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การใช้ยาไอบูโพรเฟนแก้ปวดล่วงหน้าก่อนผ่าตัด เพื่อลดอาการปวดหลังถอดยาฝังคุมกำเนิด: การศึกษาวิจัยแบบสุ่ม ปกปิดสองชั้น

Preemptive Oral Ibuprofen Improves Postoperative Analgesia Following Contraceptive Implant Removal: A Double-Blinded, Randomized Trial

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บทคัดย่อ

หลักการและเหตุผล : กระทรวงสาธารณสุขมีนโยบายส่งเสริมการใช้ยาคุมกำเนิดแบบฝัง เพื่อป้องกันการตั้งครรภ์ในวัยรุ่นและสตรีอายุ 20 ปีขึ้นไป เฉพาะกรณีหลังยุติการตั้งครรภ์ การใช้ยาแก้ปวดล่วงหน้าเพื่อการลดความเจ็บปวดจากการผ่าตัดถอดยาฝังคุมกำเนิด อาจช่วยส่งเสริมให้ผู้รับบริการมีประสบการณ์ที่ดีและตัดสินใจเลือกใช้วิธีนี้ในการคุมกำเนิดมากขึ้น

วัตถุประสงค์ : เพื่อศึกษาประสิทธิผลในการลดความเจ็บปวดของการรับประทานยาไอบูโพรเฟนก่อนการผ่าตัดถอดยาฝังคุมกำเนิด

วิธีการศึกษา : เป็นการวิจัยเชิงทดลองแบบสุ่ม ที่มีกลุ่มควบคุมปกปิดสองชั้น ศึกษาในผู้ป่วยหญิงอายุ 18-30 ปี จำนวน 76 ราย ที่มารับบริการผ่าตัดถอดยาฝังคุมกำเนิดที่โรงพยาบาลบุรีรัมย์ ผู้เข้าร่วมถูกสุ่มแบ่งเป็นสองกลุ่ม (1:1) กลุ่มศึกษาได้รับไอบูโพรเฟนก่อนและยาหลอกหลังการผ่าตัด ในขณะที่กลุ่มควบคุมได้รับยาหลอกก่อนการผ่าตัดและไอบูโพรเฟนหลังการผ่าตัด มีการบันทึกคะแนนความเจ็บปวดระหว่างการฉีดยาชาเฉพาะที่ หลังการผ่าตัดทันที และที่ 1 8 และ 24 ชั่วโมงหลังการผ่าตัด นอกจากนี้ยังบันทึกจำนวนเม็ดยาพาราเซตามอลที่ผู้ป่วยใช้ภายใน 24 ชั่วโมงหลังการผ่าตัด

ผลการศึกษา : ข้อมูลพื้นฐานของผู้เข้าร่วมวิจัย เช่น อายุ น้ำหนัก ส่วนสูง ดัชนีมวลกาย และระยะเวลาการผ่าตัด มีค่าใกล้เคียงกันในทั้งสองกลุ่ม สำหรับผลลัพธ์หลัก: การศึกษานี้เปรียบเทียบคะแนนความปวดหลังผ่าตัด ระหว่างสองกลุ่มโดยใช้สถิติ GEE พบว่าคะแนนความปวดโดยเฉลี่ยของกลุ่มรักษามีค่าต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ โดยมีค่าเฉลี่ยต่างกัน 0.6 (p-value = 0.014) หลังควบคุมปัจจัยอื่นๆ ผลลัพธ์รอง: กลุ่มรักษาใช้พาราเซตามอลน้อยกว่ากลุ่มควบคุม (0.6 เม็ด และ 1.6 เม็ด p-value = 0.001) และไม่พบหลักฐานของผลไม่พึงประสงค์ในทั้งสองกลุ่ม

สรุป : การให้ยาไอบูโพรเฟนรับประทานก่อนผ่าตัด สามารถลดคะแนนความปวดและลดปริมาณการใช้ยาพาราเซตามอลหลังผ่าตัดในผู้ป่วยที่มารับบริการถอดยาฝังคุมกำเนิด

คำสำคัญ : ถอดยาฝังคุมกำเนิด การให้ยาแก้ปวดเชิงรุกก่อนการผ่าตัด ไอบูโพรเฟน

ABSTRACT

Background : The Ministry of Public Health has a policy to promote the use of contraceptive implants to prevent pregnancy in adolescents and women over 20 years old who have recently undergone pregnancy termination. Using preemptive analgesia to reduce pain from contraceptive implant removal may help enhance the service experience and encourage more individuals to choose this method of contraception.

