Efficacy of Celecoxib on Controlling Irregular Uterine Bleeding Secondary to Jadelle® Use

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Objective: *To evaluate the efficacy of celecoxib and placebo for controlling irregular uterine bleeding in Jadelle® users.*
Design: *Randomized double blind placebo controlled trial.*
Setting: *Family Planning Clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*
Material and Method: *Forty Jadelle® users with irregular bleeding were randomly allocated into two groups. Twenty users received celecoxib 200 mg once a day for five days and the other twenty users received the placebo in the same manner. The participants were requested to maintain their daily record of bleeding, adverse effects, and satisfaction.*
Results: *The percentage of the subjects whom bleeding was stopped within 7 days after initial treatment was significantly higher in the celecoxib group than in the placebo group (70% vs. 0%; $p < 0.001$). The mean duration of bleeding-free interval was significantly longer in celecoxib than placebo group (24.0 $\pm$ 1.65 days vs. 10.0 $\pm$ 6.50 days; $p < 0.001$). The mean duration of bleeding days was significantly shorter in celecoxib than placebo group (5.0 $\pm$ 1.65 vs. 19.0 $\pm$ 6.50 days; $p < 0.001$). Patients satisfaction in celecoxib group was significantly higher than the placebo group (80% vs. 30%; $p < 0.001$). There was no detectable adverse effect in both groups.*
Conclusions: *Celecoxib was more effective than placebo in the short-term control of irregular bleeding in Jadelle® users. The mechanism of nonsteroidal anti-inflammatory drugs (NSAIDs) for the reduction of endometrial bleeding is likely from COX-2 inhibition.*

Keywords: *Adverse effects, Contraceptive agents, Female, Drug implants, Pyrazoles, Sulfonamides, Uterine hemorrhage*

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The Population Council developed Jadelle® to provide the same level of contraceptive protection as Norplant® while using fewer implants, thereby making the method easier to insert and remove[1,2]. Jadelle® is a set of two flexible cylindrical implants. Each rod contains 75 mg of the progestin levonorgestrel. Release of levonorgestrel sufficient to prevent conception is reached within 24 hours after placement of the rods and is maintained at an effective rate for five years[1,2]. Levonorgestrel concentrations in Jadelle® users are substantially below those generally observed in users of oral contraceptives containing norgestrel or levonorgestrel. The implant system is a very simple method. It is long-acting, effective, convenient, and reversible[1-4].

The most common side effect of Jadelle® use is irregular menstrual bleeding. Most women can expect some variation in menstrual bleeding patterns. Irregularities vary from woman to woman and may include prolonged menstrual bleeding, heavy bleeding, prolonged spotting, or spotting between periods. This symptom is most often encountered during the first year of use. Afterwards, it becomes less frequent[1-4]. In the Jadelle® clinical trials in King Chulalongkorn Memorial Hospital, the most common side effects

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reported at six months of follow-up was irregular bleeding[5].

Alterations to menstrual patterns represented a substantial proportion of the reasons for discontinuation of implants. A 5-years study in 594 females aged 18-40 showed that implantation of Jadelle® was generally well tolerated. Over the 5-year study duration, 17.7% of patients discontinued treatment as a result of the menstrual disorders. The treatment that could reduce the bleeding problem should improve the continuation rate[2].

The exact pathophysiological 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 metalloproteinases and the PGE_2 and $PGF_{2\alpha}$[6-10]. Prostaglandins PGE_2 and $PGF_{2\alpha}$ markedly increase during the secretory phase and reach a maximum at the time of menstruation[10-12]. In the endometrium of progesterone users, arachidonic acid metabolism appears to be disturbed, as demonstrated by a significant increase in $PGF_{2\alpha}$ and epoxide metabolites[13,14].

