Original Research

Intraperitoneal ropivacaine for post-operative pain following laparoscopic tubal ligation: a randomised double-blind placebo-controlled trial

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Background: Female sterilisation is the most common method of contraception worldwide and laparoscopic tubal sterilisation is increasingly considered as a day-surgery procedure. Therefore, pain following this procedure should be seriously addressed. Instillation of 200 to 300 mg of ropivacaine intraperitoneally has been proven effective in controlling pain after laparoscopic tubal ligation (LTL). However, extreme caution must be taken as potential serum toxicity has been reported with the instillation of 150 mg of intraperitoneal ropivacaine. In search of the lowest, most effective dose, this study aimed to evaluate the effectiveness of 112.5 mg of ropivacaine intraperitoneally in reducing post-operative pain after LTL. *Methods*: This double-blind, placebo-controlled randomised trial was conducted in an ambulatory care centre in Malaysia. Sixty-two patients scheduled for LTL were recruited. Two patients were excluded from the trial because of intraoperative complications. Sixty patients were randomised to either the placebo group (intraperitoneal normal saline, n = 30) or the ropivacaine group (intraperitoneal ropivacaine, n = 30). Pain scores (using a visual analogue score), and the need for additional analgesia were assessed at 15, 60, 120, and 240 minutes post-LTL. *Results*: We observed no significant differences in pain scores or the need for additional analgesia between the groups. *Conclusion*: 112.5 mg of ropivacaine administered intraperitoneally is not more effective than normal saline in decreasing post-operative pain after LTL.

Keywords

Intraperitoneal analgesia; Laparoscopic tubal ligation; Post-operative pain; Ropivacaine

1. Introduction

Laparoscopic tubal sterilisation is increasingly considered as a day-surgery procedure. After careful selection, patients undergoing day-surgery laparoscopic procedures may benefit from early mobilisation, earlier discharge, and reduced analgesia needs [1–6]. Despite such advantages, 35–85% of patients still experience severe post-operative pain after laparoscopic procedures [7], although it may not be comparable to the pain experienced following conventional laparotomy [8, 9].

Tubal ligation pain may originate from the ischemic pressure applied to the tubes and/or the prostaglandin release from the fallopian tube tissues [10, 11]. Further, the tubal spasm from laparoscopic tubal ligation (LTL) can produce more pain than that from diagnostic scopes [12]. Besides tissue trauma, laparoscopic procedure itself can lead to pain due the effect of carbon dioxide (CO_2) on the peritoneum and diaphragmatic nerves, in addition to visceral ligament traction [7]. Since female sterilisation is the most common method of contraception worldwide [13], pain following this procedure should be seriously addressed, as it may complicate post-operative recovery [14].

The advantages of intraperitoneal analgesia are clinically proven [15–18]. In fact, one of the elevan strategies described by Sou *et al.* [7] to reduce pain after gynaecological laparoscopic surgery included intraperitoneal analgesia. Examples of some intraperitoneally used local analgesics are lignocaine [19, 20], bupivacaine [21] meperidine [22], and recently, ropivacaine [23–27]. The latter has demonstrated a superior cardioprotective effect compared to bupivacaine [28–30], while providing longer pain relief and reducing opioid usage [31–33].

However, the regular use of intraperitoneal ropivacaine during LTL remains debatable. Significant improvement in pain scores have been shown with the intraperitoneal instillation of 200 mg [25] and 150 mg [26] ropivacaine during LTL. Extreme caution must be taken as potential serum toxicity has been reported with the instillation of 150 mg ropivacaine intraperitoneally [34]. On the contrary, nebulizing a lower dose (100 mg) of ropivacaine intraperitoneally during laparoscopic gynaecological procedures has shown no improvement in the post-operative pain score [27]. While no clinical toxicity was reported with the instillation of ropivacaine between 100 and 300 mg [35], given the rapid absorption of intraperitoneal analgesia, there is an ongoing discussion surrounding the ideal dose of ropivacaine [36] to prevent

systemic toxicity. Based on these findings, we aimed to investigate the intraperitoneal analgesic effects of ropivacaine at a dose in the range of 100 to 150 mg. In this trial, we administered 112.5 mg of ropivacaine intraperitoneally to reduce post-operative pain after LTL.

