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Comparison of the Efficacy between Conjugated Equine Estrogen versus Nonsteroidal Anti-inflammatory Drug for the Cessation of Uterine Bleeding among Contraceptive Implant Users: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the effect of conjugated equine estrogen and nonsteroidal anti-inflammatory drugs on the controlling of abnormal uterine bleeding in hormonal subdermal implant users.

Materials and Methods: Between July 2022 and April 2023, participants with etonogestrel subdermal implants who complained of abnormal uterine bleeding were randomly allocated into two groups. The study group (n = 32) received 0.625 mg of conjugated equine estrogen orally twice a daily for five days, while the control group (n = 32) received 500 mg of mefenamic acid orally three times a daily for five days. The duration of bleeding cessation was evaluated.

Results: Baseline characteristics including age, BMI, duration of implant use, endometrial thickness, and pattern of bleeding were not statistically different in both groups. The duration of bleeding cessation was significantly shorter in the conjugated equine estrogen group (5.9 ± 3.4 vs 7.9 ± 3.9 days, mean difference 2.0 days (95%CI 0.01 to 0.02, $p < 0.05$)).

Conclusion: Conjugated equine estrogen was more effective than mefenamic acid in controlling abnormal uterine bleeding in etonogestrel subdermal implant use.

Keywords: abnormal uterine bleeding, hormonal subdermal implant, conjugated equine estrogen, mefenamic acid.

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เปรียบเทียบประสิทธิภาพการใช้ยาคอนจูเกตเอสโตรเจนและยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ในการรักษาภาวะเลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝังใต้ผิวหนังการศึกษาแบบสุ่ม

สาลินี พลโยธา, ฤทัยรัตน์ ตั้งมั่นสกุลชัย, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบผลของการใช้ยาตอนจูเกตเอสโตรเจนและยาต้านการอักเสบที่ไม่ใช่เสตียรอยด์ในการควบคุมเลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝั่งใต้ผิวหนัง*

วัสดุและวิธีการ: *สตรีที่ได้รับการวินิจฉัยเบื้องต้นว่ามีภาวะเลือดออกผิดปกติทางช่องคลอดหลังจากการใช้ฮอร์โมนฝังใต้ผิวหนังชนิดอีโทโนเจสเตรลช่วงเวลาระหว่างเดือนกรกฎาคม พ.ศ. 2565 ถึง เมษายน พ.ศ. 2566 ได้รับการสุ่มแบ่งเป็นสองกลุ่มกลุ่มศึกษาได้รับยาคอนจูเกตเอสโตรเจน (0.625 มก./แคปซูล) รับประทานครั้งละ 1 แคปซูลวันละ 2 ครั้ง หลังอาหารเช้า-เย็น เป็นระยะเวลา 5 วัน จำนวน 32 คน และกลุ่มควบคุมได้รับยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ (250 มก./ แคปซูล) รับประทาน ครั้งละ 2 แคปซูล วันละ 3 ครั้ง หลังอาหารเช้า-เที่ยง-เย็น เป็นระยะเวลา 5 วัน จำนวน 32 คน ทำการประเมินจำนวนวันที่เลือดออกจนหยุดหลังได้รับการรักษา*

ผลการศึกษา: *จำนวนวันที่เลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝังใต้ผิวหนังชนิดอีโทโนเจสเตรลจนหยุดหลังได้รับการรักษาด้วยยาคอนจูเกตเอสโตรเจนน้อยกว่าการรักษาด้วยยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์อย่างมีนัยสำคัญทางสถิติ 5.9 ± 3.4 วัน และ 7.9 ± 3.9 วัน ตามลำดับ โดยค่าเฉลี่ยแตกต่างกัน 2.0 วัน (95%CI 0.01 ถึง 0.02, $p < 0.05$)*

สรุป: *กลุ่มยาคอนจูเกตเอสโตรเจนมีประสิทธิภาพในการลดจำนวนวันที่เลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝังใต้ผิวหนังชนิดอีโทโนเจสเตรล*

