



Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Immediate postoperative pain control with ropivacaine following laparoscopic-assisted vaginal hysterectomy: A randomized double-blind pilot study

Jae Young Kwack, Yong-Soon Kwon*

Department of Obstetrics and Gynecology, Nowon Eulji Medical Center, Eulji University, Seoul, Republic of Korea



ARTICLE INFO

Article history:

Accepted 17 April 2018

Keywords:

Laparoscopic hysterectomy
Ropivacaine
Postoperative pain
Uterosacral ligament

ABSTRACT

Objective: Although laparoscopic hysterectomy, a worldwide popular surgery, ensures faster recovery and less postoperative pain than with laparotomic hysterectomy, immediate pain control still improving postoperative care. We introduce an effective method, intraoperative injection of ropivacaine into both uterosacral ligaments, to control immediate postoperative pain.

Materials and methods: We performed a prospective, double-blind, and randomized study. We analyzed 40 cases of laparoscopic vaginal hysterectomy performed between July 2015 and November 2016 by a single surgeon (Y.S.K.). We randomized the enrolled patients into the ropivacaine injection group and the saline injection group. Before the vaginal stump was closed, 7.5% ropivacaine or saline (10 mL) was administered into both uterosacral ligaments, 5 mL each. In all cases, the medicine was injected transvaginally before the vaginal stump was closed. The primary outcome was the postoperative pain intensity expressed by numeric ranking scale (NRS) scores at 2, 6, 12, and 24 h after injection. The secondary outcome was the amount of analgesics demanded for pain control during the 24 h after the surgery.

Results: The pain intensity at 2 h after injection was significantly lower in the ropivacaine-injected group ($p = .0234$). There was no difference in pain intensity at 6, 12, and 24 h after injection and the amount of analgesics used. However, the total amount of opioid analgesic used was lower in the ropivacaine-injected group than in the placebo-injected group. ($p = .0251$).

Conclusion: Intraoperative ropivacaine injection into both uterosacral ligaments during laparoscopic hysterectomy can reduce early postoperative pain and consumption of analgesics to improve postoperative care.

© 2018 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

In gynecologic surgery, laparoscopic surgery is the preferred option except in patients with known contraindications. Although laparoscopy ensures faster recovery, fewer complications, and less pain than laparotomic surgery, pain control is still a major problem in postoperative care because it can reduce the advantages of the minimally invasive approach; hence, some trials have been conducted to develop strategies to reduce pain after laparoscopic surgery [1].

Intraperitoneal local anesthetic was introduced in the early 1950s, and it has since been used in various surgical procedures [2]. In gynecologic laparoscopy, local anesthetic instillation into the intraperitoneal space and local injection into the incision site are common [3–8]. After uterine surgery, visceral pain intensity is maximal, and most patients complain of lower abdominal pain [4]. Visceral pain is transmitted by the pelvic visceral plexus, which is derived from the hypogastric plexus associated with the uterus, vagina, rectum, and bladder. The uterus receives primary innervation from the uterosacral plexus (Lee-Frankenhauser plexus), which is located near the lateral side of the uterine cervix within the uterosacral ligament and which plays an important role in pain transmission [9]. Systematic analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids cannot directly block the visceral nociception despite dose regulation under patient-

* Corresponding author. Department of Obstetrics and Gynecology, Eulji Medical Center of Eulji University, School of Medicine, 68 Hangeulbiseok-ro, Nowon-gu, Seoul, Republic of Korea. Fax: +82 52 250 7168.

E-mail address: kbongchun73@naver.com (Y.-S. Kwon).

<https://doi.org/10.1016/j.tjog.2018.08.007>

1028-4559/© 2018 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

controlled analgesia (PCA). It is reasonable that direct block of the uterosacral plexus through injection of a prolonged half-life analgesic can improve pain relief to enhance recovery and reduce opioid addiction without systemic side effects. Systematic opioid analgesics can induce adverse effects including nausea, dizziness, and respiratory depression.