2. Materials and methods

2.1 Setting and participants

This study was conducted in the ambulatory care centre of Penang General Hospital, Malaysia. Written informed consent was obtained during patients' visits to the gynaecology clinic a few weeks before the date of surgery. Women who were assigned an American Society of Anaesthesiologists' (ASA) physical classification of I or II, aged between 18 and 55 years, and were scheduled to undergo LTL were considered eligible for participation. Patients with known drug allergies to substances in the local anaesthesia, ropivacaine, parecoxib, or having received analgesia 12 hours before the scheduled procedure were excluded. This study was registered and approved by the Ministry of Health Research and Ethics Committee (MREC) of the National Medical Research Register and the Clinical Research Centre (NMRR), Malaysia (NMRR-09-601-3897).

2.2 Randomisation and blinding

As shown in Fig. 1, eligible and consenting patients were randomised and allocated, on completion of their LTL, to either the ropivacaine or the placebo (normal saline) group. Group randomisation was performed according to a table of random numbers. The results were sealed in opaque envelopes and revealed after induction. Except for the research assistant, who prepared the drugs in a different room, all other medical staff, including the surgeon, and the technical staff in charge on the day of the surgery were blinded to the treatment group.

2.3 Intervention

A standard preoperative form was completed in accordance with the Department of Anaesthesia's protocol. All laparoscopies were performed in the ambulatory care centre's operation theatre at Penang General Hospital. No premedication or any form of analgesia was administered prior to the procedure. The standard anaesthetic agents used included propofol (1.5–2.5 mg/kg), fentanyl (1–2 mcg/kg), metoclopramide (10 mg), and atracurium (0.3–0.6 mg/kg). Anaesthesia was maintained with 50% nitric oxide, 50% oxygen, and 1–2% sevoflurane. No other analgesic was administered intraoperatively.

For each laparoscopy, while the patient was in supine position, a sub-umbilical incision was performed and 2.5 L of CO_2 insufflated into the peritoneal cavity. A 5-mm port was inserted sub-umbilically, and pneumoperitoneum was created using a Veress needle. Another 5-mm port was inserted into the right iliac fossa, left iliac fossa, or suprapubic region under direct vision. The ligation of both fallopian tubes was performed with Filshie clips or Falope rings.

At the end of the procedure, before the removal of the laparoscopic port, 15 mL of 0.75% ropivacaine or normal saline was splashed (7.5 mL on each tube) on both ligated tubes under direct vision, as illustrated in Fig. 2.

The abdomen was then deflated, and the 5-mm port was removed under direct vision. The skin was opposed using a subcuticular technique with absorbable sutures. The skin at both port sites was infiltrated with the remaining 5 mL of ropivacaine 0.75% in both groups, following the standard analgesia regimen. Reversal of neuromuscular blockade was achieved with atropine (20 μg/kg) and neostigmine (50 μg/kg). After extubation, the patient received 40% oxygen by mask until reaching full consciousness.

2.4 Post-operative management

Post anaesthesia, the patient was observed in the post-anaesthesia care unit (PACU). Each patient informed the medical staff in charge, who was blinded to the treatment group, of their pain severity using a visual analogue score between 0 and 10 (0 being no pain and 10 being the most severe pain) at 15, 60, 120, and 240 minutes after arrival to the PACU. Medical staff also assessed the need for additional pain relief (intravenous parecoxib 40 mg). After 4 hours post-procedure, the patient's suitability for discharge was assessed according to the standard local protocol.

2.5 Sample size and statistical analysis

In this study, the sample size calculation was performed by referring to a previous study [25]. The mean pain score at two hours post LTL in the ropivacaine group was 2.03 and that of the control group was 0.97. Assuming that the standard deviation is 1.4, with a two-sided significance level of 5% and power of 80%, the minimum number needed for each group was 30.

Statistical analysis was performed using standard parametric and non-parametric statistics with JMP Pro 14.1 (SAS Institute Inc., Cary, NC, USA). Data are expressed as mean $\pm$ standard deviation or number (%). Fisher's exact test was used to analyse categorical variables, and the independent sample t-test or Mann-Whitney test was used to analyse continuous variables. A two-sided P-value < 0.05 was considered as the threshold for significance.

