Thai J Obstet Gynaecol 2024 February 27;1-8.
Online ahead of print

GYNAECOLOGY

Ibuprofen and Intraperitoneal Lidocaine Instillation for Relieving Intraoperative Pain during Postpartum Tubal Ligation via Minilaparotomy: A Randomized Controlled Trial

Jen Sothornwit, M.D.* ,
Yada Jaruamornjit, M.D.*,
Srinaree Kaewrudee, M.D.*,
Woraluck Somboonporn, M.D.*,
Nuntasiri Eamudomkarn, M.D.*

** Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

ABSTRACT

Objectives: This randomized study evaluated the effects of preemptive ibuprofen, intraperitoneal lidocaine instillation, or both for pain relief during postpartum tubal ligation (PPTL) via minilaparotomy.

Materials and Methods: Ninety-two heathy mothers who opted for PPTL were randomized into four groups and received either 400 mg of oral ibuprofen and intraperitoneal instillation of 20 ml of isotonic sodium chloride solution (Group I), oral placebo and intraperitoneal instillation of 20 ml of 1% lidocaine 20 ml (Group L), both ibuprofen and intraperitoneal instillation lidocaine (Group IL), or placebo and intraperitoneal isotonic sodium chloride solution (Group P).

Results: The mean intraoperative numerical rating scale (NRS) in group IL was significantly lower than in group P (mean difference -2.48, 95% CI -4.47 to -0.49, p = 0.007). No significant difference was found in the intra-operative NRS between groups I and L when compared to group P (mean difference -1.61 [95% CI -3.60 to 0.38], and 0.70 [95% CI -1.29 to 2.69], respectively), nor was there any significant difference in pain score immediately or one-hour post-operation.

Conclusion: Preemptive ibuprofen and intraperitoneal lidocaine instillation alone did not provide effective pain relief for postpartum tubal resection. However, multimodal analgesia using both agents was effective as intra-operative (but not post-operative) pain control.

Keywords: ibuprofen, intraperitoneal lidocaine, NSAIDs, postpartum tubal resection, sterilization.

Correspondence to: *Jen Sothornwit, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. E-mail: jensoth@kku.ac.th*

Received: 31 May 2023, **Revised:** 12 September 2023, **Accepted:** 20 September 2023

ไอบูโพรเฟนและการหยอดยาลิโดเคนในช่องท้องเพื่อบรรเทาอาการปวดระหว่างการทำหมันหลังคลอดโดยการผ่าตัดแบบเปิดหน้าท้องขนาดเล็ก: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

เจน โสธรวิทย์, ญาดา จารุอมรจิต, นันทสิริ เอี่ยมอุดมกาล, วรลักษณ์ สมบูรณ์พร, ศรีนารี แก้วฤดี

บทคัดย่อ

วัตถุประสงค์: *การศึกษาแบบสุ่มนี้ประเมินผลของไอบูโพรเฟนก่อนการผ่าตัด การหยอดยาลิโดเคนในช่องท้อง หรือทั้งสองอย่างในการบรรเทาอาการปวดระหว่างการทำหมันหลังคลอด โดยการผ่าตัดเปิดหน้าท้องขนาดเล็ก*

วัสดุและวิธีการ: *มารดาที่มีสุขภาพแข็งแรงจำนวน 92 รายที่เลือกการทำหมันหลังคลอด ได้รับการสุ่มออกเป็นสี่กลุ่ม และได้รับไอบูโพรเฟนแบบรับประทาน 400 มก. และการหยอดสารละลายไอโซโทนิกโซเดียมคลอไรด์ 20 มล. (กลุ่มที่ I) ยาหลอกแบบรับประทาน และการหยอดยา 1 % ลิโดเคน 20 มล. เข้าช่องท้อง (กลุ่ม L) ทั้งไอบูโพรเฟนและลิโดเคนแบบหยอดยาในช่องท้อง (กลุ่ม IL) หรือยาหลอกและสารละลายไอโซโทนิกโซเดียมคลอไรด์ในช่องท้อง (กลุ่ม P)*