Bupivacaine and ropivacaine are local analgesics that are commonly used for nerve block and intraperitoneal application. Ropivacaine is a long-acting amino amide local anesthetic drug with duration of drug action of two to eight hours; it has been shown to effectively reduce pain without clinical toxicity. Compared with bupivacaine, ropivacaine acts preferentially on pain and sensory nerves rather than motor nerve block, so it is suitable for immediate pain control after uterine surgeries. Also, ropivacaine shows lower systemic and cardiac toxicity than bupivacaine because of its higher clearance rate [10–14].

In the current study, ropivacaine was injected into both uterosacral ligaments at the end of laparoscopic hysterectomy in an attempt to evaluate the efficacy of intraoperative local ropivacaine injection for managing early postoperative pain in patients with laparoscopic hysterectomy.

Materials and methods

Setting and participants

We conducted a single-center, randomized, double-blind, placebo-controlled study. The Ethical Committee of Ulsan University Hospital approved the study on June 26, 2015 (IRB File No.2015-05-016-003). We analyzed 40 cases of laparoscopic-assisted vaginal hysterectomy (LAVH) performed between July 2015 and November 2016 by a single surgeon; all patients provided written informed consent. Patients aged over 18 and below 80 years who underwent LAVH were eligible for inclusion in the study, and we recruited patients one day before the surgery. Exclusion criteria were laparotomic conversion during the surgery; combined endometriosis with consequent severe adhesion leading to inability to discriminate the uterosacral ligament and inject into it; confirmed malignancy; history of allergy to NSAIDs, opioids, and other medication; or having received analgesics 12 h before the surgery. We estimated the sample size as 22 per each group, using sample calculator (<https://stattools.crab.org>) at 0.90 power and type I error of 0.05 (two-sided) with a difference of 2 based on NRS score > 2 perceived to be clinically relevant and variance estimate of 2.0. Considering a dropout rate of 10%, we included a total of 50 patients with 25 in each group.

Randomization and blinding

We assigned enrolled patients into one of two groups in a random 1:1 ratio sequence: ropivacaine injection or saline injection. Specifically, the research assistant picked a sealed paper with the allocation number and handed that sealed paper to the person in charge of designating group assignments based on the allocated number before the surgery. The ropivacaine or saline solution was delivered to the operation room just before the administration. All researchers who participated in the surgery and data collection were blinded until completion of data analysis.

Interventions

General anesthesia was induced, and the patient was placed in a dorsal lithotomy position with endotracheal intubation. A uterine manipulator (Hangzhou Shikonghou Medical Equipment Co. Ltd., Beijing, China) was placed in the uterine cavity to facilitate moving

the uterus into the optimal position during excision and suturing. Intra-abdominal pressure was maintained at 13 mmHg with carbon dioxide gas. In all LAVH procedures, three 5 mm trocar access sites were uniformly created. To reduce bias, all surgical procedures were conducted by a single surgeon. When the uterus was completely removed, ropivacaine (10 mL) or saline solution (10 mL) was injected into the lateral side of both uterosacral areas, 5 mL each, transvaginally before the stump was closed (Fig. 2). All patients were injected transvaginally before the vaginal stump was closed. Ropivacaine hydrochloride 7.5% (7.5 mg/mL) manufactured by Reyon Pharmaceutical Co., Ltd. (Seoul, South Korea) was used in the ropivacaine group, and the saline group was administered a sodium chloride solution (9 g/1000 mL) manufactured by JW Pharmaceutical (Seoul, South Korea). Ropivacaine and saline solutions cannot be discriminated visually because they are both colorless and transparent.

