Original Article

Effectiveness of Etoricoxib 120 mg in Pain Relief during IUD Insertion: A Randomized, Double-Blind, Placebo Controlled Clinical Trial

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Objective: To evaluate the effectiveness of Etoricoxib 120 mg in pain relief during intrauterine device [IUD] insertion and to evaluate factors related to pain during IUD insertion.

Materials and Methods: The study design was randomized, double-blind, placebo-controlled trial. Informed consents were obtained. Baseline characteristics were recorded. One hundred thirty women participated in the present research, 65 subjects were placed into each group equally by simple computerized randomization. IUD was inserted, pain score was evaluated, and the analysis was performed. There was no dropout.

Results: More than 50% of subjects experienced significant pain immediately after IUD insertion. Etoricoxib 120 mg before the procedure did not significantly reduce the pain. Etoricoxib seems to be effective among women who never had vaginal delivery. The median pain score was 7 in the placebo group and 5 in the Etoricoxib group. Ninety-two-point-nine percent of the participant in the placebo group had significant pain compared to 66.7% in the Etoricoxib group.

Conclusion: Etoricoxib 120 mg does not help in relieving pain as preemptive analgesia for IUD insertion. However, it seems to be more effective for women who never experienced vaginal delivery.

Keywords: Etoricoxib, IUD insertion, Pain scores, Preemptive analgesia

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There is a variety of effective contraceptive methods available for women seeking a contraceptive method to protect them against pregnancy. Their choice normally reflects their preference to the method. Some choose a condom while the other resort to hormonal oral contraceptive pills [OCP], subdermal implantation of the implant, injectable methods, intrauterine device [IUD], sterilization, safe period, or barrier methods to suit their wants and needs. Globally, OCP has been extensively used. The IUD is much preferred by women in the United State of America [USA], whereas use of the IUD is much lower in Thailand, 0.8% to 1.2% of the total prevalence of contraceptive use between 2006 and 2012[1]. This has much due to the fear of pain that the device may produce, especially pain during IUD insertion.

Etiology of pain has not been confirmed, but vasovagal effect has been reported. This has led to create the "ideal" IUD producing no pain at insertion or at initial use. The IUD development has been continuously active within the last four decades by inserting hormone such as levonorgestrel or substance such as copper within the design of the IUD to reduce pain that may occur among users[2,3]. In addition, in the last few decades, studies about IUD insertion and pain that may occur during the procedure and after initiation of use, have been done to promote IUD use among a wide range of women across the globe. There are many interventions to reduce pain during IUD insertion and initial use, however, the results are conflicting, and many have shown the ineffective use of analgesia and/or non-steroidal anti-inflammatory drugs [NSAID][4-12]. Some authorities have even recommended close counseling before insertion and at initial use as an "oral analgesia" for pain relief[2-4].

Etoricoxib 120 mg has been reported to be the best choice for controlling acute post-operative pain compared to other NSAID such as ibuprofen or acetaminophen[7]. It is a selective inhibitor of cyclo-oxygenase 2 [COX-2] with moderate rate of absorption when given orally. The maximum plasma drug con-

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centration occurs after about an hour, and the extent of absorption is similar in oral and intravenous. In Thailand, use of analgesic control or NSAID among women before IUD insertion has been practiced, but there have been no systematic reports or studies to evidence the outcomes of such practice. The present study aimed to evaluate whether Etoricoxib 120 mg was effective in reducing pain among women having the IUD insertion. In addition, it would determine if other factors such as history of vaginal delivery, history of IUD insertion, body mass index [BMI], size of uterus, timing during insertion, and providers skill and experience were related to pain produced by IUD insertion.

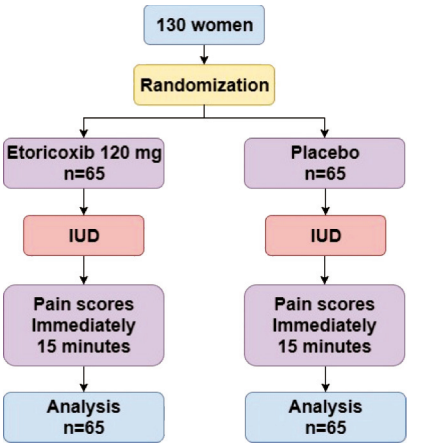

Figure 1. Study procedure.