Objective : To assess the efficacy of preoperative ibuprofen administration in reducing pain related to contraceptive implant removal surgery.

Methods : This was a double-blinded, randomized trial involving 76 female patients aged 18-30 years who underwent contraceptive implant removal at Buri Ram Hospital. Participants were randomly allocated (1:1) to the study group received ibuprofen preoperatively and placebo postoperatively, while the control group received placebo preoperatively and ibuprofen postoperatively. Pain scores were recorded during local anesthetic injection, immediately after the procedure, and at 1, 8 and 24 hours postoperatively. Additionally, the number of paracetamol tablets consumed by the patients within 24 hours postoperatively was recorded.

Results : Participants' baseline characteristics like age, weight, height, BMI, and operative time were similar between groups. Primary Outcome: This study compared the postoperative pain scores between both groups using generalized estimating equations (GEE) statistics. The analysis revealed that the average overall pain score of the treatment group was significantly lower than that of the control group, with a mean difference of 0.6 (p-value = 0.014) after controlling for other factors. Secondary Outcomes: The number of paracetamol tablets used in the treatment group was lower than in the control group (0.6 tablets vs. 1.6 tablets, p-value = 0.001). Adverse Outcomes: There was no evidence of adverse outcomes in either group.

Conclusions : The use of preemptive oral ibuprofen decreased pain scores and postoperative paracetamol consumption in patients undergoing contraceptive implant removal.

Keywords : contraceptive implant removal, preemptive analgesia, ibuprofen.

Background

The contraceptive implant is a longacting, highly effective and convenient birth control method.[1-2] It consists of a synthetic progestin hormone in powder form contained in a small plastic rod that is inserted under the skin on the inner side of the upper arm to provide contraception for up to 3 years.[2-6] As a result of the Ministry of Public Health's efforts to promote the use of contraceptive implants for preventing teenage and unwanted pregnancies in women over 20 years old, there has been an increase in the number of individuals opting for contraceptive implants.[7-9] After the 3-year period, recipients need to undergo a minor surgical procedure to remove the implant. Local anesthesia is injected to numb the area, and paracetamol or ibuprofen is prescribed for postoperative pain relief.[10] Clients and physicians agreed that the fear of pain associated with both insertion and removal is a disadvantage of this contraceptive method for young women.[11] Reducing pain from contraceptive implant removal through preemptive analgesia with preoperative ibuprofen may improve the patient experience and encourage recipients to choose this contraceptive method again.[12]

The concept of preemptive analgesia suggests that administering an analgesic before a painful event is more effective than giving it afterward. It is based on two main postulates: first, that an analgesic given before nociception (pain perception) is more effective than one given after; and second, that this beneficial effect lasts beyond the analgesic's pharmacological action. Providing analgesics before a procedure helps prevent pain pathway sensitization, thereby reducing pain levels and the need for additional analgesics during and after surgery or injury.[13-15] It is an important therapeutic approach that uses combinations of local anesthetics, neuraxial blockade, and inhibition of mediators of central neuroplasticity to prevent mechanisms of self-perpetuating pain.[16-17] After the concept of preemptive analgesia gained widespread acceptance, the benefits of preemptive analgesia in relieving postoperative pain and reducing analgesic consumption received clinical and research attention for many years.[18] A meta-analysis by Ong and colleagues on the efficacy of preemptive analgesia for acute postoperative pain management indicated that preemptive analgesia showed some beneficial effects with non-steroidal anti-inflammatory drug (NSAID) administration.[19] Ibuprofen, a NSAID, works by reducing the production of prostaglandins, which contribute to pain and inflammation. When taken orally, ibuprofen is rapidly absorbed, with maximal analgesic efficacy achieved within 1-2 hours after dosing. However, it demonstrates an onset of analgesic action at around 20 minutes.[20] Notably, ibuprofen is more effective than acetaminophen when used as preemptive analgesia.[21] Studies suggest that taking oral ibuprofen before surgery can be effective in reducing postoperative pain intensity and delaying the peak of pain, particularly in the first few hours after surgery. Research on preemptive analgesia with oral ibuprofen shows promise for managing postoperative pain, especially following procedures like dental care.[22-23] Nevertheless, as far as we are aware, there have been no