All participants were managed with a standardized protocol. In the post-anesthesia care unit, fentanyl citrate 78.5 µg/mL (50 µg as fentanyl; Myungmoon Pharmaceutical Co., Seoul, South Korea) was administered once. Subsequently, the pain was controlled by an

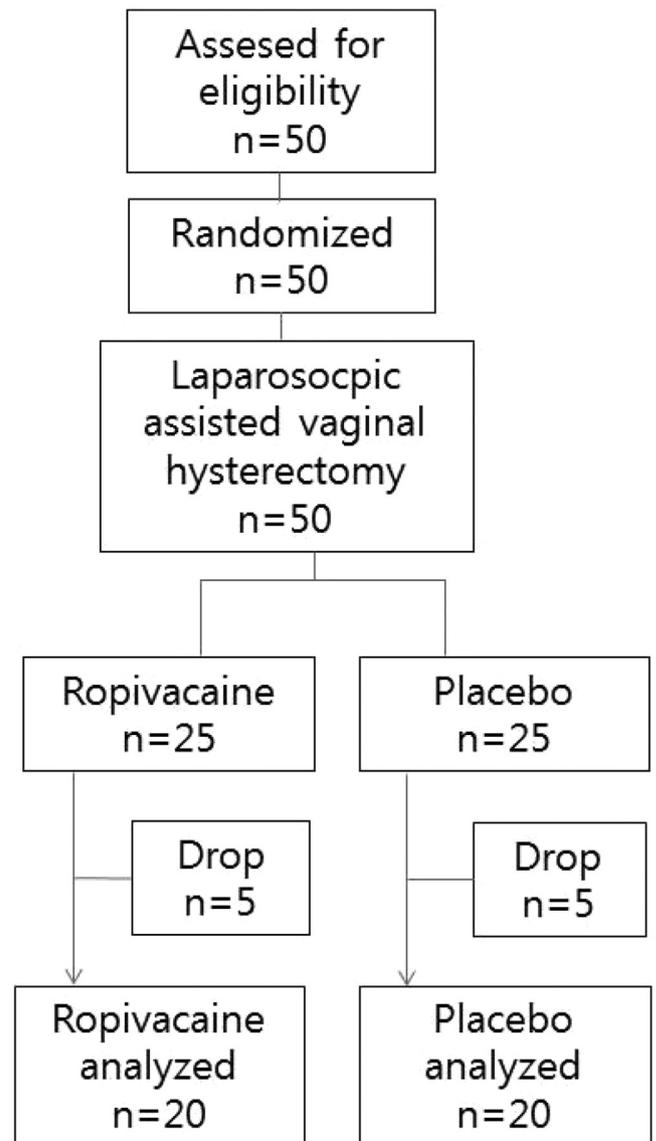


Fig. 1. Flow sheet for analysis.

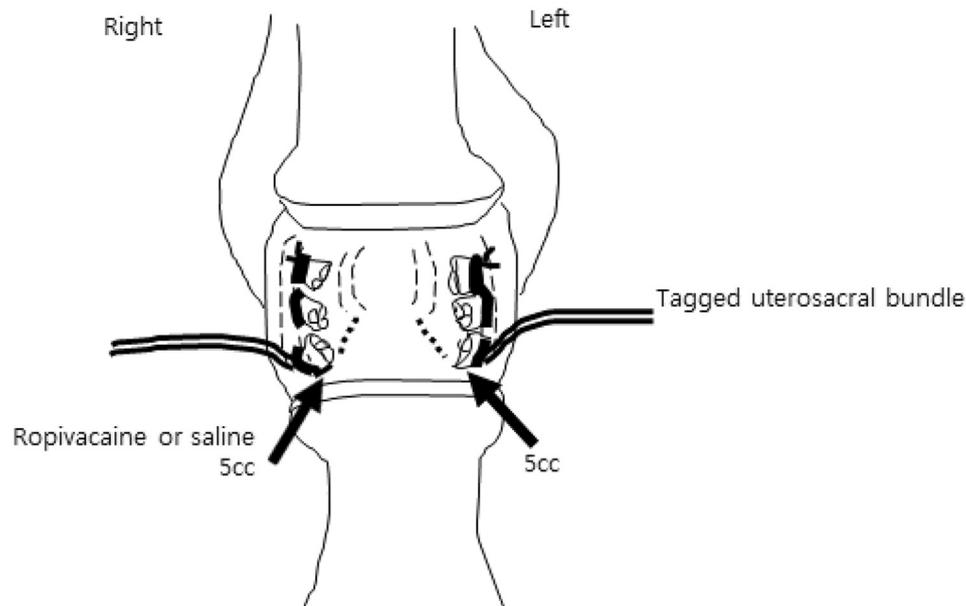


Fig. 2. Methods of injecting ropivacaine or saline via vaginal access before closing the vagina.