Materials and Methods

Study design

The present study was a prospective, randomized, double-blinded, placebo controlled clinical trial to assess whether Etoricoxib 120 mg could relieve pain during IUD insertion and at initial use. One hundred thirty women were screened to be allocated into two groups, study drug and placebo, by computer generated blocks with varying sizes, stratified by center.

Study participants

All women of reproductive age who came to the Family Planning Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand between April 2016 and April 2017 for family planning service were approached and invited to participate in the present study. Healthy women 18 to 45 years of age, BMI between 18.5 to 30 kg/m^2, multiparous or nulliparous, no contraindication to IUD insertion, no underlying diseases, no contraindication to use Etoricoxib 120 mg, and no history of previous contraceptive IUD use were screened for the study. Women who met all the above-mentioned criteria were eligible for the study and asked for their willingness to participate in the study. For those who expressed their interest, a detailed explanation about the nature of the study were provided. Women who were interested to join the study signed the consent forms before starting the study procedure. One hundred thirty women were enrolled into the study, 65 for each group. Each participating woman was asked to take either Etoricoxib 120 mg or placebo 60 minutes before the IUD was fitted (Figure 1).

Study materials

Either Etoricoxib 120 mg or the placebo was provided to the participating women by computer randomized allocation 60 minutes before commencement of the IUD insertion procedure. Sequentially, numbered opaque envelops were prepared by a member of the research team not involved in the enrollment and follow-up procedures. Both Etoricoxib 120 mg and the placebo were put into capsules to create the identical appearance, and were put in the package. The placebo was a plain, simple, and safe edible tablet of powder, mixing with no substance. This procedure was done at the central supply. The pharmacy dispended the study drugs based on the randomization scheme to ensure allocation concealment.

The IUD used in the present study was the Copper T380, which currently gained popularity worldwide and in Thailand. The possible mechanism of contraceptive effectiveness of Copper T380 is enhanced by copper continuously released into the uterine cavity, as well as its interference with sperm transportation and fertilization, which in turn prevents the embryo implantation, and the copper from IUD acting as the spermicidal agent. In addition, contraceptive efficacy has been claimed for duration of up to ten years. The pregnancy rate has been reported to be less than one pregnancy per woman year. The Etoricoxib 120 mg group was performed by the well-trained medical team serving currently at family planning clinic using standard manufacturer approved technique, including placement of a tenaculum at the anterior lip of the cervix and doing uterine sounding to measure the length of uterine cavity. No cervical dilatation or misoprostol was used for each case of IUD fitting.

Data collection and analysis

A face to face interview with a pre-coded

questionnaire was developed to collect women personal or demographic data such as age, education, income, BMI, residence and religion, history of contraceptive use, obstetric history such as para, and mode of child delivery. The family planning social worker, one of the research team took care of this procedure. Women were shown the 100-mm Visual Analog Scale [VAS] when asked about their feelings to each pain related to IUD insertion three times, before the IUD insertion, immediately after IUD insertion, and 15 minutes after IUD insertion. Pain scores were divided into two categories, pain score 0 to 3, considered as mild to moderate pain, and 4 to 10 as severe pain.

Data of 130 women were analyzed for their background information, medical history and three times analysis of the pain scores by VAS. The number and percentage were presented for women's background data. Chi-square test was used for comparison variables between groups. A *p*-value smaller than 0.05 was considered as statistically significant.

Approval of the Siriraj Institutional Research Board [SiIRB]

The present research project had been approved by the IRB of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand on February 29, 2016, IRB No. Si 143/2016.

Results

One hundred thirty women taking either Etoricoxib 120 mg or placebo were included in the present analysis, 65 women for each group. Table 1 shows the demographic characteristics of the women of the two groups. Both groups were comparable regarding to age, educational level, area of residence, religion, marital status, and income.

Table 2 shows the medical characteristics of women between the drug and placebo groups. It was observed that mean BMI of women in the placebo group was likely to be overweight, 53.8% vs. 40%. Women in the Etoricoxib group was more likely to be multiparous, 56.9% vs. 41.6%, but there was no difference in the number of vaginal delivery between the two groups, Etoricoxib 72.3% and placebo group 78.5%. Use of OCP was the most prevalent among women in the present study, Etoricoxib 75.4% and placebo 72.3%. Previous IUD use among women in both groups was similar; 41.5% in Etoricoxib and 47.7% in placebo group.

