Preemptive Analgesic Efficacy of Parecoxib for Reducing Postoperative Pain in Patients Undergoing Gynecological Surgery

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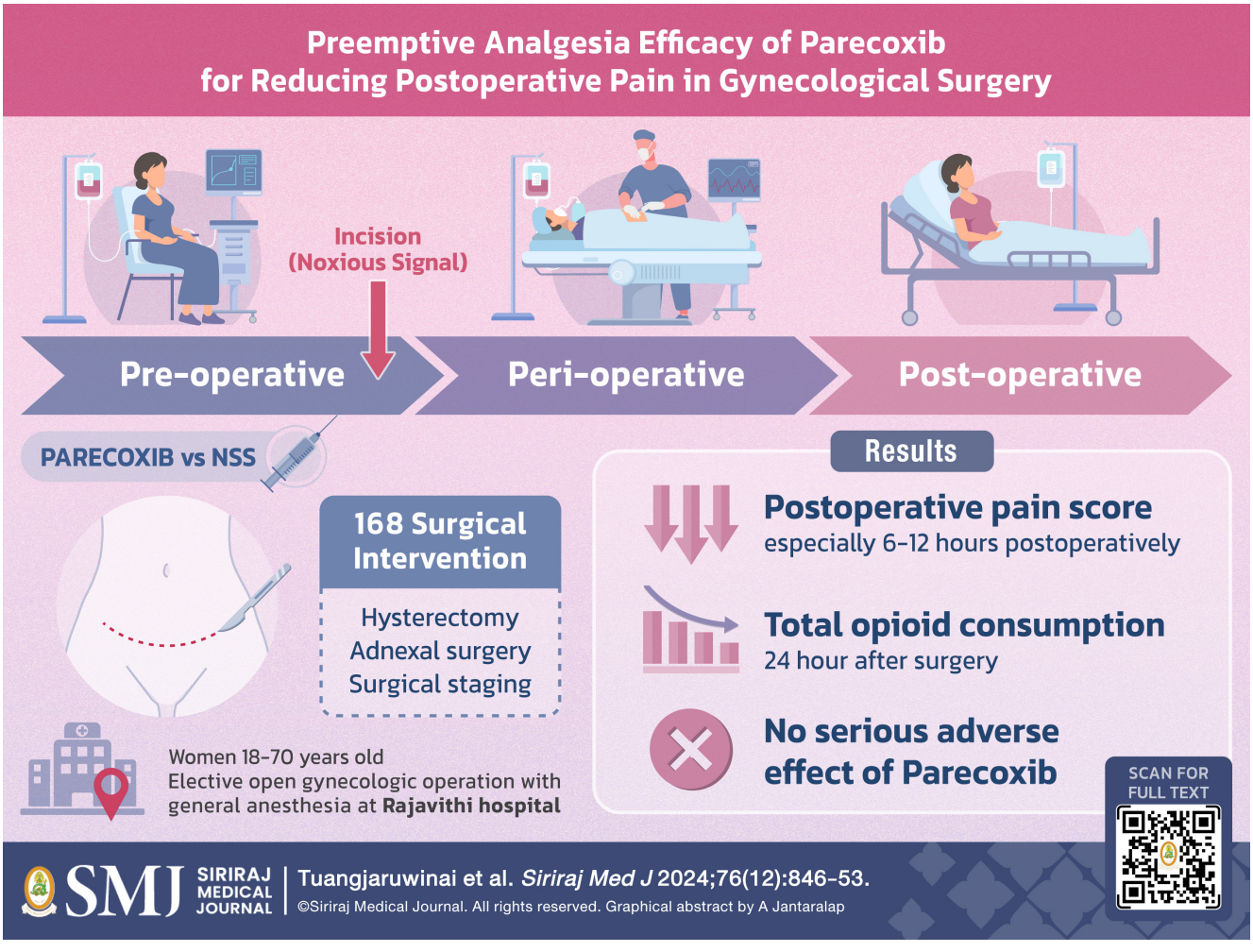

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ABSTRACT

Objective: This study aimed to evaluate the effectiveness of preemptive parecoxib in reducing postoperative pain following gynecological surgery.