ผลการศึกษา: *ค่าเฉลี่ยระดับคะแนนความปวดแบบตัวเลข (numerical rating scale) ในกลุ่ม IL ต่ำกว่ากลุ่ม P อย่างมีนัยสำคัญ (ความแตกต่างเฉลี่ย -2.48, 95% CI -4.47 ถึง -0.49, p = 0.007) ไม่พบความแตกต่างอย่างมีนัยสำคัญในคะแนนความปวดแบบตัวเลขระหว่างผ่าตัดระหว่างกลุ่ม I และ L เมื่อเปรียบเทียบกับกลุ่ม P (ความแตกต่างเฉลี่ย -1.61 [95% CI -3.60 ถึง 0.38] และ 0.70 [95% CI -1.29 ถึง 2.69] ตามลำดับ) และไม่มีความแตกต่างอย่างมีนัยสำคัญในคะแนนความเจ็บปวดทันทีหรือหลังการผ่าตัดหนึ่งชั่วโมง*

สรุป: *การให้ไอบูโพรเฟนล่วงหน้าหรือหยอดยาลิโดเคนในช่องท้องเพียงอย่างเดียวไม่ได้ช่วยบรรเทาอาการปวดอย่างมีประสิทธิภาพสำหรับการผ่าตัดทำหมันหลังคลอด อย่างไรก็ตาม การระงับปวดแบบพหุวิธีโดยใช้ยาทั้งสองชนิดมีประสิทธิผลในการควบคุมความเจ็บปวดระหว่างการผ่าตัด (แต่ไม่ใช่หลังการผ่าตัด)*

คำสำคัญ: *ไอบูโพรเฟน, ลิโดเคนในช่องท้อง, NSAIDs, การผ่าตัดท่อนำไข่หลังคลอด, การทำหมัน*

Introduction

Tubal ligation is a method of permanent contraception with a failure rate of less than 1%.1 Globally, it is one of the most common methods of contraception[2]. Minilaparotomy is an attractive option for postpartum tubal ligation (PPTL) due in part to its safety and short required operative time[3]. However, this procedure can involve varying degrees of pain and discomfort. This can be considered as a significant obstacle for women opted for PPTL. Pain management therefore is crucial to the procedure's success and can be provided via general, regional, or local anesthesia[4]. Although general and regional anesthesia are highly effective[5], they require an anesthesiologist and are relatively costly compared to local anesthesia. As a result, they are not always practicable, particularly in low-resource settings[6].

Although various local analgesics are available for intraoperative pain relief, few have been investigated. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce prostaglandin production by inhibiting cyclooxygenase (COX) enzyme[7]. Ibuprofen is a preferred NSAID for postpartum/lactating women due to its particularly low concentrations in breastmilk and short half-life[8]. This makes ibuprofen an attractive possible choice for pain relief in PPTL. A recent systematic review on intervention for pain control during PPTL reported only three randomized controlled trials (RCTs) evaluating lidocaine instillation and intramuscular morphine, either alone or in combination4 and none evaluating the effectiveness of NSAIDs.

Preemptive analgesia is the introduction of antinociceptive treatment prior to painful stimuli[9]. This approach to pain management is considered promising for surgery, as the timing of the painful stimulus is known. The objective of this study was to explore the effectiveness of preemptive ibuprofen and intraperitoneal lidocaine for pain management in PPTL.

Materials and Methods

This randomized, double-blinded, placebo-controlled study was conducted at Srinagarind Hospital, a university hospital in northeast Thailand, from March 2021 to April 2022. It was approved by The Khon Kaen University Ethics Committee for Human Research (HE631087). The trial was also registered with www.thaiclinicaltrials.org (TCTR20200712001). Healthy women aged 18-45 years who (a) delivered within 72 hours before tubal ligation, (b) desired permanent contraception, (c) had American Society of Anesthesiologists (ASA) physical status of I[10], (d) had no contraindication for surgery, and (e) had given consent for PPTL were eligible for this study. We excluded women with (a) body mass index (BMI) ≥ 30 kg/m^2, (b) previous pelvic inflammatory disease or pelvic surgery, (c) contraindications for ibuprofen, or (e) lidocaine allergy. We followed the CONSORT guideline[11].