NSAID, ketorolac tromethamine 15 mg (Ketorac® 1 ampoule: 30 mg/mL) manufactured by Hanmi Pharmaceutical Co., Ltd. (Seoul, South Korea), and an opioid, meperidinechloride 25 mg (Pethidine®, 1 ampoule: 25mg/0.5 mL) manufactured by Jeil Pharmaceutical Co., Ltd. (Seoul, South Korea). Two hours after the injection, the patients arrived in the ward where they evaluated their pain scores, and 15 mg of ketorolac tromethamine was injected once routinely. If the patient experienced subsequent pain, ketorolac was the first choice for prorenata. Pain scores were reevaluated after 30 min, and if pain persisted, the NSAID was administered again. After 30 min after NSAID injection pain score was re-evaluated. Opioid was administered when the pain score was checked >4 NRS. Participants were not permitted PCA so that we could monitor their analgesic usage, but if the patients were unable to tolerate pain despite injection of intravenous analgesia, PCA was allowed optionally; patients under PCA were excluded from the analysis. Metoclopramide was used as a postoperative antiemetic as occasion demanded.

Outcome assessment

Baseline data were patients' age, body mass index, duration of surgery, duration of anesthesia, pre- and postoperative hemoglobin levels, and estimated blood loss during the surgery. The primary outcome was postoperative pain intensity expressed by a visual analogue scale (10 mm) at 2, 6, 12, and 24 h after the injection with an 11-point NRS 11: 0 represented no pain and 10 represented worst pain imaginable, and the score was measured using a numbered scale bar matched with figures of facial expressions. The secondary outcome was the amount of analgesics administered during the 24 h after the surgery. The treatment duration and amount in milligrams of administered analgesics (ketorolac tromethamine and meperidinechloride) were recorded.

Statistical analysis

We conducted the data analysis using MedCalc statistical software version 17.2 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2016). All data were expressed as

mean \pm standard deviation for continuous variables and percentage for categorical variables. We compared continuous variables using Student's *t* test for parametric data or the Mann–Whitney test for non-parametric data, and we considered $P \leq .05$ statistically significant. We compared the categorical variables using the Chi-square test or Fisher's exact test.

Results

Among 50 eligible patients, all were randomized, and ten were excluded. Among the 10 patients, two patients, one each in the ropivacaine and saline groups, were excluded because of the operative finding of grade IV endometriosis, one patient in the ropivacaine group was excluded because of injection of other analgesics, and the other seven patients opted for PCA after the surgery despite their pre-surgery agreement to not use PCA; of these, three patients were from the ropivacaine group and four were from the saline group. Thus, we analyzed 20 patients who received ropivacaine and 20 who received the placebo (Fig. 1). The ropivacaine and saline subgroups showed no statistical differences in patients' characteristics (Table 1).

Postoperative pain intensity showed significant differences at 2 h after administration of ropivacaine or placebo solution ($p = .023$); the ropivacaine group showed a mean NRS score of 4.60 ± 1.54 and the saline group, 6.32 ± 2.38 . However, there were no differences in NRS pain score at 6, 12, and 24 h after injection (Table 2). There was no difference between the two groups in the total amount of additional NSAIDs for additional pain control. However, the patients who received saline required more opioid (13.04 ± 19.76 mg, pethidine hydrochloride) than did those who received ropivacaine injection (3.26 ± 11.44 mg, pethidine hydrochloride; $p = .025$; Table 3).

Discussion

Compared with laparotomic surgery, laparoscopic surgery has less pain at the incision and approach sites, but postoperative visceral pain still needs to be controlled immediately after operations. Various factors are involved in the postoperative pain of

Table 1
Characteristics of patients who underwent laparoscopic-assisted vaginal hysterectomy.