Materials and Methods: A double-blind, randomized study involved 168 patients undergoing laparotomy gynecological procedures, including total hysterectomy, adnexal surgery, and surgical staging, between November 2023 and July 2024. Patients were randomly assigned to receive either intravenous parecoxib (n = 82) or normal saline (n = 86) 15 minutes before surgery. Postoperative pain was measured using a visual analog scale at 2, 6, 12, and 24 hours. Morphine consumption within the first 24 hours post-surgery was recorded, along with any adverse events related to parecoxib and the length of hospital stay.

Results: Mean pain scores at 2, 6, 12, and 24 hours postoperatively were lower in the treatment group compared to the control group (5.3 vs. 5.7, $p = 0.261$; 3.7 vs. 5.0, $p < 0.001$; 3.3 vs. 5.1, $p < 0.001$; 3.5 vs. 4.0, $p = 0.164$, respectively). The mean 24-hour postoperative morphine consumption was significantly lower in the treatment group (4 ± 8 mg vs. 8 ± 5 mg, $p < 0.001$). No significant adverse events occurred between the groups. The total length of hospital stay was similar between the two groups (3.4 ± 1.8 vs. 3.5 ± 1.4 days, $p = 0.698$).

Conclusion: Preemptive parecoxib significantly reduced pain at 6 and 12 hours post-surgery and reduced morphine use within 24 hours, with no significant effect on hospital stay duration in gynecological surgery.

Keywords: Preemptive analgesia; parecoxib; gynecological surgery; postoperative pain (Siriraj Med J 2024; 76: 846-853)

INTRODUCTION

Postoperative pain is a common occurrence after any type of surgical procedure, with the most severe pain typically occurring within the first 24 hours. Poorly managed postoperative pain can lead to undesirable side effects, such as a prolonged recovery time, reduced quality of life, and increased use of opioids.[1] Excessive opioid use can cause adverse effects, including nausea, vomiting, and respiratory depression.[2] Therefore, effective postoperative pain management is important. Currently, a multimodal analgesic regimen is often utilized to relieve pain and minimize opioid-related side effects.[3] In addition to systemic treatments such as oral paracetamol and NSAIDs, regional and local analgesia are also studied and applied to reduce postoperative pain. For example, local dexamethasone infiltration[4] and transversus abdominis plane (TAP) blocks[5] are used. Recently, the concept of preemptive analgesia has been introduced to reduce postoperative pain. Administering analgesics before noxious stimuli are triggered can block pain receptors in the peripheral and central nervous systems. This results in reduced transmission of pain signals, leading to more effective short-term and long-term pain control.[6]

Various drugs and methods are used for preemptive analgesia, including local anesthesia, epidural blocks, intravenous N-methyl-d-aspartate (NMDA) antagonists, and especially nonsteroidal anti-inflammatory drugs (NSAIDs).[7] Considering that patients must fast before surgery, selective cyclooxygenase 2 (COX2) inhibitors are preferred over non-selective COX inhibitors due to their lower risk of side effects such as nausea, stomach pain, and gastric ulcers.[8] One of the most commonly used and cost-effective drugs in Thailand is parecoxib. This COX2 selective inhibitor has an onset time of approximately 7–14 minutes, reaches its peak analgesic effect at 2 hours, and has a duration of action of 6–24 hours[9], making it suitable for use as a preemptive analgesic. Although postoperative pain management follows the principles of multimodal analgesia, there is no standardized protocol for preemptive analgesia. Hence, we conducted research to evaluate the efficacy of parecoxib as preemptive analgesia to reduce postoperative pain in patients undergoing gynecological surgery.

MATERIALS AND METHODS

A prospective, double-blind, randomized controlled study was carried out at Rajavithi Hospital after receiving authorization from the Rajavithi Hospital ethics committee. The study involved patients undergoing total abdominal hysterectomy either with or without salpingo-oophorectomy, adnexal surgery (ovarian cystectomy and unilateral or bilateral salpingo-oophorectomy), and complete surgical staging under general anesthesia between November 2023 and July 2024.

The inclusion criteria were the female sex, age 18–70 years, capable of communicating in the Thai language, and an American Society of Anesthesiologists (ASA) physical status of I or II. The exclusion criteria were allergy to

NSAIDs, sulfa drugs, or opioids; underlying conditions that contraindicated NSAID use (e.g., coronary artery disease, cerebrovascular disease, a history of gastrointestinal bleeding, peptic ulcer, peripheral arterial disease, impaired renal or liver function with a glomerular filtration rate < 30 mL/min, or Child–Pugh class B or higher); blood pressure ≥ 160/110 mmHg on the day of admission; and antiplatelet medicine use within 7 days prior to surgery. In addition, patients who experienced intraoperative bowel or bladder injury were excluded.