คำสำคัญ: *เลือดออกผิดปกติทางช่องคลอด,ฮอร์โมนฝังใต้ผิวหนัง, ยาคอนจูเกตเอสโตรเจน, ยาเมเฟนามิค แอซิด*

Introduction

The hormonal subdermal implant is the first long-acting progestin contraceptive method, The Population Council's registered trademark for one capsule implant releasing Etonogestrel[1]. The implant is efficacious and convenient and presents fewer user compliance problems[2]. However, abnormal uterine bleeding is the most common reason for discontinuing its use[1,2]. Abnormal uterine bleeding is common in the first month of use but diminishes with continued use[2]. Mechanism of abnormal uterine bleeding in subdermal implant users were abnormal endometrial vessels and abnormal endometrial environment[2]. Although these side effects are not dangerous, they can be upsetting, necessitating counseling and support to overcome discontinuation[3].

There are several treatment options available for women who have abnormal uterine bleeding while using hormonal subdermal implants, including conjugated equine estrogen, ethinyl estradiol, combined hormonal contraceptives, and nonsteroidal anti-inflammatory drugs such as mefenamic acid, ibuprofen, and tranexamic acid[4-7].

Conjugated equine estrogen and nonsteroidal anti-inflammatory drugs have been used to reduce bleeding[8]. Previous studies have shown that conjugated equine estrogen is significantly reduces irregular bleeding in hormonal subdermal implant users[8].

A recent study compared the efficacy of mefenamic acid and placebo, and they found that mefenamic acid was more effective in short-term control of irregular bleeding and spotting within 7 days after initiation of treatment (76% vs 27%, respectively), and the mean number of days of bleeding and spotting after initiation of mefenamic acid treatment (11.6 vs 17.2 days, respectively). The effectiveness of mefenamic acid treatment, reinforcing the hypothesis that the mechanism of this disorder involves altered prostaglandin production[9,10]. In another study comparing the efficacy of, combined oral contraceptive pills vs mefenamic acid, 76.0% vs 35.7% of women who received combined oral contraceptive pills stopped bleeding within seven days after the initiation treatment[11]. Moreover, the mean duration of bleeding and spotting days in combined oral contraceptive pills was significantly shorter than mefenamic acid group (7.29 ± 3.16 vs 10.57 ± 4.14 days)[11].

The most common adverse effect of combined oral contraceptive pills is breakthrough bleeding, but women who use combined oral contraceptive pills will also complain of nausea, headaches, abdominal cramping, breast tenderness, and an increase in vaginal discharge or decreased libido. So, most of these women being intolerant to the side effects of combined oral contraceptive pills and long duration of use usually stop using it while under the protocol[11,12]. Alternatively, conjugated equine estrogen induces endometrial epithelial proliferation and may thus effectively terminate prolonged bleeding episodes in progestogen users with short course therapy and fewer side effects than combined hormonal contraceptives[4-6, 8]. Thus far, no study has demonstrated that conjugated equine estrogen significantly reduces irregular bleeding in users of hormonal subdermal implants.

No study has compared the efficacy of conjugated equine estrogen and nonsteroidal anti-inflammatory drugs in the treating of bleeding irregularities in hormonal subdermal implant users. In the current study, we evaluated the effectiveness of conjugated equine estrogen and nonsteroidal anti-inflammatory drugs in the control of abnormal uterine bleeding in hormonal subdermal implant users.

Materials and Methods

This single-blind, randomized controlled trial study was conducted at the Department of Obstetrics and Gynecology, Khon Kaen Hospital. It was approved by the Khon Kaen Hospital Institute Review Board in Human Research (reference number: KEF65014).

Eligible participants included non-pregnant

women aged ≥ 15 years used single rod of 68 mg etonogestrel insertion for 3 to 36 months for the first time, complained of abnormal uterine bleeding for the first time and to exhibit none of exclusion criteria were applied: 1) gynecological or medical diseases was cause uterine bleeding, 2) contraindication or allergy to estrogen or nonsteroidal anti-inflammatory drugs, 3) chronic use of nonsteroidal anti-inflammatory drugs before the enrollment.