Comparison of characteristics of IUD insertion procedure is shown in Table 3. There was no statistically significant difference in the mean uterine sound, 7.3±0.9 cm for Etoricoxib and 7.5±0.9 cm for placebo, and mean of IUD insertion time, 25.8±15.3 seconds for Etoricoxib and 23.7±13.9 seconds for placebo. In addition, there was no statistical difference in the skill and experience of providers, either the OB-GYN Residents or the Fellows, $p = 0.380$.

Pain scores related to the IUD insertion are shown in Table 4. Median pain scores before IUD insertion, immediately after IUD insertion, and 15 minutes after

Table 1. Comparison of baseline demographic characteristics between the 2 groups

Characteristics	Etoricoxib (n = 65)	Placebo (n = 65)	*p*-value
Age (years), mean ± SD	34.6±7.4	36.1±6.8	0.230
Education			0.106
Less than bachelor degree	44 (67.7)	35 (53.8)	
Bachelor degree or higher	21 (32.3)	30 (46.2)	
Residence			0.079
Bangkok	28 (43.0)	38 (58.5)	
Others	37 (57.0)	27 (41.5)	
Religion			0.500
Buddhist	63 (96.9)	64 (98.5)	
Others	2 (3.1)	1 (1.5)	
Marital status			0.583
Married	33 (50.8)	31 (47.7)	
Single	32 (49.2)	34 (52.3)	
Income (Baht)			0.388
<50,000	55 (84.6)	51 (78.4)	
≥50,000	10 (15.4)	14 (21.6)	

Data presented as mean ± SD or n (%)

Table 2. Comparison of baseline clinical characteristics between the 2 groups

Characteristics	Etoricoxib (n = 65)	Placebo (n = 65)	*p*-value
BMI (kg/m^2), mean ± SD	24.4±3.3	24.9±3.3	0.380
BMI category			0.114
Normal	39 (60.0)	30 (46.2)	
Overweight	26 (40.0)	35 (53.8)	
Parity			0.064
1	28 (43.1)	38 (58.4)	
≥2	37 (56.9)	27 (41.6)	
Ever had vaginal delivery	47 (72.3)	51 (78.5)	0.415
Previously used contraception			
OCP	49 (75.4)	47 (72.3)	0.690
Emergency contraception	25 (38.5)	21 (32.3)	0.463
IUD	27 (41.5)	31 (47.7)	0.480
DMPA	34 (52.3)	32 (49.2)	0.726
Implant	15 (23.1)	9 (13.8)	0.175
Condom	38 (58.5)	41 (63.1)	0.590

OCP = oral contraceptive pills; IUD = intrauterine device; DMPA = depot medroxyprogesterone acetate

Data presented as mean ± SD or n (%)

IUD insertion were not statistically significant different between the two groups, $p = 0.549$, 0.873, and 0.680, respectively. Moreover, report of severe pain, pain score ≥4, immediately after IUD insertion and 15 minutes after IUD insertion had no statistically significant difference between the two groups, $p = 1.000$ and 0.571, respectively.

Evaluation of pain scores stratified by vaginal delivery experience compared between the two groups. Table 5 shows that among women who never had vaginal delivery, median pain scores immediately after IUD insertion was statistically significant lower in the Etoricoxib group than in the placebo group (interquartile range [IQR] 2, 6.25) vs. 7 (IQR 5, 8), $p = 0.022$. However, no difference was observed at 15 minutes after IUD insertion. Furthermore, the Etoricoxib group had relatively lower proportion of reporting severe pain than placebo group, but without statistical significance in the two groups, 66.7% vs. 92.9% immediately after IUD insertion, and 5.6% vs. 28.6%, 15 minutes after IUD insertion. Nevertheless, no statistically significant difference in median pain scores and severe pain scores were observed in either groups of having previous vaginal delivery at every time point (Table 5).