The subjects were allocated to two groups using stratified block randomization. The parecoxib group was administered 40 mg (2 mL) of intravenous parecoxib 15 minutes prior to the operation, whereas the control group received 2 mL of intravenous normal saline. Both patients and assessors were blinded to the group allocation, with the groups labeled as A (the parecoxib group) or B (the control group). All patients were introduced to the visual analog scale (VAS), a pain evaluation instrument that ranges from 0 (no pain) to 10 (the most severe pain), the day before surgery.

All patients received standard general anesthesia and were then transported to the post-anesthesia care unit after surgery. Perioperative and immediate postoperative (0–2 hours) analgesic administration was recorded by the anesthesia nurse. Once transferred to the gynecology ward, pain assessments were conducted by the ward nurses (who had been trained by the researchers) at 2, 6, 12, and 24 hours after surgery, based on the surgical documentation time. Pain was assessed using the VAS, and any potential medication side effects were recorded at these specified times.

During the first 24 hours after surgery, morphine was administered for pain management, with dosages based on the patient's pain scores at the specified times. Standing orders were provided for the first 24 hours postoperatively. For a pain score > 7, morphine was injected intravenously at a dose of 0.075 mg/kg; for a pain score between 5 and 7, the dosage was 0.05 mg/kg. Morphine was not administered for a pain score < 5. After the first 24 hours after surgery, the patients were administered standard pain relievers as prescribed individually by the attending doctor, including oral analgesics such as paracetamol and NSAIDs, as well as intravenous morphine.

The primary outcome was the VAS pain scores assessed during the first 24 hours following surgery. The secondary outcomes were postoperative opioid consumption within 24 hours, the adverse effects of parecoxib, and the hospital length of stay after surgery.

Statistical analysis

Before commencing the study, the sample size was estimated based on primary outcome data from a prior trial, which reported a postoperative pain score of 2.85 ± 1.24 in the parecoxib group and 3.41 ± 1.27 in the placebo group at 24 hours after surgery. Given a power of 80% and a significance level of 0.05, 79 patients would be required for each group. To accommodate a possible 10% dropout or exclusion rate, a total of 176 individuals (88 patients per group) were enrolled.

SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Results are presented as means and standard deviations (SD) for normally distributed variables and as medians and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables were compared using the chi-square test and unpaired t-test was used for normally distributed data while the Mann-Whitney U test was used for non-normally distributed data. A p-value of < 0.05 was considered statistically significant.

RESULTS

We recruited a total of 176 patients, but we excluded 8 for the following reasons: 3 patients underwent myomectomy, 2 patients experienced bowel/bladder injury, 1 patient had a laparoscopic operation, and 2 patients underwent tumor biopsy, which was not within the operation criteria. Therefore, we included 168 patients in the study, with 82 in the parecoxib group and 86 in the control group. Age, body mass index (BMI), ASA class, previous abdominal surgery history and surgical indication did not differ significantly between the groups (Table 1). Similarly, the operation, type of skin incision, presence of intra-abdominal adhesion, operative time, blood loss, and intraoperative and immediate postoperative analgesia did not differ significantly between the groups (Table 2).

We compared the preoperative baseline and postoperative VAS pain scores between the parecoxib and control groups on the day prior to surgery, and at 2, 6, 12, and 24 hours following surgery. The parecoxib group consistently experienced a lower average VAS pain score compared with the control group, with a significant difference at 6 and 12 hours after surgery. The baseline VAS pain score did not differ between the groups (Table 3).

The parecoxib group received a significantly lower amount of morphine within the initial 24-hour period after surgery compared with the control group (4 ± 8 and 8 ± 5 mg, respectively, $p < 0.05$). The total hospital length of stay after surgery did not differ significantly

TABLE 1. Baseline patient characteristics.