3. Results

Seventy-four patients were invited to participate in this study during their gynaecological visits. Among them, nine declined to participate and three were found ineligible. At the beginning of the study, 62 patients agreed to participate and provided consent for LTL. However, two patients were excluded from the placebo (n = 1) and ropivacaine groups (n = 1) because of intraoperative complications (severe adhesions requiring extended general anaesthesia and port entry failure requiring conversion to a mini-laparotomy, respectively). Therefore, 60 patients received their allocated treatments. The placebo group (n = 30) received 15 mL of normal saline intraperitoneally, and the ropivacaine group (n = 30) received
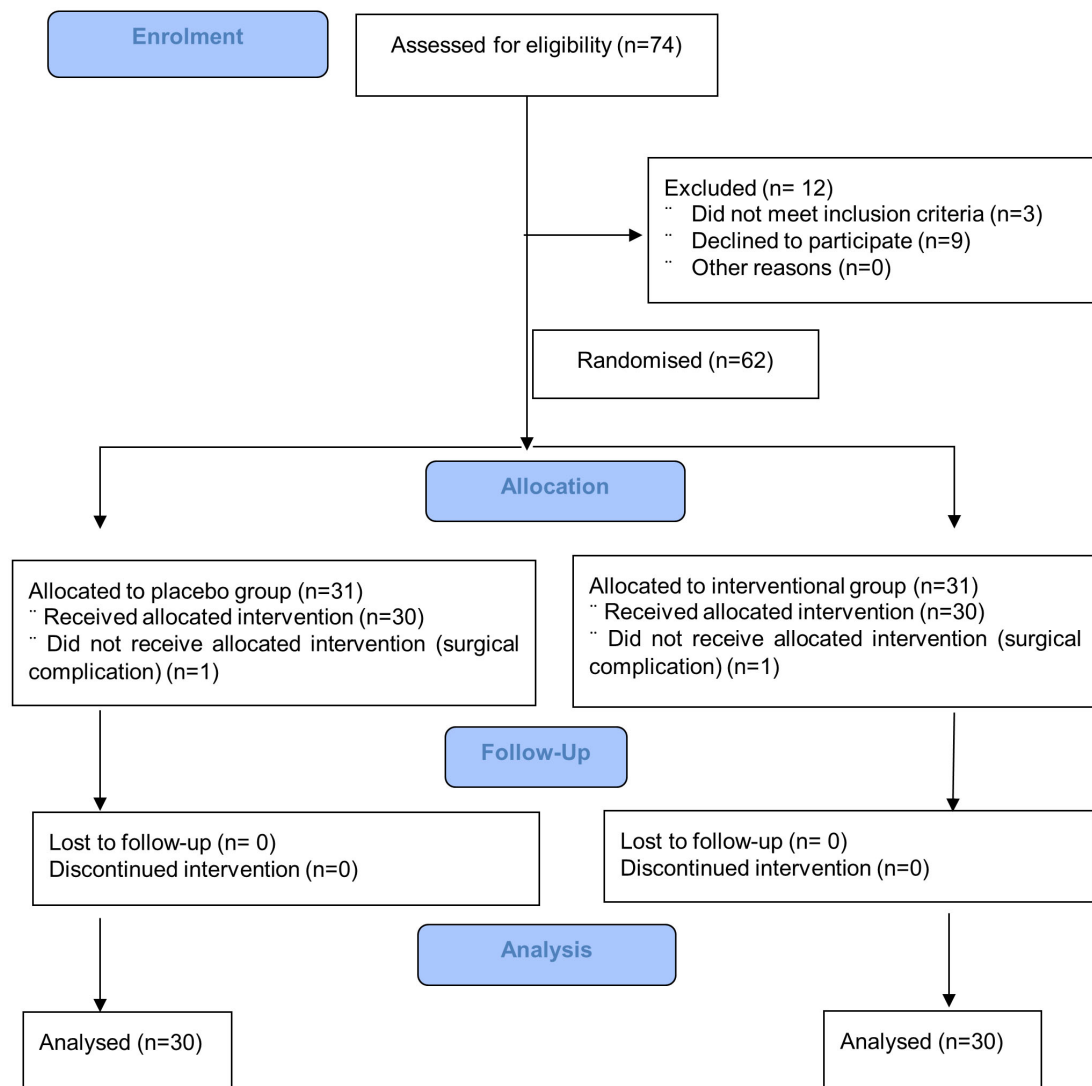
Fig. 1. Consort flow chart.

an instillation of 15 mL of 0.75% ropivacaine (equivalent to 112.5 mg). The characteristics of all patients are shown in Table 1. There were no significant differences between groups in terms of age, parity, number of miscarriages, or previous surgeries.