Non-steroidal anti-inflammatory drugs are prostaglandin (PG) inhibitors used in gynecological practice to relieve dysmenorrhea and to treat menorrhagia[15-18]. However, a complete understanding of the mechanisms whereby PG inhibitors reduce menstrual blood loss is, to date, still undetermined. There are two prostanoids, thromboxane A2 (TXA_2) and prostacyclin (PGI_2), which plays an essential role in maintaining vascular homeostasis. TXA_2 is primarily synthesized in platelets (which express only COX-1) and promotes platelet aggregation and vasoconstriction. In contrast to TXA_2, PGI_2 is the main product of vascularendo- thelial cells and is a potent vasodilator and inhibits platelet aggregation.

To decrease the bleeding of the endometrium, it would be ideal to selectively block the synthesis of PGI_2 only without decreasing TXA_2 formation, as the latter is a platelet pro aggregating vasoconstrictor[19-21]. In the past, there have been no NSAIDs that possessed this ability because conventional NSAIDs are non-selective cyclooxygenase (COX) inhibitors and thus block the formation of both TXA_2 and PGI_2 pathways (Fig. 1). At present, two isoforms of the COX enzyme (COX-1 and COX-2) have been identified. COX-1 is the only isoform available in platelets where it converts arachidonic acid into TXA_2. COX-1 is also the main isoform expressed in the gastric mucosa where it catalyzes the biosynthesis of cytoprotective PGs. The expression of COX-2 is increased during inflammation, during cellular transformation, and in the central nervous system and renal tissues under normal conditions. Based on the hypothesis that selective inhibition of COX-2 would maintain the anti-inflammatory efficacy of conventional NSAIDs, without compromising the gastrointestinal cyto-protective effects of COX-1-dependent PGs, several selective COX-2 inhibitors have been developed. Recent research has demonstrated the role of COX-2 enzyme in the production of PGs that have their functions under normal physiologic conditions as in vascular homeostasis. COX-2 seems to be the main enzyme responsible for the production of PGI_2. These findings demonstrated that the selective COX-2 inhibitor should be an ideal NSAIDs to decrease the bleeding of the endometrium[22-24]. Some of the advantages of selective COX-2 inhibitor treatment are, for instance, less GI toxicity, ease of administration (once daily dose), short course of treatment and relief of pelvic pain.COX-2 inhibitors may be more effective in decreasing the bleeding than conventional NSAIDs by selectively inhibiting the synthesis of PGI_2 only without decreasing TXA_2 formation[28,29]. The treatment of 40 mg per day of valdecoxib for five days was proved to decrease vaginal bleeding and spotting from DMPA[23]. One reason for choosing Jadelle® for women who came to the family planning clinic was personal or medical reasons for discontinuing use of the oral contraceptive pills, so that the estrogenic compound would not be appropriate to treat this side effect. The primary objective of the present study was to evaluate the efficacy of celecoxib and placebo for controlling irregular uterine bleeding in Jadelle® users.

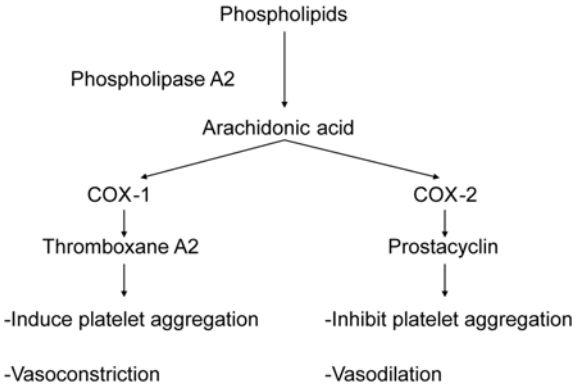

Fig. 1 Prostacyclin and thromboxane A2 pathways

The secondary objective was to compare patient satisfaction between the celecoxib group and placebo group.

Material and Method

The present study was undertaken in the Family Planning Clinic, Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Participants were recruited from women using Jadelle® who voluntarily came to the clinic with complaints of irregular uterine bleeding. Irregular uterine bleeding was 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[30]. All participants who were recruited to the present study required to have the following inclusion and the exclusion criteria.