Characteristic	Parecoxib group (n = 82)	Control group (n = 86)	*p*
Age (years), mean ± standard deviation	47.9 ± 12.9	47.7 ± 14.5	0.918[a]
Body mass index (kg/m^2), mean ± standard deviation	26.1 ± 6.0	25.9 ± 5.8	0.874[a]
American Society of Anesthesiologists class, n (%)			
I	27 (32.9)	26 (30.2)	0.707[b]
II	55 (67.1)	60 (69.8)	
Underlying condition, n (%)	34 (41.5)	30 (30.9)	0.337[b]
Hypertension	21 (25.6)	42 (48.8)	
Diabetics mellitus	4 (4.9)	6 (7.0)	
Thyrotoxicosis	3 (3.7)	4 (4.7)	
Chronic kidney disease	0 (0.0)	1 (1.2)	
Human immunodeficiency virus	3 (3.7)	1 (1.2)	
Systemic lupus erythematosus	1 (1.2)	2 (2.3)	
Others*	6 (7.3)	6 (7.0)	
Drug allergy, n (%)	2 (2.4)	6 (7.0)	0.167[b]
Penicillin	2 (2.4)	4 (4.8)	
Ciprofloxacin	0 (0.0)	1 (1.2)	
Warfarin	0 (0.0)	1 (1.2)	
Previous abdominal surgery, n (%)	28 (34.1)	31 (36.0)	0.796[b]
Appendectomy	5 (6.1)	3 (3.5)	
Cesarean section	16 (19.5)	16 (18.6)	
Tubal abortion	6 (7.3)	12 (14.0)	
Nephrectomy	1 (1.2)	0 (0.0)	
Diagnosis, n (%)			0.996[b]
Leiomyoma	23 (28)	23 (26.7)	
Adenomyosis	8 (9.8)	8 (9.3)	
Leiomyoma with adenomyosis	17 (20.7)	19 (22.1)	
Ovarian tumor	5 (6.1)	4 (4.7)	
Cervical cancer	22 (26.8)	26 (30.2)	
Endometrial cancer	5 (6.1)	5 (5.8)	
Ovarian cancer	2 (2.4)	1 (1.2)	

[a] Unpaired *t*-test.

[b] Chi-square test.

* Including anemia, epilepsy, deep vein thrombosis, and pulmonary embolism.

TABLE 2. Surgical data.

Surgical factor	Parecoxib group (n = 82)	Control group (n = 86)	*p*
Operation, n (%)			0.996[b]
Total abdominal hysterectomy ± SO	42 (51.2)	44 (51.2)	
Adnexal surgery (cystectomy/USO/BSO)	12 (14.6)	13 (51.2)	
Surgical staging	28 (34.1)	29 (33.7)	
Surgical incision, n (%)			0.670[b]
Vertical	45 (54.9)	50 (58.1)	
Transverse	37 (45.1)	36 (41.9)	
Intraabdominal adhesion, n (%)			0.976[b]
Yes	37 (45.1)	39 (45.3)	
No	25 (54.9)	29 (54.7)	
Operative time (minutes), mean ± standard deviation	134.7 ± 38.9	141.1 ± 45.9	0.413[a]
Estimated blood loss (mL), median (IQR)	250 (100-450)	200 (100-300)	0.417[c]
Intraoperative analgesia, median (IQR)			
Morphine (mg)	9 (7-10)	8 (6-10)	0.367[c]
Fentanyl (mEq)	50 (0-100)	63 (0-100)	0.747[c]
Paracetamol (mEq)	0 (0-1,000)	0 (0-1,000)	0.845[c]
Marcaine (mL)	0 (0-0)	0 (0-0)	0.597[c]
Nefopam (mg)	0 (0-0)	0 (0-0)	0.306[c]
Immediate postoperative analgesia, median (IQR)			
Morphine (mg)	0 (0-3)	0 (0-3)	0.627[c]
Fentanyl (mEq)	0 (0-0)	0 (0-0)	0.106[c]
Pethidine (mg)	0 (0-0)	0 (0-0)	0.329[c]
Nefopam (mg)	0 (0-0)	0 (0-0)	0.306[c]

[a] Unpaired *t*-test.
[b] Chi-square test.
[c] Mann–Whitney U test.

TABLE 3. Comparison of the visual analog scale pain scores.

	Parecoxib group (n = 82)	Control group (n = 86)	Mean difference	95% confidence interval	*p*
Baseline pain score, mean ± standard deviation	0.1 ± 0.3	0.1 ± 0.3	0.04	(-0.13, 0.05)	0.314
Postoperative pain score, mean ± standard deviation					
2 hours	5.3 ± 2.9	5.7 ± 2.5	-0.46	(-1.28, 0.35)	0.261
6 hours	3.7 ± 2.2	5.0 ± 2.1	-1.38	(-2.03, 0.72)	<0.001*
12 hours	3.3 ± 1.8	5.1 ± 2.3	-1.75	(-2.37, -1.13)	<0.001*
24 hours	3.5 ± 2.2	4.0 ± 2.4	-0.49	(-1.18, 0.20)	0.164

* Significant difference ($p < 0.05$).

between the parecoxib and control groups (3.2 ± 1.8 and 3.5 ± 1.4 days, respectively, p = 0.698). Finally, no significant adverse events occurred between the two groups (Table 4).