published reports regarding the utilization of preemptive ibuprofen for contraceptive implant removal surgery.

However, no studies have compared whether taking ibuprofen before or after contraceptive implant removal has differential effects on pain reduction.

Objective

To evaluate the efficacy of administering preoperative oral ibuprofen in reducing pain related to contraceptive implant removal surgery, we assessed the primary outcome: the average pain score (numeric rating scale: 0-10) measured four times within the initial 24 hours. Additionally, we evaluated secondary outcomes such as the requirement for paracetamol and the occurrence of adverse effects (AEs).

Methods

Study designs

This double-blind, placebo-controlled, randomized trial was conducted from September 2023 to February 2024 at the family planning clinic of Buri Ram Hospital in Thailand. The study protocol was approved by the Buri Ram Hospital Ethics Committee for Human Research (reference number BR 0033.102.1/64, dated September 4th., 2023) and adhered to the principles of the Declaration of Helsinki.

Participants

Women seeking contraceptive implant removal were eligible to participate. Inclusion criteria included women aged 18-50 years old who were willing to receive phone calls from researchers for postoperative follow-up after contraceptive implant removal and could read and write Thai. Exclusion criteria were patients with a history of NSAID allergy, history of gastritis, gastrointestinal bleeding, asthma, renal failure; use of antipyretic analgesics within 7 days before surgery; inability to palpate the contraceptive implant at the upper arm region due to deeper than normal insertion or implant migration; presence of skin lesions on the arm with the implant; and desire to have a new contraceptive implant inserted in the same arm.

Interventions

At the family planning clinic, the eligible participants were informed about the study protocol and detailed instructions for using the 0-10 numerical rating scale (NRS) for postoperative pain assessment. They were advised to contact the operator in case of any doubt.

All operations were performed by the same attending doctor to minimize differences between operators. After taking the medication per randomization 30 minutes prior, all participants were placed in the supine position with their planned procedure arm flexed and externally rotated with their hand next to their head. The contraceptive implant was located and marked at the lower tip. The skin was cleaned with chlorhexidine, and 2% lidocaine with adrenaline was injected at the removal site. An approximately 2 mm incision was then made using an 11-blade scalpel directly over the distal end of the implant. Gentle manual pressure was applied to push the distal tip of the implant up

into the incision. A curved hemostat was then used to gently grasp and remove the entire implant.[24] Pressure was applied to stop any bleeding. Sutures were typically not required.[25] The removal site was dressed with a sterile gauze and covered with a waterproof adhesive bandage. After the procedure, participants in the study group received a placebo, while those in the control group received ibuprofen. The rescue analgesic drug (paracetamol 500 mg per tablet) was administered based on patient needs, with instructions to take 1 tablet at least 6 hours apart.

Outcome measures

Patient characteristics were collected through interviews and review of medical records. Pain scores were evaluated using the NRS at five distinct time points: during anesthetic administration, immediately after implant removal, and at 8 and 24 hours post-surgery. Following the procedure, patients were interviewed via telephone by a clinical interviewer blinded to their intervention status, to assess pain scores, total paracetamol consumption (number of tablets) within the initial 24 hours, and the occurrence of adverse effects, including drug allergies, dyspepsia, nausea, vomiting, and bleeding.

