Implanon users can be treated with exogenous estrogen[6]. However, its mechanism of action has not been elucidated. The potential risks and disadvantage of exogenous estrogen must be considered. Lack of exogenous estrogen is one of the advantages of long-acting contraception such as Implanon. Some women cannot tolerate with the side effects of estrogen. Others may have a contraindication to estrogen use. According to the study, mefenamic acid was effective with low side effects and short duration of treatment. Therefore, mefenamic acid should be a reasonable choice to treat the irregular bleeding in Implanon use. However, counseling and reassurance are still required, as irregular bleeding is a known side effect of Implanon use. The limitation of the present study was its short follow-up period. Further study should be conducted using a long-term follow up. In conclusion, mefenamic acid was more effective than placebo in short-term control of irregular bleeding and spotting associated with Implanon use.

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การประเมินสิทธิภาพของยา Mefenamic acid และยาหลอกในการควบคุมภาวะเลือดออกจากการใช้ยาฝังคุมกำเนิด Implanon

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วัตถุประสงค์ *: เพื่อประเมินประสิทธิภาพของยา Mefenamic acid และยาหลอกในการควบคุมภาวะเลือดออกจากการใช้ยาฝังคุมกำเนิด Implanon*

ชนิดของการวิจัย *: การวิจัยเชิงทดลอง*

สถานที่ทำการวิจัย *: หน่วยวางแผนครอบครัว โรงพยาบาลจุฬาลงกรณ์*

วิธีวิจัย *: ผู้มารับบริการฝังยาคุมกำเนิด Implanon ที่หน่วยวางแผนครอบครัวที่มีภาวะเลือดออกจำนวนทั้งหมด 50 คน จะถูกแบ่งออกเป็น 2 กลุ่มโดยวิธีการสุ่ม, ผู้รับบริการที่ได้รับยา Mefenamic acid จำนวน 25 ราย โดยได้รับยาในขนาด 500 มิลลิกรัม เวลาเช้า, กลางวันและเย็นเป็นเวลา 5 วัน และผู้รับบริการที่ได้รับยาหลอกเป็นจำนวนทั้งหมด 25 ราย โดยได้รับยาหลอกในลักษณะเดียวกัน, ช่วงระยะเวลาที่ติดตามผู้รับบริการทุกคนจะต้องบันทึกภาวะเลือดออกในแต่ละวันว่าหยุดหรือไม่หยุด จากนั้นนำผลที่ได้มาวิเคราะห์หาร้อยละของจำนวนผู้รับบริการที่มีภาวะเลือดหยุดในสัปดาห์แรกและมีระยะเวลาที่เลือดหยุดติดต่อกัน ตั้งแต่ 20 วันขึ้นไปและวิเคราะห์หาค่าเฉลี่ยจำนวนวันที่มีเลือดออกในระยะเวลา 4 สัปดาห์โดยการเปรียบเทียบในระหว่าง 2 กลุ่ม*

ผลการวิจัย *: ร้อยละของผู้รับบริการที่มีภาวะเลือดหยุดในสัปดาห์แรกหลังการรักษาและมีระยะเวลาที่เลือดหยุดติดต่อกันตั้งแต่ 20 วันขึ้นไปในกลุ่ม Mefenamic acid สูงกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (65.20%, 21.70%; P< 0.05 และ 56.50%, 21.70%; P<0.05 ตามลำดับ) และหลังจากการตรวจติดตามครบ 4 สัปดาห์หลังการรักษา, ค่าเฉลี่ยจำนวนวันที่มีเลือดออก ในกลุ่ม Mefenamic acid ต่ำกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (10.52, 16.78 วัน ; P < 0.05)*

สรุป *: ยา Mefenamic acid มีประสิทธิภาพในการควบคุมภาวะเลือดออกจากการใช้ยาฝังคุมกำเนิด Implanon มากกว่ายาหลอก*