DISCUSSION

In this randomized controlled experiment, we assessed the efficacy of preemptive analgesia using parecoxib to reduce postoperative pain and opioid usage in patients following gynecological surgery. We found that preemptive administration of parecoxib significantly reduced the VAS pain score at 6 and 12 hours after surgery compared with placebo, supporting the hypothesis that preemptive analgesia improves pain management outcomes. The finding that the VAS pain score at 2 hours after surgery did not differ between the two groups may be explained by immediate postoperative analgesic drugs given at 0–2 hours after surgery would still have an effect lasting up to 2 hours after surgery.

The reduction in overall morphine usage within the first 24 hours after surgery in the parecoxib group further supports the effectiveness of preemptive parecoxib administration. By reducing opioid usage, parecoxib may help minimize the risk of adverse effects associated with opioids, such as nausea, vomiting, and respiratory depression[2], thereby improving patient recovery and satisfaction.

Several trials have examined the effectiveness of parecoxib in reducing postoperative pain in the context of gynecological surgery. Unlike previous studies that focused on specific types of surgeries, we included patients undergoing a diverse range of laparotomy gynecological procedures, such as hysterectomy, adnexal surgery, and surgical staging for malignant gynecological diseases. This comprehensive inclusion enabled us to obtain a better understanding of parecoxib's efficacy in various surgical procedures.

Amornrat et al.[10] compared the preemptive administration of parecoxib to a placebo in patients who underwent abdominal hysterectomy and conservative surgery. The patients in the parecoxib group had significantly lower pain levels at 6 and 12 hours after surgery, along with a decrease in total opioid intake within the first 24 hours. These findings align with our outcomes. Similarly, Bunyavejchevin et al.[11] carried out a double-blinded randomized controlled trial on patients undergoing diagnostic laparoscopy. They showed that parecoxib significantly lowered both shoulder and incisional pain compared with placebo. The authors also reported reduced use of rescue analgesia without significant differences in postoperative side effects.[11] Nong et al.[12] also reported benefits of using parecoxib in setting of gynecological cancer surgery. Patients treated with parecoxib had significantly lower morphine use and pain scores, along with higher

TABLE 4. Total opioid consumption, the hospital length of stay, and adverse effects.

	Parecoxib group (n = 82)	Control group (n = 86)	*p*
Total morphine consumption (mg), median (IQR)	4 (0-8)	8 (5-10)	<0.001[c]
Postoperative morphine consumption (mg), median (IQR)			
2 hours	1 (0-4)	3 (0-4)	0.340[c]
6 hours	0 (0-3)	3 (0-3)	<0.001*[c]
12 hours	0 (0-0)	3 (0-4)	<0.001*[c]
24 hours	0 (0-3)	0 (0-3)	0.718[c]
Total hospital length of stay after surgery (day), mean ± standard deviation	3.4 ±1.8	3.5 ± 1.4	0.698[a]
Adverse effects, n (%)			0.331[b]
Nausea	0 (0.0)	3 (3.5)	
Vomit	2 (2.4)	1 (1.2)	
Epigastric pain	0 (0.0)	0 (0.0)	

[a] Unpaired *t*-test.
[b] Chi-square test.
[c] Mann–Whitney U test
* Significant difference ($p < 0.05$).

satisfaction compared with those in the control group. In contrast, Ratchanon et al.[13] observed that while parecoxib reduced postoperative meperidine use in patients who underwent laparoscopic gynecological surgery, the decrease in the pain scores was not statistically significant. This might be due to the specific surgical methods and how pain is generated differently in laparoscopic compared to open surgeries. Overall, while most studies support the use of parecoxib in reducing postoperative pain as well as opioid consumption, its efficacy may vary depending on the specific surgical procedure.

In our study, we closely observed the side effects of preemptive parecoxib after gynecological surgery. We found that only a few patients experienced mild side effects similar to those in patients who received placebo. The low incidence of side effects in our study suggests that parecoxib is a safe option for preemptive analgesia in patients undergoing gynecological surgery. However, clinicians should remain aware of potential complications, particularly in patients with a cardiovascular disease, kidney impairment, or gastrointestinal symptoms.