Sample size

The sample size estimation was based on the preliminary review of routine clinical practice data, the mean numeric rating pain score in the group receiving routine postoperative ibuprofen was 3.5 with a standard deviation of 3, while in the group receiving preoperative ibuprofen, the mean was 0.8 with a standard deviation of 3. Sample size estimation using two independent mean comparisons with a two-sided alpha of 0.05 and statistical power of 90%, allowing for a 30% dropout rate, yielded 38 patients per group, for a total of 76 patients.

Randomization and blinding

Participants were randomly allocated (1:1) using block randomization. Those assigned to the study group received oral ibuprofen before surgery and a placebo afterward, while the control group received a placebo before surgery and oral ibuprofen afterward. The placebo tablets resembled the ibuprofen tablets used in the study. Allocation concealment was ensured by sealing the randomization list in opaque envelopes. The research assistant prepared the study drugs for clinic nurses based on this list. A dedicated nurse, not involved in treatment, administered the sealed study drugs to patients. All participants were blinded to whether they were in the study or control group. To maintain the double-blind nature of the trial, research assistants assessing outcome variables and the physician conducting the surgery were also blinded to group allocation. This step may have contributed to mitigating biases in the study results.

Statistical analysis

Data were analyzed using STATA software (Stata Corporation, College Station, TX, USA). Differences between the study and control

groups were investigated using the χ^2 test and independent t-test to compare baseline data depending on continuous or categorical variables. To obtain an unbiased estimate of treatment effects, this study used the intention-to-treat principle, with participants analyzed in the group to which they had been randomized. Therefore, all data were adopted in GEE to compare changes in outcome variables with respect to the baseline between the 2 groups with adjustments for baseline data. All analyses were considered statistically significant with a p value <0.05.