Table 3. Comparison of characteristics of IUD insertion procedure between the 2 groups

Characteristics	Etoricoxib (n = 65)	Placebo (n = 65)	*p*-value
Uterine sound (cm), mean ± SD	7.3±0.9	7.5±0.9	0.306
IUD insertion time (seconds), mean ± SD	25.8±15.3	23.7±13.9	0.399
Provider			
Resident	54 (83.1)	50 (76.9)	0.380
Fellow	11 (16.9)	15 (23.1)	

IUD = intrauterine device

Data presented as mean ± SD or n (%)

Table 4. Comparison of pain scores between the 2 groups

Pain scores	Etoricoxib (n = 65)	Placebo (n = 65)	*p*-value
Timing of evaluation, median (IQR)			
Before IUD insertion	0 (0, 0)	0 (0, 0)	0.549
Immediately after IUD insertion	4 (1.5, 6)	4 (2, 6)	0.873
15 minutes after IUD insertion	0 (0, 2)	0 (0, 1.5)	0.680
Pain score ≥4			
Immediately after IUD insertion	36 (55.4)	36 (55.4)	1.000
15 minutes after IUD insertion	6 (9.2)	8 (12.3)	0.571

IUD = intrauterine device; IQR = interquartile range

Data presented as median (IQR) or n (%)

Table 5. Comparison of pain scores between the 2 groups, stratified by vaginal delivery experience

Pain scores	Etoricoxib	Placebo	*p*-value
Never had vaginal delivery (n = 32)	n = 18	n = 14	
Timing of evaluation, median (IQR)			
- Immediately after IUD insertion	5 (2, 6.25)	7 (5, 8)	0.022
- 15 minutes after IUD insertion	0 (0, 0.25)	0 (0, 1.5)	0.251
Pain score ≥4			
- Immediately after IUD insertion	12 (66.7)	13 (92.9)	0.104
- 15 minutes after IUD insertion	1 (5.6)	4 (28.6)	0.142
Ever had vaginal delivery (n = 98)	n = 47	n = 51	
Timing of evaluation, median (IQR)			
- Immediately after IUD insertion	4 (1, 6)	3 (1, 5)	0.470
- 15 minutes after IUD insertion	0 (0, 2)	0 (0, 1)	0.170
Pain score ≥4			
- Immediately after IUD insertion	24 (51.1)	23 (45.1)	0.555
- 15 minutes after IUD insertion	5 (10.6)	4 (7.8)	0.734

IUD = intrauterine device; IQR = interquartile range

Data presented as median (IQR) or n (%)

Discussion

Intrauterine device or IUD is one of the most effective methods in long-acting reversible contraceptive methods. However, pain during insertion or at the initial use is the most important factor reducing the popularity of its use. After four decades of a long trail of research to reduce pain in IUD insertion, there seems to be no best analgesia or NSAIS to overcome this attribute of the IUD application. Etoricoxib claimed to be the most effective medication for pain control but does not seem to work out well among women in the present study. Some studies using NSAIDs such as ibuprofen, misoprostol, or lidocaine to reduce pain at insertion of IUD reported no effect of these NSAIDs on pain relief, which is similar to the present study[10-12]. In this study, factors such as history of vaginal child delivery is likely to reduce pain, but history of previous IUD insertion seems to increase pain. Other factors such as BMI, size of uterus, timing during IUD insertion, and provider have no association with pain. In addition, there is no statistically significant difference of pain at different period of time, before IUD insertion, immediately after IUD insertion, and 15 minutes after IUD insertion between the medication and the placebo groups.

Women with no previous vaginal delivery seemed to have less pain than those who did. Although women in the placebo group were slightly overweight and more women in the medication group were more multiparous, report of pain among the two groups were similar.

The strength of the present research is that it was a randomized clinical trial that used the double blind technique for evaluation, and collected all the data of each woman within one visit, which took only short time and received excellent cooperation. Moreover,

the participants had chosen to have device insert with medication for pain relief. They could resort to this medication when they feel pain related to the used device, and they could feel free to contact our research team whenever problems occurred after the procedure. Future research should focus on women with and without medication to avoid the 'placebo effects' occurring in the present study.

The limitation of the present research was mixing of the subjects in term of vaginal child delivery experience, which might have some effect on the results, and there were limited samples in subgroup analysis.