After obtaining written informed consent, participants were randomly assigned to one of four groups. Group I (Ibuprofen) received 400 mg of oral ibuprofen one hour before surgery and intraperitoneal instillation of 20 ml of isotonic sodium chloride solution immediately after approaching the intraperitoneal cavity. Group L (Lidocaine) received an oral placebo one hour before surgery and intraperitoneal instillation of 20 ml of 1% lidocaine immediately after approaching the intraperitoneal cavity. Group IL (Ibuprofen+Lidocaine) received 400 mg of oral ibuprofen one hour before surgery and intraperitoneal instillation of 20 ml of 1% lidocaine immediately after approaching the intraperitoneal cavity. Group P (Placebo) received an oral placebo one hour before surgery and intraperitoneal instillation of 20 ml of isotonic sodium chloride solution immediately after approaching the intraperitoneal cavity. The lidocaine dosage was chosen based on a previous study[12]. Group allocation was performed via computer-generated variable block randomization, and the results were concealed in sealed opaque envelopes. The surgeon, patient, and assistants were all blinded to the randomization sequence. There were no labels to identify the solution or tablet administered.

Participants were advised to practice assessing their pain using a numerical rating scale (NRS, 0 = no pain; 10 = the most severe pain) before the procedure. Non-invasive blood pressure and pulse oximeter

monitoring was employed before, during, and after the procedure. Participants were brought into the operating room one hour after receiving either ibuprofen or a placebo. The trained 2nd year residents infiltrated 10 ml of 1% lidocaine into the skin and behind the rectus sheath of each woman. Numbness was tested prior to making the subumbilical skin incision. After approaching the intraperitoneal cavity, 20 ml of either saline or 1% lidocaine were instilled at both sides of the fallopian tubes (10 ml each). Tubal ligation was performed by a resident using the Pomeroy technique one minute after instillation. Patients received rescue drugs if their pain score was > 5. Research assistants who were blinded to the assigned intervention assessed the severity of pain when tying the second fallopian tube and immediately and one hour after the procedure. Side effects of lidocaine and ibuprofen, such as epigastric discomfort, tinnitus, disorientation, and perioral numbness, were monitored and documented for one hour after surgery.

A sample size of n = 20 per group was required to provide 80% power and alpha 0.05 level comparison to detect meaningful differences in pain intensity (NRS = 2.4)[13]. Assuming a 5% rate of withdrawal, we calculated a final sample size of 23 per group. We performed analyses using SPSS (version 16.0, SPSS Inc., Chicago, IL). Age and BMI were documented, as were duration of surgery, intra-operative pain (while tying the fallopian tube), post-operative pain (immediately and one hour after surgery), rescue medication use (meperidine and diazepam), and adverse effects (e.g., epigastric pain, dizziness, nausea, nor vomiting). Multiple comparisons were conducted using Bonferroni and Dunnet's tests. The p value < 0.05 was considered to be statistically significant. For Bonferroni test, p value < 0.008 was deemed to have statistical significance.

Results

Of 168 postpartum women who were approached, 76 were excluded: 31 who did not meet the inclusion criteria, 39 who declined to participate, three with previous pelvic surgery, and three with BMI ≥ 30 kg/m^2 (Fig. 1). The mean age of participants was 32.6 years. As shown in Table 1, the four groups were comparable in terms of baseline characteristics. However, duration of surgery was slightly longer in Groups I and P.