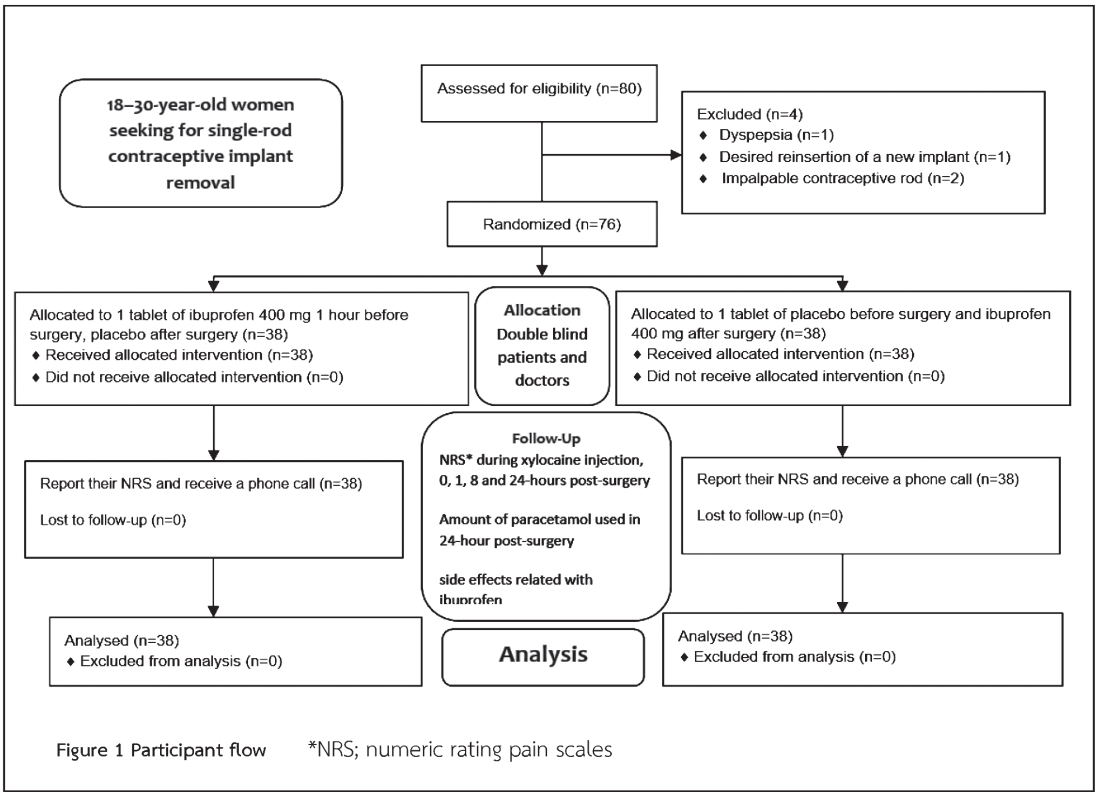

Figure 1 Participant flow *NRS; numeric rating pain scales

Results

Eighty patients were initially recruited, but four were subsequently excluded due to the following criteria: 1 patient presented with dyspepsia, 1 patient desired reinsertion of a new implant and 2 patients had impalpable implants. Consequently, this randomized controlled trial analyzed data from 76 women undergoing contraceptive implant removal, with 38 allocated to the preoperative ibuprofen group and 38 to the postoperative ibuprofen (control group). (Figure 1)

Baseline data

The average age of participants was 20.5 years old, just three years before starting contraceptive implants, still in their adolescence (means, 20 years in both groups), weight, height and body mass index were within the normal range (means, 57, 158 and 22.6 respectively). Both groups exhibited similar baseline characteristics regarding age, weight, height, BMI, and operative time (Table 1).

Table 1. Patients' characteristics and surgical data.

Characteristics	Treatment (n=38)	Control (n=38)	p-value
Age (yr) mean ± SD	20.4 ± 2.8	20.6 ± 2.2	0.748
Weight (kg) mean ± SD	58.1 ± 10.4	55.9 ± 11.0	0.381
Height (cm) mean ± SD	159.3 ± 5.0	157.8 ± 4.5	0.174
Body mass index (kg/m^2) Mean ± SD	22.9 ± 4.0	22.4 ± 4.4	0.648
Operative time (min) Mean ± SD	3.9 ± 0.8	3.9 ± 0.8	0.889

Effects of the Intervention

Primary Outcome: This study compared the postoperative pain scores (NRS) between both groups using GEE statistics. The analysis revealed that the average overall pain score of the treatment group was significantly lower than that of the control group, with a mean difference of 0.6 (p-value = 0.014) after controlling for other factors. (Table 2)

Secondary Outcomes: The number of paracetamol tablets used in the treatment group was lower than in the control group (0.6 tablets vs. 1.6 tablets, p-value = 0.001).

Adverse Outcomes: There was no adverse drug reactions, such as allergic reactions, gastritis, bleeding, or postoperative bruising, were found in either group.

Table 2. Pain score in each period of observation.

Group	Pain score (mean ± SD)					
	During xylocaine injection	Immediate after surgery	1 hours after surgery	8 hours after surgery	24 hours after surgery	Overall mean difference
Treatment (n=38)	2.1 ± 1.9	0.2 ± 0.8	0.1 ± 0.1	0.6 ± 1.2	0.4 ± 0.9	0.6*
Control (n=38)	4.6 ± 2.1	0.5 ± 1.1	0.9 ± 1.9	2.0 ± 2.1	1.7 ± 2.2	

*statistical significance using GEE statistic

Discussion

The majority of participants were around 20 years old, just three years before starting contraceptive implants, still in their adolescence, which aligns with the Department of Health's aim to promote the use of contraceptive implants among adolescents.[7] The prevalence of contraceptive implant use is increasing and the incidence of teenage and unintended pregnancies are decreasing. However, some women hesitate to use this method due to its side effects, and because they are afraid of leaving an implant rod inside their body and fear the implant insertion and removal pain. While the insertion and removal procedures are only minor procedures, the procedures are associated with anxiety and pain.[12]