The inclusion criteria were as follows:

1. Current Jadelle® users for a period of 3 months before enrolling in the present study
2. Current bleeding on the day of participation
3. Age 20-45 years
4. BMI 19-30 kg/m^2
5. Normal pelvic examination and normal transvaginal ultrasonography

The exclusion criteria were as follows:

1. Gynecological or medical disease that could cause abnormal uterine bleeding
2. Adverse reaction to NSAIDs
3. History of allergy to sulfonamides
4. History of hepatic impairment or renal insufficiency
5. Current breastfeeding
6. Previous treatment for Jadelle®-related bleeding for a period of 3 months prior to recruitment
7. Anemic symptoms or shock

Upon admission, a gynecological examination and a vaginal ultrasound were performed in order to rule out any other possible confounding causes for the bleeding. Vaginal ultrasound was performed with the use of real-time sector scanner (Toshiba, SSA-220A, Capasee II, Japan; 6.0-MHz endovaginal probe). Forty subjects were recruited and randomly assigned into two treatment groups using a random number table. One group with 20 subjects was given celecoxib (celebrex®) with a dose of one capsule (200 mg/capsule) a day for a period of five days, and the other group with 20 subjects was given a placebo administered in the same manner. Celecoxib and placebo were packed in opaque sealed envelopes with labeled number. Assignment of both groups was double-blind, and the treatment was not identified on the clinical form but was instead identified by code numbers, which were translated only at the end of the present study (Fig. 2).

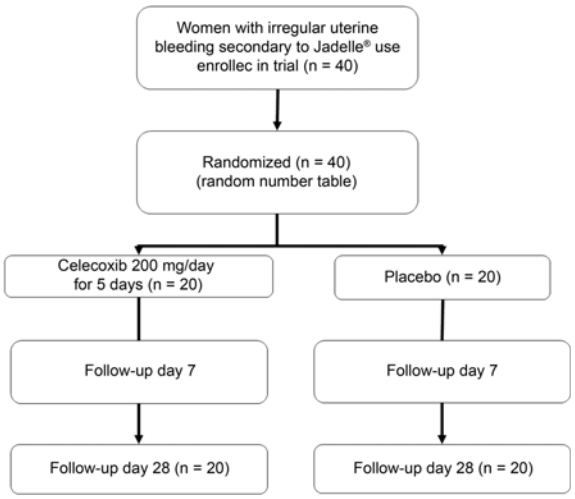

Fig. 2 Summary of patients randomized to celecoxib or placebo

During the follow-up periods, the participants were requested to keep a daily record of bleeding any adverse effects and satisfaction for the treatment. They were also required to return to the clinic at the end of weeks 1 and 4 after the initial treatment. The percentage of women who stopped bleeding within seven days, the length of the bleeding-free interval in the 28 days, the number of bleeding days after the initial treatment, and the percentage of women who were satisfied with the treatment were analyzed. Our primary outcome variable was the percentage of women who stopped bleeding within seven days after initiation of treatment.

The sample size was based on the percentage of women who stopped bleeding within seven days after initiation of treatment(within a 4-week period of follow-up) in the treatment group and in the placebo group from a study using mefenamic acid for treatment of irregular uterine bleeding in Norplant® users. The percentage of women who stopped bleeding within seven days after initiation of treatment was 76% in the treatment group and 27% in the placebo group[26]. It was determined that the authors would need 17 women for each group to detect a significant difference (α = 0.05, β = 0.1). The authors expected 10% of cases to drop out. Thus, 19 women for each group were needed.

All data were collected, coded, and analyzed using SPSS software (SPSS® 15.0 for Windows). Continuous variables were compared with the independent Student's t-test, whereas the $\chi 2$ test (or Fisher's Exact Tests when appropriate) was used to compare proportions between groups. The p-value < 0.05 was considered statistically significant. Due to the current World Health Organization statement that all women being recruited into clinical trials must provide informed consent, ethical approval of the present study was obtained from the Ethical Committee on Research on Human at the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Signature approval was obtained on the informed consent form.