Characteristics	Ropivacaine (n = 20)	Placebo (Saline) (n = 20)	p
Age, years ^a	48 (40–67)	48 (39–61)	0.305
Number of vaginal deliveries ^b	1.10 ± 1.02 (0–3)	1.15 ± 0.99 (0–3)	0.876
BMI, kg/m ^b	24.89 ± 2.61 (21.7–30.98)	25.20 ± (20.8–32.2)	0.741
Surgical time, min ^a	73.00 ± 37.78 (30–165)	65.53 ± 27.93 (35–130)	0.673
Anesthetic time, min ^a	104.00 ± 36.62 (60–200)	97.38 ± 29.03 (60–170)	0.736
Preoperative Hb, mg/dL ^b	12.42 ± 1.42 (10.3–15.2)	12.23 ± 1.73 (8.9–14.5)	0.697
Postoperative Hb, mg/dL ^b	11.29 ± 1.21 (8.4–13.3)	11.28 ± 1.52 (8.5–13.1)	0.989
Preop Hb-Postop Hb ^b	1.14 ± 1.00	0.95 ± 0.92	0.536
EBL, mL ^a	50 (20–500)	50 (10–100)	0.462

BMI, body mass index; EBL, estimated blood loss.

^a Data were expressed as median (range).

^b Data were expressed as mean ± standard deviation (range).

Table 2
Pain scores between the ropivacaine and placebo groups.

Hours	Ropivacaine N = 20	Placebo (Saline) N = 20	p	95% CI
2	4.60 ± 1.54 (2–8)	6.32 ± 2.38 (3–10)	0.023	0.422 to 3.009
6	4.40 ± 2.28 (1–8)	4.32 ± 1.73 (1–7)	0.199	–1.404 to 1.235
12	3.95 ± 1.90 (1–8)	3.26 ± 1.49 (1–9)	0.947	–2.014 to 0.640
24	2.90 ± 0.79 (2–5)	2.52 ± 1.35 (1–6)	0.113	–1.102 to 0.355

Data were expressed as mean ± standard deviation (range).

laparoscopic surgery including visceral pain induced by dissection, shoulder and scapular pain, stretching pain due to pneumoperitoneum, and incision pain from the trocar site [1,15]. In this study, vaginal access is part of the procedure, and history of vaginal delivery can affect the patient's pain intensity. Most of the women who participated in this study were multiparous, and there was no significant difference in number of vaginal deliveries between the two groups (Table 1). Intraperitoneal local injection has been a focus of studies since the 1950s. Previous studies used instilled or nebulized delivery modes for peritoneal distribution [5,7,11,14–16]. With the advent of laparoscopic surgery, intraperitoneal administration of local anesthetics focused on the delivery to the peritoneum through methods such as nebulization or spraying [17]. Moreover, a study of continuous infusion of 0.5% levobupivacaine into the peritoneal cavity following laparoscopic hysterectomy indicated that there were no opioid-sparing effects [18]. With regard to the mode of intraperitoneal administration, we focused on the direct effect of the intraperitoneal lesion using the nerve-block concept, which is different from previous studies. Infiltration has the potential to directly block neural transmission of pain by transiently blocking the pelvic afferent sensory nerve fibers of the Lee-Frankenhausner nerve plexus, an important structure in signaling pain pathways.

Visceral pain intensity is maximal during the first few hours immediately after the surgery, and ropivacaine infiltration is effective in controlling early pain because it is most effective during

the immediate postoperative period. In our study, there were significant differences in pain intensity in the first 2 h immediately following laparoscopic hysterectomy, at the first 2 h. Immediate pain control improves quality of postoperative care during the hospital stay. Ropivacaine infiltration to the uterosacral area was effective in hysterectomy, suggesting that local injection might mostly control focal visceral pain compared with directly blocking the afferent nerve pathway. Although the exact mechanism remains unknown, the decreased amount of opioid in the ropivacaine group is partly indicative of the effect of early postoperative pain control within the first 24 h after the surgery.