Pain scores during local anesthesia injection were lower in the preemptive ibuprofen group compared to the control group, likely because ibuprofen is rapidly absorbed and begins its analgesic action within 20 minutes after oral administration. In this study, pain scores

for both groups were lowest immediately after the procedure and at 1 hour post-procedure, due to the effects of the local anesthetic. However, despite ibuprofen's duration of action being around 6 hours, pain scores at 8 and 24 hours post-procedure were still lower in the preemptive ibuprofen group compared to the control group. This suggests that the beneficial effect of preemptive analgesia lasts beyond the analgesic's pharmacological action.

The pain from contraceptive implant removal arises during the local anesthetic injection and post-procedural pain after the local anesthetic wears off. In routine clinical practice, pain is managed by administering analgesics like paracetamol and/or ibuprofen after the procedure, with additional doses when pain occurs.[26] A study by Mapaisankit in 2021 found that spraying ethyl chloride spray instead of injecting local anesthetic was effective in reducing the pain during anesthetic administration and overall pain for one-rod contraceptive implant removal, but was associated with higher pain scores during the procedure.[12] However, ethyl chloride spray is not widely available in general hospitals and is more expensive than injectable local anesthetics. Therefore, the method of reducing pain during anesthetic injection using spray anesthetic is not yet popular.

For patients undergoing minor surgery, it is often the anesthesia itself that is the most painful part of the procedure. The pain is due to the perforation of the skin, the injected liquid activating stretch receptors in the deeper tissues, and the chemical composition of the injected substance.[27] The results of this study showed that changing the timing of 400 mg ibuprofen administration from post-procedure to pre-procedure reduced pain scores during local anesthetic injection. Additionally, patients who received preoperative ibuprofen had lower pain scores than the control group and reduced the need for postoperative paracetamol, which can help reduce side effects from paracetamol use and provide better outcomes for patients.

This study has several strengths. First, by having all procedures performed by a single surgeon, it minimizes the potential impact of differences in technique, needle size, or local anesthetic injection on pain levels. This strengthens the internal validity and allows for a clearer evaluation of the intervention (preemptive ibuprofen) itself. Second, the study design is an RCT where patients, surgeons, and outcome assessors were blinded to group assignments. Third, this appears to be the first study to investigate the use of preemptive oral ibuprofen for mitigating pain associated with contraceptive implant removal. This originality adds to the significance of the findings. Fourth, the study focuses on ibuprofen, a readily available and affordable pain reliever with a relatively low side effect profile. This practical choice enhances the potential real-world application of the findings. Fifth, the results show statistically significant reductions in pain during local anesthetic injection and decreased postoperative paracetamol use in the preemptive ibuprofen group, suggesting a clear benefit for pain management. Lastly, including paracetamol use as a secondary outcome measure provides additional support for the effectiveness of preemptive ibuprofen. However, while the results of this study demonstrate statistically significant pain score reduction with ibuprofen compared to placebo and a clinical reduction in postoperative paracetamol use, the study did

not compare patient satisfaction levels between the two groups. Therefore, it is premature to conclude whether preemptive ibuprofen administration would lead to greater patient satisfaction among contraceptive implant users and potentially encourage increased uptake of this contraceptive method among adolescents.

Recommendations for Future Research

Future studies should include measures of patient satisfaction to assess the impact of preemptive ibuprofen on overall patient experience. A comprehensive cost-effectiveness analysis comparing preemptive ibuprofen to other pain management methods is necessary to inform clinical decision-making. By addressing these limitations and conducting further research, we can gain a more comprehensive understanding of the pain management during contraceptive implant removal, particularly among adolescents.

Conclusion

Based on the results of this preemptive analgesia study, it is concluded that changing the timing of oral ibuprofen administration from postoperative to preoperative by 30 minutes is effective in relieving pain during local anesthesia injection, reducing pain from contraceptive implant removal, and decreasing paracetamol consumption without increasing side effects.

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