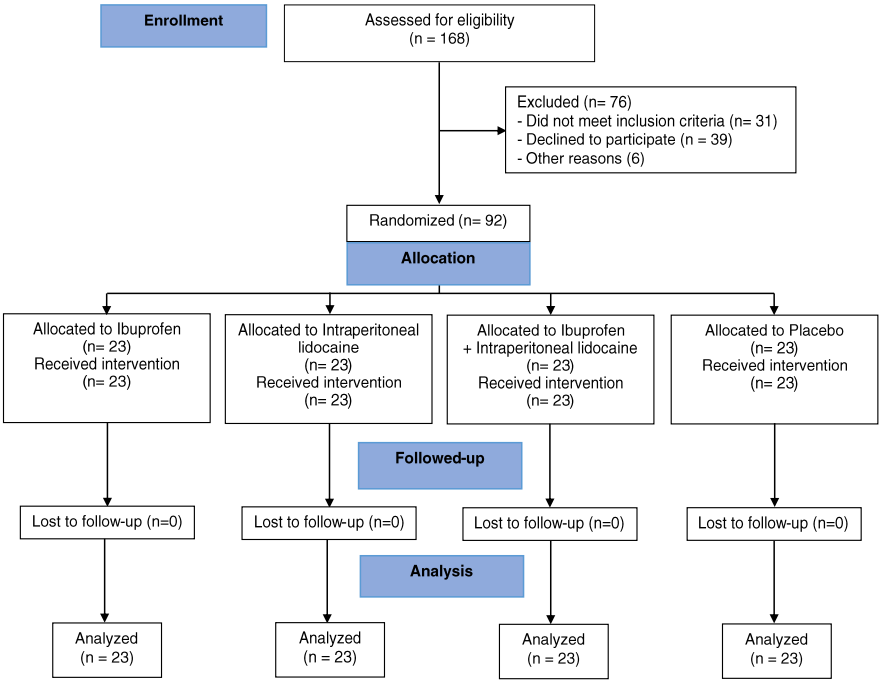

Fig. 1. Flow diagram of the study

Table 1. Demographic data.

Characteristics	Group I (Ibuprofen) n=23	Group L (Intraperitoneal lidocaine) n=23	Group IL (Ibuprofen with Intraperitoneal lidocaine) n=23	Group P (Placebo) n=23
Age (years)	33.4 ± 3.5	33.1 ± 4.6	32.0 ± 3.9	31.8 ± 4.0
Weight (kg)	60.7 ± 7.0	63.7 ± 7.2	66.1 ± 6.5	63.3 ± 8.3
Height (cm)	158.6 ± 4.1	160.5 ± 6.2	159.8 ± 6.1	159.9 ± 5.6
BMI (kg/m^2)	24.2 ± 2.9	24.7 ± 1.8	25.0 ± 3.0	24.7 ± 2.5
Duration of surgery (min)	34.3 ± 16.7	29.9 ± 12.1	30.0 ± 16.7	36.4 ± 14.1

Data presented as mean ± standard deviation
NRS: numerical rating score, BMI: body mass index

Mean NRS was lowest in group IL (3.3 ± 2.6), followed by group L (4.2 ± 2.6). There were no obvious differences in terms of post-operative pain at any time point (Table 2). Preemptive ibuprofen was not effective when compared to placebo (mean difference [MD] 0.70 [95% CI -1.29 to 2.69]), but mean NRS in the IL groups were substantially lower than in the non-lidocaine groups (group I and P; MD -3.17 [95% CI -5.16 to -1.18] and -2.48 [95% CI -4.47 to -0.49], respectively). Effects of lidocaine did not differ significantly from ibuprofen or placebo. No significant differences in postoperative pain were observed (Table 3). The number of paracetamol tablets required did not differ substantially across the four groups.

Although the proportion of patients who required rescue medication were lower in groups L and IL than in group P (Table 4), these differences were not statistically significant (odds ratio (OR) 0.30 95% CI [0.08 to 1.1] and 0.70 [0.22 to 2.26], respectively). Participants reported no adverse effects or serious adverse events during the study period.

Table 2. Intra-operative and post-operative NRS.

Characteristics	Group I (Ibuprofen) n=23	Group L (Intraperitoneal lidocaine) n=23	Group IL (Ibuprofen with Intraperitoneal lidocaine) n=23	Group P (Placebo) n=23
Intraoperative NRS	6.5 ± 2.4	4.2 ± 2.6	3.3 ± 2.6	5.8 ± 2.3
Immediate post-operative NRS	5.6 ± 3.3	5.8 ± 3.0	5.8 ± 2.6	5.5 ± 2.5
1-hour post-operative NRS	2.0 ± 1.9	3.0 ± 1.9	2.4 ± 2.1	3.0 ± 1.9

Data presented as mean ± standard deviation
NRS: Numerical rating score

Table 3. Intra-operative, immediately post-operative, and 1-hour post-operative NRS.