While parecoxib contributed to reducing the amount of opioids taken and postoperative pain, there was not a significant difference in the hospital length of stay between the parecoxib and control groups. A possible reason for this finding is that the gynecology department at Rajavithi Hospital typically discharges patients after about 3 days of recovery. Generally, patients are well enough to leave the hospital by that time unless they experience complications that require a longer stay. Our data show that both the treatment and control groups had a hospital stay of 3.2 ± 1.8 days and 3.5 ± 1.4 days, respectively, which matches this usual care pattern.

However, this study comes with some limitations. First, the sample size, although sufficient for detecting differences in pain scores, may not be large enough to generalize the findings across all types of gynecological surgery. Second, the potential applicability of our data to different clinical situations may be limited due to our focus on a single center. Finally, the absence of a standardized protocol for the postoperative care of patients in this study might have influenced the hospital length of stay after surgery.

In conclusion, we demonstrated that preemptive parecoxib administration effectively lowered postoperative pain and opioid consumption in patients who underwent gynecological surgery. While the hospital length of stay did not differ between the parecoxib and control groups, the pain relief provided by parecoxib and its safety profile indicate that this drug is a viable choice for postoperative pain control, even in a diverse patient population undergoing various types of gynecological surgery.

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DECLARATION

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to this study.

Author Contributions

Conceptualization and methodology, P.T., S.T. ; Investigation, P.T. ; Formal analysis, P.T. ; Visualization and writing – original draft, P.T. ; Writing – review and editing, P.T. ; Funding acquisition, P.T. ; Supervision, S.T. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

ChatGPT version 4o were used to correct the manuscript grammar.

REFERENCES

1. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287-98.
2. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105-S20.
3. Schwenk ES, Mariano ER. Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean J Anesthesiol. 2018;71(5):345-52.
4. Smitasiri R, Chanthasenanont A, Chitkoolsamphan Y, Pongrojpaw D, Benchahong S, Suwannarurk K. Dexamethasone and Lidocaine Effects in 24 hours Post Cesarean Pain Reduction under Spinal Anesthesia: A Randomized Controlled Trial. Siriraj Med J. [Internet]. 2024 Sep. 1 [cited 2024 Oct 9];76(9):567-72. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/268510
5. Boonyapalanant C, Woranisarakul V, Jitpraphai S, Chotikawanich E, Taweemonkongsap T, KC HB, et al. The Efficacy of Inside-Out Transversus Abdominis Plane Block vs Local Infiltration before Wound Closure in Pain Management after Kidney Transplantation: A Double-blind, Randomized Trial. Siriraj Med J. [Internet]. 2022 Apr. 1 [cited 2024 Oct. 9];74(4):233-8. Available from:

https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/256916
6. Ohnesorge H, Gunther V, Grunewald M, Maass N, Alkatout I. Postoperative pain management in obstetrics and gynecology. J Turk Ger Gynecol Assoc. 2020;21(4):287-97.
7. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg. 2005;100(3):757-73.
8. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000; 284(10):1247-55.
9. Pfizer. Dynastat (parecoxib sodium) - product information. Available from: https://labeling.pfizer.com/ShowLabeling.aspx?id=12244 [Accessed 12 August 2023].
10. Arponrat P, Pongrojpaw D, Tanprasertkul C, Suwannarurk K, Bhamarapravatana K. Postoperative pain relief in major gynaecological surgery by perioperative parecoxib administration: Thammasat University Hospital Study. J Med Assoc Thai. 2015;98(7):636-42.
11. Bunyavejchevin S, Prayoonwech C, Sriprajittichai P. Preemptive analgesic efficacy of parecoxib vs placebo in infertile women undergoing diagnostic laparoscopy: randomized controlled trial. J Minim Invasive Gynecol. 2012;19(5):585-8.
12. Nong L, Sun Y, Tian Y, Li H, Li H. Effects of parecoxib on morphine analgesia after gynecology tumor operation: a randomized trial of parecoxib used in postsurgical pain management. J Surg Res. 2013;183(2):821-6.
13. Ratchanon S, Phaloprakarn C, Traipak K. Pain control in laparoscopic gynecologic surgery with/without preoperative (preemptive) parecoxib sodium injection: a randomized study. J Med Assoc Thai. 2011;94(10):1164-8.