Only a few trials of intraperitoneal infiltration of local anesthetics directly to the site of operation have been reported. Local intraperitoneal infiltration was applied in studies of cholecystectomy [19], appendectomy [20], and laparoscopic sterilization [21]. The systemic levels of local intraperitoneal anesthetics are detectable in the serum after 2 min, reaching a maximal concentration after 10–30 min; systemic toxicity can occur, whereas local anesthetics have a relatively wide safety margin. In a review study, Kahokher et al. reported a dose range of ropivacaine of 100–300 mg and a mean C_{max} of 0.66–3.76 µg/mL in a previous study. T_{max} was achieved at 15–35 min post-administration. On the basis of previous studies and the dose permitted by the Korea Food and Drug Administration (7.5–225 mg) for infiltrative anesthesia, we injected a total dose of 75 mg ropivacaine as 10 cc of ropivacaine hydrochloride 7.5% solution (7.5 mg/mL). Because of the lack of clinical toxicity studies, careful consideration was required for dosing to prevent potential toxic effects [2].

One limitation of this study is that it was designed as a small study. Also, we focused on visceral pain alone without considering other types of pain. However, in our experience, most patients complain of abdominal pain immediately after the surgery, and shoulder or back pain is revealed shortly thereafter. Immediate postoperative pain is the most intense and acute, and thus it must be controlled. Therefore, early management of postoperative pain is the crucial point for pain control after surgery. Additionally, visceral pain is the primary point for early postoperative pain control, and

Table 3
Total amount of analgesics.

	Ropivacaine N = 20	Placebo (Saline) N = 20	p
Additional NSAID			
ketorolac tromethamine (mg)	13.67 ± 17.47 (0–45)	13.04 ± 12.22 (0–45)	0.676
Opioid			
meperidinechloride (mg)	3.26 ± 11.44 (0–50)	13.04 ± 19.76 (0–75)	0.025

Data were expressed as average ± standard deviation (range).

NSAID, Nonsteroidal anti-inflammatory drug.

thus we evaluated the pain scores during the first 24 h after injection of ropivacaine. Effective intraoperative local injection not only controls pain but also reduces the release of stress hormones and neurotransmitters that disturb postoperative recovery. Moreover, as a result of pain in the immediate postoperative period, movement of respiratory muscles decreases and the patient tends to under-ventilate, causing atelectasis and mucus retention and increasing the chance of infection. Pain control in the early postoperative period facilitates normal respiration and prevents postoperative pulmonary complications [22].

In conclusion, intraoperative local ropivacaine infiltration targeting the uterine nerve plexus can reduce early postoperative pain and consumption of analgesics in patients following laparoscopic-assisted hysterectomy.

Conflicts of interest statement

All authors declare that they have no conflicts of interest or conflicting financial ties.

Acknowledgement

None.