	Mean difference	95% CI	p value
Intraoperative NRS			
Group IL VS Group L	-0.87	-2.86 to 1.12	1.000
Group IL VS Group I	-3.17	-5.16 to -1.18	< 0.001*
Group IL VS Group P	-2.48	-4.47 to -0.49	0.007*
Group L VS Group I	-2.30	-4.29 to -0.31	0.014
Group L VS Group P	-1.61	-3.60 to 0.38	0.190
Group I VS Group P	0.70	-1.29 to 2.69	1.000
Immediate post-operative NRS			
Group IL VS Group L	0.04	-2.23 to 2.31	1.000
Group IL VS Group I	0.26	-2.01 to 2.53	1.000
Group IL VS Group P	0.35	-1.92 to 2.62	1.000
Group L VS Group I	0.22	-2.05 to 2.49	1.000
Group L VS Group P	0.30	-1.97 to 2.58	1.000
Group I VS Group P	0.09	-2.18 to 2.36	1.000
1-hour post-operative NRS			
Group IL VS Group L	-0.52	-2.07 to 1.03	1.000
Group IL VS Group I	0.48	-1.08 to 2.03	1.000
Group IL VS Group P	-0.52	-2.07 to1.03	1.000
Group L VS Group I	1	-0.55 to 2.55	0.513
Group L VS Group P	0	-1.55 to 1.55	1.000
Group I VS Group P	-1	-2.55 to 0.55	0.513

Multiple comparisons were conducted using the Bonferroni test and Dunnet's test.
* Statistical significance ($p < 0.008$)
Group IL: ibuprofen + lidocaine, Group I: ibuprofen, Group L: lidocaine, Group P: placebo, NRS: numerical rating scale, CI: confidence interval

Table 4. Rescue medication requirement during the operation.

Treatment group	Rescue medication required (%)	Unadjusted OR (95% CI)
Group I	12/23 (52.2)	1.19 (0.37 to 3.8)
Group L	5/ 23 (21.7)	0.30 (0.08 to 1.1)
Group IL	9/23 (39.1)	0.70 (0.22 to 2.26)
Group P	11/23 (47.8)	Reference

Multiple comparisons were conducted using the Bonferroni test and Dunnet's test.
* statistical significance ($p < 0.008$)
Group IL: ibuprofen + lidocaine, Group I: ibuprofen, Group L: lidocaine, Group P: placebo, NRS: numerical rating scale, OR: odds ratio, CI: confidence interval

Discussion

We found that ibuprofen with lidocaine instillation was the most effective method of pain relief during PPTL. However, lidocaine instillation or ibuprofen alone did not exhibit similar effectiveness. None of the regimens differed in terms of postoperative pain reduction.

Although preemptive analgesia has long been practiced, in our study, administration of preemptive ibuprofen was inadequate to control pain during PPTL. This was consistent with a previous study, which found that providing morphine one hour preoperatively was not effective at improving intraoperative pain[14]. Furthermore, other studies have found that preemptive NSAID usage in patients undergoing laparoscopic tubal ligation only resulted in a trivial pain reduction[15,16]. A recent systematic review on preoperative NSAID administration also yielded mixed results[17]. This may be explained by the fact that the type of operation and location of pain differed across studies[18]. Although ibuprofen did not have any remarkable effect in our study, further research is needed to evaluate that of other types and dosages of NSAIDs for this procedure. Our results contrasted with those of a study by Visalyaputra et al[14], in which intraperitoneal lidocaine effectively alleviated pain during PPTL. This difference might be due to the lower dosage of lidocaine used in this study. Furthermore, we found that this effect became more pronounced when lidocaine was given in conjunction with preemptive ibuprofen. This is because of the synergistic effect of multiple analgesics, each targeting different receptors of the pain pathway (multimodal analgesia)[19, 20]. The enhanced recovery after surgery (ERAS) recommendations for gynecologic surgery suggest using multimodal analgesia employing multiple agents that address distinct routes to minimize opioid consumption and hasten recovery[21,22]. However, the protocol needs to be adjusted to increase the effect size and extend the effect to cover postoperative pain. Our results showed no difference in postoperative pain, even in the group anesthetized using the multimodal method. This was consistent with previous studies[12,14]. The explanation for this might be that lidocaine and ibuprofen both have a short half-life[23, 24]. Use of a combination of drugs with a longer half-life is worth consideration for future research.

To our knowledge, this is the largest sample size to be enrolled in a double-blind RCT evaluating pain control for PPTL. However, there were limitations pertaining to the subjective nature of pain perception and varying skill level of the residents who performed the operation.

Conclusion

Our study showed that preemptive ibuprofen and intraperitoneal lidocaine instillation alone were not effective at relieving pain in postpartum tubal resection. Multimodal analgesia using both agents was effective for intraoperative (but not postoperative) pain control.