Participants were informed of the study at the family planning clinic. Written informed consent was obtained from each participant before enrollment. Participants were randomly allocated by computer generation using a block of four into two groups, the conjugated equine estrogen group (study group) and the mefenamic acid group (control group). Allocation concealment was achieved using sealed opaque envelopes.

Baseline characteristics were recorded, including age, body mass index (BMI), baseline characteristics of abnormal uterine bleeding (spotting, hypermenorrhea, and menorrhagia), and endometrial thickness. The participants were informed about the outcomes and were asked to record any episode of "abnormal uterine bleeding" (spotting, hypermenorrhea, and menorrhagia) after using etonogestrel subdermal implants. Spotting was defined as unexpected bleeding with no required tampons or sanitary napkins. Hypermenorrhea was defined as heavy bleeding over 80 ml, menorrhagia was defined as bleeding longer than 7 days, and "no bleeding" was defined as the duration of bleeding cessation after treatment[13,14]. After enrollment, a gynecological examination, urine pregnancy test, and transabdominal ultrasound were performed to rule out any other possible confounding causes of bleeding or spotting and measurement of endometrial thickening.

Sixty-four subjects were recruited: the study group (n = 32) received 0.625 mg of conjugated equine estrogen orally twice daily for five days, and the control group (n = 32) received 500 mg of mefenamic acid orally three times daily for five days. The pharmacist prepared all the drugs and kept them in a sealed opaque package. The assignment of both groups was blinded. The treatment was not identified in the case record form until code numbers were broken at the end of the study.

All participants were appointed at the end of week 1 after their initial treatment at the clinic or by phone. During the follow-up period, the participants were told of the bleeding cessation, the total number of bleeding or spotting days, and any other adverse effects to the investigator. If the bleeding did not stop, two additional capsules of tranexamic acid (500 mg/capsule) were administered orally twice daily for 5 days.

The sample size was calculated based on a pilot study of 30 participants with a power of 90%, α level of 0.05, and a dropout rate of 10%. A total of 64 participants (32 in each group) was required. Data were analyzed based on an intention-to-treat analysis using STATA version 14. The Student's t-test and Chi-squared or Fisher's exact test were used to analyze continuous and categorical data, as appropriate. A p-value < 0.05 was considered statistically significant.

Results

Between June 2022 and April 2023, 64 eligible women who visited the family planning clinic at Khon Kaen Hospital were enrolled in the study and randomly assigned into two groups (32 in the study group and 32 in the control group). No dropouts occurred (Fig. 1). Baseline characteristics were similar between the groups, including age, body mass index (BMI), baseline characteristics of abnormal uterine bleeding, and endometrial thickness (Table 1).