Results

Forty women were enrolled. No participant dropped out from the study. The 40 subjects were included in the study analysis. The numbers of subjects treated with celecoxib and with placebo were 20 in each group. There were no significant differences between the groups regarding mean age, parity, BMI, the duration of Jadelle® use and the endometrial thickness (Table 1). Of the total subjects, 70% treated with celecoxib stopped bleeding, whereas 0% in the placebo group stopped bleeding within seven days after the initial treatment. There were significant differences between the groups ($p < 0.0001$). The mean duration of bleeding-free interval was significantly longer in celecoxib than placebo group (24.0 ± 1.65 days vs. 10.0 ± 6.50 days; $p < 0.001$). The mean duration of bleeding days (within 28 days of the follow-up period) was significantly shorter in celecoxib than the placebo group (5.0 ± 1.65 vs. 19.0 ± 6.50 days; $p < 0.001$). There was no detectable adverse effect in both groups. Eighty percent of patient in the celecoxib group were satisfied with the treatment. Patients satisfaction in the celecoxib group was significantly higher than placebo group (80% vs. 30%; $p < 0.001$).

Discussion

Jadelle® is the two rods of progestin only contraceptive implant, the most common problem for progestin only contraceptive users is the change in menstrual bleeding, which is the major cause of premature termination[1-4]. Participants in the present study were women admitted to the clinic due to their bleeding complaints during Jadelle® implant use. The present study is the first clinical trial that evaluates the effect of COX-2 inhibitor for the treatment of uterine bleeding irregularities in Jadelle® users. The results of the present study show that the percentage of women whose bleeding stopped within seven days after the initiation of the treatment was significantly higher after celecoxib treatment (70% of celecoxib group vs. 0% of placebo group). This finding is similar to those in other studies previously published, which stated that the medical treatment was more effective than placebo for alleviating the bleeding in progestin only contraceptive users[25-27]. The proportion of women whose bleeding stopped within seven days after the initiation of the treatment with no adverse effect from COX-2 inhibitor were similar to the previous study of Nathirojanakun et al[25]. There were a few adverse effects in the mefenamic acid group found in the study of Kaewrudee et al[26].

It is hypothesized that selective inhibition of COX-2 may be more effective in decreasing bleeding than conventional NSAIDs by selectively inhibiting the synthesis of PGI2 only without decreasing TXA_2 formation. The authors thus directly tested this hypothesis by using a selective COX-2 inhibitor as the ideal NSAIDs to decrease irregular uterine bleeding in Jadelle® users.

The percentage of the subjects whom bleeding was stopped within seven days after initial treatment was significantly higher in the celecoxib group than in the placebo group (70% vs. 0%; $p < 0.001$).The mean duration of bleeding days was significantly shorter in celecoxib than placebo group (5.0 ± 1.65 vs. 19.0 ± 6.50

Table 1. Baseline characteristics of the two groups (mean $\pm$ SD)

	Celecoxib group (n = 20)	Placebo group (n = 20)	p-value
Age (year)	34.10 ± 7.40	29.50 ± 9.84	0.10
Parity	2.20 ± 1.50	1.50 ± 0.51	0.06
BMI (kg/m^2)	21.90 ± 3.82	23.30 ± 2.45	0.17
Duration of Jadelle® use (month)	13.00 ± 10.70	9.70 ± 8.04	0.27
Endometrial thickness (mm)	3.97 ± 0.74	3.57 ± 2.03	0.41

days; $p < 0.001$). The mean duration of bleeding-free interval was significantly longer in celecoxib than placebo group (24.0 ± 1.65 days vs. 10.0 ± 6.50 days; $p < 0.001$). Patients satisfaction in celecoxib group was significantly higher than in the placebo group (80% vs. 30%; $p < 0.001$). There was no detectable adverse effect in both groups. The present study also demonstrated the effectiveness of celecoxib treatment and evaluated satisfaction of patient. The present study verifies the hypothesis that the mechanism of NSAIDs to reduce the endometrial bleeding is likely from COX-2 inhibition. There were no known serious complications found.