Acknowledgments

We would like to acknowledge Dr. Dylan Southard for editing this MS via the KKU Publication Clinic (Thailand). This work was supported by the Khon Kaen University Faculty of Medicine in Thailand [IN63313].

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. World Health Organization. Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health, United States Agency for International Development. Family Planning: A global handbook for providers. Available from: https://apps.who.int/iris/bitstream/handle/10665/260156/9780999203705-eng.pdf?sequence=1 [accessed 11 September 2022].
2. United Nations, Department of Economic and Social Affairs, Population Division (2019). Contraceptive Use by Method 2019: Data Booklet (ST/ESA/SER.A/435).
3. Kumar A, Pearl M. Mini-laparotomy versus laparoscopy for gynecologic conditions. J Minim Invasive Gynecol 2014;21:109-14.

4. Werawatakul Y, Sothornwit J, Laopaiboon M, Lumbiganon P, Kietpeerakool C. Interventions for intra-operative pain relief during postpartum mini-laparotomy tubal ligation. Cochrane Database Syst Rev 2019;2:CD011807.
5. Aaronson J, Goodman S. Obstetric anesthesia: not just for cesareans and labor. Semin Perinatol 2014;38:378-85.
6. Aisien AO, Olarewaju RS, Ujah IA, Mutihir JT, Sagay AS. Anaesthesia for minilaparotomy female sterilization in JUTH, Nigeria: a fourteen-year review. Afr J Med Med Sci 2001;30:119-21.
7. Ghlichloo I, Gerriets V. Nonsteroidal anti-inflammatory drugs (NSAIDs). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
8. Ibuprofen. Drugs and Lactation Database (LactMed). National Library of Medicine (US); 2021.
9. Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138-43.
10. Doyle DJ, Goyal A, Garmon EH. American Society of Anesthesiologists Classification. StatPearls. StatPearls Publishing; 2022.
11. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Obstet Gynecol 2010;115:1063-70.
12. Rattanalappaiboon D, Werawatakul Y, Tharnprisan P, Prasit M. Intraperitoneal lidocaine for decreasing intra-operative pain during postpartum tubal resection in Srinagarind Hospital. J Med Assoc Thai 2012;95:477-81.
13. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? Pain 2003;105:151-7.
14. Visalyaputra S, Lertakyamanee J, Pethpaisit N, Somprakit P, Parakkamodom S, Suwanapeum P. Intraperitoneal lidocaine decreases intraoperative pain during postpartum tubal ligation. Anesth Analg 1999;8:1077-80.
15. Buggy DJ, Wall C, Carton EG. Preoperative or postoperative diclofenac for laparoscopic tubal ligation. Br J Anaesth 1994;73:767-70.
16. Dunn TJ, Clark VA, Jones G. Preoperative oral naproxen for pain relief after day-case laparoscopic sterilization. Br J Anaesth 1995;75:12-4.
17. Doleman B, Leonardi-Bee J, Heinink TP, Boyd-Carson H, Carrick L, Mandalia R, et al. Pre-emptive and preventive NSAIDs for postoperative pain in adults undergoing all types of surgery. Cochrane Database Syst Rev 2021;6:CD012978.
18. Liu L, Yi J, Wasson MN. Techniques for Preemptive Analgesia in Gynecologic Surgery. J Minim Invasive Gynecol 2019;26:197.
19. Kaye AD, Urman RD, Rappaport Y, Siddaiah H, Cornett EM, Belani K, et al. Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. J Anaesthesiol Clin Pharmacol 2019;35(Suppl 1):S40-5.
20. Schwenk ES, Mariano ER. Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean J Anesthesiol 2018;71:345-52.
21. Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer 2019;29:651-68.
22. Altman AD, Robert M, Armbrust R, Fawcett WJ, Nihira M, Jones CN, et al. Guidelines for vulvar and vaginal surgery: Enhanced Recovery After Surgery Society recommendations. Am J Obstet Gynecol 2020;223:475-85.
23. Becker DE, Reed KL. Local anesthetics: Review of pharmacological considerations. Anesth Prog 2012;59:90-102.
24. Mazaleuskaya LL, Theken KN, Gong L, Thorn CF, FitzGerald GA, Altman RB, et al. PharmGKB summary: ibuprofen pathways. Pharmacogenet Genomics 2015;25:96-106.