Conclusion

In the present study, Etoricoxib 120 mg is not likely to successfully relieve pain after IUD insertion. It is observed that even though Etoricoxib 120 mg could not work well in reducing pain at different time points of IUD insertion procedure, women who never had vaginal delivery reported having lower pain than those who had other means of child delivery such as Caesarian section or nulliparous. This implies that, to some extent, this medication still can work well. Having history of previous IUD use has increased pain as compared to those who never have used. Factors such as BMI, size of uterus, timing during IUD insertion, and providers are not associated with the level of pain. "Placebo effect" should be handled carefully when women report about their feelings.

According to the results of IUD insertion procedure, the result showed that more than 50% of the women still experienced pain during and after procedure. As a provider, we should be aware of this and apart from the verbal counseling before procedure, the research should be focusing on pain relief to reach the high standard care of IUD insertion as well as reducing the stigma on IUD use.

Further studies with larger sample size for adequate evaluation of the results should be considered. Some specific subgroups such as in women who never have vaginal delivery are also interesting to evaluate the effectiveness of Etoricoxib. Others effective methods for pain relief or even the combinations of various techniques should be investigated.

What is already known on this topic?

IUD insertion is one of the popular methods of contraception[1]. The side effects from IUD insertion can be irregular bleeding, dysmenorrhea, heavy period, and intrauterine infection. Apart from the side effects, insertion skills and experiences of providers as well as pain associated with the IUD insertion have also contributed to the low use of this method[2]. The theory of pre-emptive analgesia such as Ibuprofen before the IUD insertions has been applied for some time, however, the results are not impressive[8]. This has led to the no information of this theory included in the standard of practice for pain relief during IUD insertion[12].

What this study adds?

More than half of the study women experienced pain immediately after insertion. The study drug, Etoricoxib 120 mg before the procedure did not significantly reduced the pain, but it seems to be more effective for women who never experienced vaginal delivery. More research should be conducted to determine the reduction of pain in the women who had experienced during the IUD insertion procedure. Even though the Etoricoxib 120 mg has been the most advanced medication as a pre-emptive oral analgesia, it was not likely to reduce pain during procedure in the present study.

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Potential conflicts of interest

None.

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ประสิทธิภาพของยา Etoricoxib 120 มิลลิกรัม ในการลดการเจ็บปวดขณะใส่ห่วงคุมกำเนิด: การศึกษาเปรียบเทียบแบบสุ่มและปกปิดสองทางกับยาหลอก

สิวะพร พีระนันทรังษี, มานพชัย ธรรมคันโธ

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของยา Etoricoxib 120 มิลลิกรัม ในการลดการเจ็บปวดขณะใส่ห่วงคุมกำเนิด และศึกษาปัจจัยที่มีผลต่อความเจ็บปวด

วัสดุและวิธีการ: การศึกษานี้เป็นการทดลองแบบสุ่ม ปกปิดสองทาง กับยาหลอก มีการแสดงความจำนงในหนังสือเจตนาแสดงความยินยอมเข้าร่วมการศึกษา ข้อมูลเบื้องต้นได้จากผู้ร่วมการศึกษา 130 คน แบ่งเป็นกลุ่มละ 65 คน แบบสุ่ม มีการใส่ห่วงคุมกำเนิด และเก็บข้อมูลเพื่อนำไปวิเคราะห์

ผลการศึกษา: มากกว่า 50% ของผู้ร่วมการศึกษาให้คะแนนความเจ็บปวดอย่างมีนัยสำคัญหลังการใส่ห่วงทันที Etoricoxib 120 มิลลิกรัม ก่อนหัตถการไม่ช่วยลดความเจ็บปวดอย่างมีนัยสำคัญทางสถิติ อย่างไรก็ตามยาวิจัยดูเหมือนจะมีประสิทธิภาพในการลดความเจ็บปวดในสตรีที่ไม่เคยผ่านการคลอดทางช่องคลอดมาก่อน มัธยฐานของคะแนนความเจ็บปวด คือ 7 (92.9%) ในกลุ่มยาหลอก และ 5 (66.7%) ในกลุ่มยาศึกษา

สรุป: Etoricoxib 120 มิลลิกรัม ไม่ช่วยลดความเจ็บปวดในการใส่ห่วงคุมกำเนิด แต่มีประสิทธิภาพในกลุ่มที่ไม่เคยคลอดทางช่องคลอด