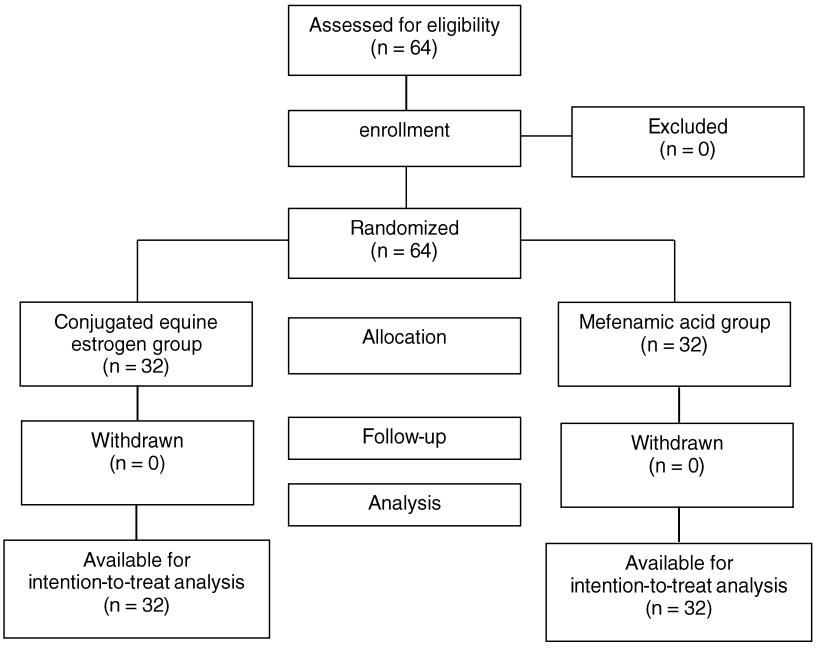

Fig. 1. Study flow.

Table 1. Demographics and Clinical characteristics of participants.

	Conjugated equine estrogen (n = 32)	**Mefenamic acid (n = 32)**	**p value**
Age (years)	19.5 ± 4.1	18.9 ± 3.6	0.52[t]
BMI (kg/m^2)	21.6 ± 4.1	20.2 ± 4.6	0.19[t]
Duration of implant use (months)	7.5 ± 5.9	5.3 ± 4.0	0.19[t]
Endometrial thickness (mm.)	4.0 ± 2.4	3.7 ± 2.5	0.36[c]
Pattern of bleeding, n (%)			0.69[f]
- Spotting	18 (56.3)	19 (59.4)	
- Menorrhagia	4 (12.4)	2 (6.2)	
- Hypermenorrhea	10 (31.3)	11 (34.4)	

Data were presented as number (%), mean ± standard deviation.
P value corresponded to [t] Student t-test, [c] Chi-square test or [f] Fisher's exact test.

The duration of bleeding cessation after initial treatment was significantly shorter in the conjugated equine estrogen group, about 5.9 days, than in the mefenamic acid group, about 7.9 days (5.9 ± 3.4 days vs 7.9 ± 3.9 days). The mean difference was 2.0 days (95% CI 0.01 to 0.02, p = 0.01). Bleeding patterns after

contraceptive implants were categorized as follows: the spotting subgroup in the conjugated equine estrogen group (56.3%) and the mefenamic acid group (59.4%); the hypermenorrhea subgroup in the conjugated equine estrogen group (31.3%) and the mefenamic acid group (34.4%); the menorrhagia subgroup in the conjugated equine estrogen group (12.4%); and the mefenamic acid group (6.2%). For the premarin group, persistent bleeding after treatment within 7 days is the spotting subgroup (27.8%), the hypermenorrhea subgroup (10%), and there are no cases in the menorrhagia subgroup. Therefore, in the mefenamic acid group, persistent bleeding after treatment within 7 days is the spotting subgroup (36.8%), the hypermenorrhea subgroup (18.2%), and there were no cases in the menorrhagia subgroup (Table 2).

Table 2. Result.

	Conjugated equine estrogen (n = 32)	Mefenamic acid (n = 32)	Mean difference (95% confidence interval)	p value
Duration of bleeding cessation (day)*	5.9 ± 3.4	7.9 ± 3.9	2.0 (0.01-0.02)	0.01[t]
≤ 7 Days to bleeding cessation n (%)	26 (81.3)	23 (71.9)	-	0.38[c]
Adverse events, n (%)	1 (3.1)	3 (9.4)	-	0.61[f]
- Stomach upset or cramps				0.36 [c]
Duration of medication adherence (day)	4.6 ± 0.8	4.9 ± 0.34	0.3 (0.51-0.35)	0.43[t]
Reason for non-adherences	3 (9.4)	2 (6.3)	-	1.00[f]
- Get better from bleeding				

Data were presented as number (%), mean ± standard deviation
P value corresponded to [t] Student t-test, [c] Chi-square test, [f] Fisher's exact test.
* Significant at p value < 0.05

The percentage of bleeding cessation within 7 days after initiation of treatment was higher in conjugated equine estrogen than in the mefenamic acid group (81.3% vs 71.9%) (Table 2).