According to the present study, celecoxib is a reasonable choice to treat the irregular bleeding side effect of Jadelle®. However, counseling and reassurance are still required. Irregular bleeding is a known side effect during the first year of Jadelle® use. With continuing use, the occurrence of bleeding can be reduced dramatically. The limitation of the present study is the short follow-up period. Long-term adverse effects of selective COX-2 inhibitors and long-term administration of celecoxib, in order to treat irregular bleeding in Jadelle® users, should be closely monitored.

In conclusion, celecoxib is effective for short-term control of irregular bleeding in Jadelle® users. The mechanism of NSAIDs for the reduction of endometrial bleeding is likely from COX-2 inhibition.

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การประเมินประสิทธิภาพของยา celecoxib และยาหลอกในการควบคุมภาวะเลือดออกจากการใช้ยาฝังคุมกำเนิด Jadelle®

กฤษณา บัวแสง, สุรศักดิ์ ฐานีพานิชสกุล

วัตถุประสงค์: เพื่อประเมินประสิทธิภาพของยา celecoxib และยาหลอกในการควบคุมภาวะเลือดออกจากการใช้ยาฝังคุมกำเนิด Jadelle®

ชนิดของการศึกษา: การศึกษาเชิงทดลอง

สถานที่ทำการวิจัย: หน่วยวางแผนครอบครัว โรงพยาบาลจุฬาลงกรณ์

วัสดุและวิธีการ: ผู้มารับบริการฝังยาคุมกำเนิด Jadelle® ที่หน่วยวางแผนครอบครัวที่มีภาวะเลือดออกจำนวนทั้งหมด 40 คน จะถูกแบ่งออกเป็น 2 กลุ่มโดยวิธีการสุ่ม, ผู้รับบริการที่ได้รับยา celecoxib จำนวน 20 ราย โดยได้รับยาในขนาด 200 มิลลิกรัม วันละครั้งเป็นเวลา 5 วัน และผู้รับบริการที่ได้รับยาหลอกเป็นจำนวนทั้งหมด 20 ราย โดยได้รับยาหลอกในลักษณะเดียวกัน, ช่วงระยะเวลาที่ติดตามผู้รับบริการทุกคนจะต้องบันทึกภาวะเลือดออกในแต่ละวันว่าหยุด หรือ ไม่หยุด, อาการข้างเคียงจากการใช้ยา และความพึงพอใจในผลการรักษา

ผลการศึกษา: ร้อยละของผู้รับบริการที่มีภาวะเลือดหยุดในสัปดาห์แรกหลังการรักษาในกลุ่ม celecoxib สูงกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (70%, 0%; $p < 0.001$) ระยะเวลาที่เลือดหยุดติดต่อกันในช่วงเวลา 28 วันในกลุ่ม celecoxib สูงกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (24.0 ± 1.65, 10.0 ± 6.50 วัน; $p < 0.001$) ค่าเฉลี่ยจำนวนวันที่มีเลือดออกในกลุ่ม celecoxib ต่ำกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (5.0 ± 1.65, 19.0 ± 6.50 วัน; $p < 0.001$) ความพึงพอใจในผลการรักษาในกลุ่ม celecoxib สูงกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (80%, 30%; $p < 0.001$) และไม่พบผลข้างเคียงจากการใช้ยาจากทั้ง 2 กลุ่ม

สรุป: ยา celecoxib มีประสิทธิภาพในการควบคุมภาวะเลือดออกจากการใช้ยาฝังคุมกำเนิด Jadelle® มากกว่ายาหลอก กลไกของยาต้านอักเสบที่ไม่ใช่สเตียรอยด์ ในการลดเลือดออกน่าจะเกิดจากการยับยั้งเอนไซม์ ไซโคออกซิจิเนส-2