References

- [1] Mouton WG, Bessell JR, Otten KT, Maddern GJ. Pain after laparoscopy. *Surg Endosc* 1999;13:445–8.
- [2] Kahokehr A, Sasmour T, Vather R, Taylor M, Stapelberg F, Hill AG. Systemic levels of local anaesthetic after intra-peritoneal application—a systematic review. *Anaesth Intensive Care* 2010;38:623–38.
- [3] Chou YJ, Ou YC, Lan KC, Jawan B, Chang SY, Kung FT. Preemptive analgesia installation during gynecologic laparoscopy: a randomized trial. *J Minim Invasive Gynecol* 2005;12(4):330–5.
- [4] Goldstein A, Grimault P, Henique A, Keller M, Fortin A, Darai E. Preventing postoperative pain by local anesthetic instillation after laparoscopic gynecologic surgery: a placebo-controlled comparison of bupivacaine and ropivacaine. *Anesth Analg* 2000;91:403–7.
- [5] Marks JL, Ata B, Tulandi T. Systematic review and metaanalysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. *J Minim Invasive Gynecol* 2012;19:545–53.
- [6] Saccardi C, Gizzo S, Vitagliano A, Noventa M, Micaglio M, Parotto M, et al. Pericisional and intraperitoneal ropivacaine administration: a new effective tool in pain control after laparoscopic surgery in gynecology: a randomized controlled clinical trial. *Surg Endosc* 2016;30:5310–8.
- [7] Scalia Catenacci S, Lovisari F, Peng S, Allegrì M, Somaini M, Ghislanzoni L, et al. Postoperative analgesia after laparoscopic Ovarian cyst resection: double-blind multicenter randomized control trial comparing intraperitoneal nebulization and peritoneal instillation of ropivacaine. *J Minim Invasive Gynecol* 2015;22:759–66.
- [8] Somaini M, Brambillasca P, Ingelmo PM, Lovisari F, Catenacci SS, Rossini V, et al. Effects of peritoneal ropivacaine nebulization for pain control after laparoscopic gynecologic surgery. *J Minim Invasive Gynecol* 2014;21:863–9.
- [9] Quinn MJ, Kirk N. Differences in uterine innervation at hysterectomy. *Am J Obstet Gynecol* 2002;187:1515–20.
- [10] Callesen T, Hjort D, Mogensen T, Schouenborg L, Nielsen D, Reventlid H, et al. Combined field block and i.p. instillation of ropivacaine for pain management after laparoscopic sterilization. *Br J Anaesth* 1999;82:586–90.
- [11] Cha SM, Kang H, Baek CW, Jung YH, Koo GH, Kim BG, et al. Peritrocal and intraperitoneal ropivacaine for laparoscopic cholecystectomy: a prospective, randomized, double-blind controlled trial. *J Surg Res* 2012;175:251–8.
- [12] Kucuk C, Kadiogullari N, Canoler O, Savli S. A placebo-controlled comparison of bupivacaine and ropivacaine instillation for preventing postoperative pain after laparoscopic cholecystectomy. *Surg Today* 2007;37:396–400.
- [13] Labaille T, Mazoit JX, Paqueron X, Franco D, Benhamou D. The clinical efficacy and pharmacokinetics of intraperitoneal ropivacaine for laparoscopic cholecystectomy. *Anesth Analg* 2002;94:100–5.
- [14] Park YH, Kang H, Woo YC, Park SG, Baek CW, Jung YH, et al. The effect of intraperitoneal ropivacaine on pain after laparoscopic colectomy: a prospective randomized controlled trial. *J Surg Res* 2011;171:94–100.
- [15] Kaufman Y, Hirsch I, Ostrovsky L, Klein O, Shnaider I, Khoury E, et al. Pain relief by continuous intraperitoneal nebulization of ropivacaine during gynecologic laparoscopic surgery—a randomized study and review of the literature. *J Minim Invasive Gynecol* 2008;15:554–8.
- [16] Johnson NP, Farquhar CM, Crossley S, Yu Y, Van Peperstraten AM, Sprecher M, et al. A double-blind randomised controlled trial of laparoscopic uterine nerve ablation for women with chronic pelvic pain. *BJOG* 2004;111:950–9.
- [17] Kahokehr A, Sasmour T, Soop M, Hill AG. Intraperitoneal local anaesthetic in abdominal surgery - a systematic review. *ANZ J Surg* 2011;81:237–45.
- [18] Andrews V, Wright JT, Zakaria F, Banerjee S, Ballard K. Continuous infusion of local anaesthetic following laparoscopic hysterectomy—a randomised controlled trial. *BJOG* 2014;121:754–60.
- [19] Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. *Anesth Analg* 2006;103:682–8.
- [20] Kang H, Kim BG. Intraperitoneal ropivacaine for effective pain relief after laparoscopic appendectomy: a prospective, randomized, double-blind, placebo-controlled study. *J Int Med Res* 2010;38:821–32.
- [21] Alexander CD, Wetchler BV, Thompson RE. Bupivacaine infiltration of the mesosalpinx in ambulatory surgical laparoscopic tubal sterilization. *Can J Anaesth* 1987;34:362–5.
- [22] Kelkar KV. Post-operative pulmonary complications after non-cardiothoracic surgery. *Indian J Anaesth* 2015;59(9):599–605.