Four participants experienced mild symptoms of stomach upset in the present study: one in the conjugated equine estrogen group and three in the mefenamic acid group. Notwithstanding, symptoms Nausea/vomiting, Headache, Breast tenderness or swelling were not severe enough to discontinue the treatment (Table 2).

The mean duration of adherence was not significantly different between the conjugated equine estrogen, about 4.5 days and mefenamic acid groups, about 4.9 days (4.5 ± 0.8 days vs 4.9 ± 0.3 days, p = 0.428). The reason for non-adherence was that participants were feeling well enough to skip doses: 3 in the study group and 2 in the control group (Table 2).

In the satisfaction study with both medication groups, it was found that in the Premarin group, there was a high satisfaction rate of 75%. Additionally, in the mefenamic acid group, a satisfaction rate of 66.7% was observed.

Discussion

The results of the current trial showed that the duration of bleeding cessation after the initial treatment was significantly shorter in the study (conjugated equine estrogen) group than in the control (mefenamic acid) group (5.9 ± 3.4 days vs 7.9 ± 3.9 days, mean difference 2.0 days (95%CI 0.01 to 0.02, p < 0.05).

Conjugated equine estrogen was more effective than mefenamic acid in controlling abnormal uterine bleeding associated with hormonal subdermal implant use, which demonstrates that conjugated equine estrogen is effective in reducing irregular bleeding among hormonal subdermal implant users. The most common bleeding pattern after contraceptive implants was spotting (57.8%), hypermenorrhea (32.8%), and menorrhagia (9.4%). The percentage of women who stopped bleeding within 7 days after initiation of treatment was higher after conjugated equine estrogen treatment than after mefenamic acid treatment (81.3% vs 71.9%, p = 0.38), albeit the difference was not statistically significant. The percentage of bleeding cessation within 7 days after mefenamic acid treatment is like those of a previously published study (76.0%)[7]. The patient group with a high incidence of persistent bleeding after treatment within 7 days is the spotting subgroup in the premarin group (27.8%), and the mefenamic acid group (36.8%). When subgroup bleeding patterns were analyzed, it was observed that conjugated equine estrogen had a lower percentage of persistent bleeding compared to mefenamic acid in all subgroups. Conjugated equine estrogen induces endometrial epithelial proliferation and may effectively terminate prolonged bleeding episodes in progestogen users. Exogenous estrogens (i.e., conjugated equine estrogen, either alone or in combination with levonorgestrel) have successfully been used to treat irregular or prolonged bleeding during contraceptive implants[4,6]. Furthermore, conjugated equine estrogen has low side effects and mild symptoms of stomach upset, which is not a common reason for discontinued use.

However, effectively managing uterine bleeding in etonogestrel subdermal implant users hinges on the importance of providing comprehensive counseling to anticipate erratic bleeding prior to device insertion[5]. While many individuals may accept this irregular bleeding pattern, the associated discomfort could potentially impact their overall quality of life. The study found that conjugated equine estrogen could be considered as an alternative treatment option due to its characteristics of being user-friendly, having a shorter treatment duration, fewer side effects, and high efficacy in addressing uterine bleeding among users of contraceptive implants.

The strength of this study lies in its design as a randomized controlled trial with an appropriate sample size and an absence of dropouts. However, a limitation of the research is the lack of investigation into the duration of recurrent bleeding in patients, which could offer valuable insights for guiding patients in the selection of either of these two medications. Conducting further studies with extended follow-up periods could furnish additional information regarding the safety and efficacy of these treatments.

Conclusion

Conjugated equine estrogen was more effective than mefenamic acid in controlling abnormal uterine bleeding associated with etonogestrel subdermal implants with low side effects and short duration of treatment. Hence, conjugated equine estrogen is a reasonable choice for treating the abnormal uterine bleeding side effects of hormonal subdermal implants.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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