We found no significant differences in the patients' pain scores between the placebo and the ropivacaine groups at 15, 60, 120, and 240 minutes ($P > 0.05$) after LTL. As shown in Fig. 3, patients randomised to the placebo group documented a mean pain score of 4.14 (standard deviation 2.61) at 15 minutes while the patients from the ropivacaine group scored 3.9 (standard deviation 2.09) [95% confidence interval −0.99 to 1.47; $P = 0.70$]. At 60 minutes, patients from the placebo group scored 3.33 (standard deviation 2.28) and the patients assigned to the ropivacaine group provided a pain score of 3.13 (standard deviation 1.87) [95% confidence interval −0.88 to 1.28; $P = 0.71$]. At 120 minutes, pain scores of

2.79 (standard deviation 1.40) and 2.23 (standard deviation 1.21) were recorded from patients in the placebo and ropivacaine group, respectively [95% confidence interval −0.16 to 1.27; $P = 0.13$]. Patients assigned to the placebo group recorded a pain score of 2.78 (standard deviation 1.86) at 240 minutes, and patients in the ropivacaine group scored 2.1 (standard deviation 1.48) [95% confidence interval −0.34 to 1.72; $P = 0.19$]. The need for additional analgesia in the form of intravenous parecoxib was also not statistically different ($P = 0.68$) between the groups. Three patients from each group required additional analgesia at 15 minutes after LTL. At 60 minutes postoperatively, two patients from each group requested additional analgesia. The need for additional analgesia at 120 post LTL was recorded in 5 patients from the placebo group and 2 from the ropivacaine group. No patient requested additional analgesia after 4 hours post-procedure. Pain was reported in the shoulder tip in 13 pa-

Table 1. Demographic data and descriptions of patients undergoing laparoscopic tubal ligation.

	Treatment group		*P*-value
	Placebo (n = 30)	Ropivacaine (n = 30)	
Age group (years), n (%)			
19–25	1 (3.3%)	0	0.08
31–35	13 (43.3%)	11 (36.7%)	
36–40	9 (30%)	8 (26.7%)	
>41	7 (23.3%)	11 (36.7%)	
Parity, median (IQR)	4 (4–5)	4 (2–5)	0.77
Number of miscarriages, median (IQR)	1 (1–2)	2 (1–3)	0.33
Previous abdominal surgery n (%)			
No previous surgery	27 (90%)	22 (73.3%)	0.28
Pfannenstiel	1 (3.3%)	4 (13.3%)	
Lanz	2 (6.7%)	2 (6.7%)	
Others	0	1 (3.3%)	
Missing data	0	1 (3.3%)	

Data are shown in n (%), mean ± standard deviation or median (IQR). Significance test was determined using the Fisher's exact test.
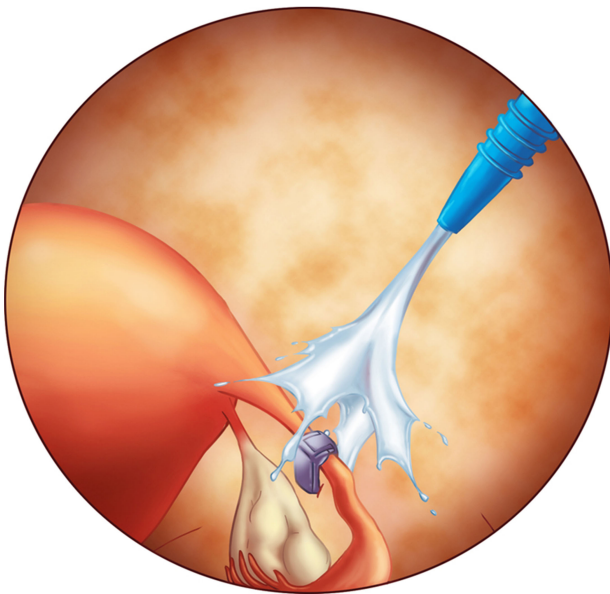

Fig. 2. Illustration of intraperitoneal ropivacaine splashing on the ligated tubes during laparoscopic tubal ligation.

tients, at the port insertion site in 22 patients, as generalised abdominal pain in 16 patients, and as non-specific pain in 9 patients. There was no statistical difference between the placebo and ropivacaine groups in terms of pain location as shown in Table 2. No patients were admitted to the ward for complications related to the surgery or to the drug (e.g., inadequate pain relief, surgical complication, hypotension, nausea, bradycardia, urinary retention and other related symptoms). All patients in both groups were discharged at 4 hours post-procedure.

Table 2. Description of post-operative pain according to the treatment groups.

	Placebo (n)	Ropivacaine (n)	*P*-value
Shoulder tip pain	7 (23%)	6 (20%)	1.00
Port incision site pain	10 (33%)	12 (40%)	0.79
Generalised abdominal pain	9 (30%)	7 (23%)	0.77
Non-specific pain	4 (1.3%)	5 (1.6%)	1.00

Data are shown in n (%). Significance test was determined using Fisher's exact test.
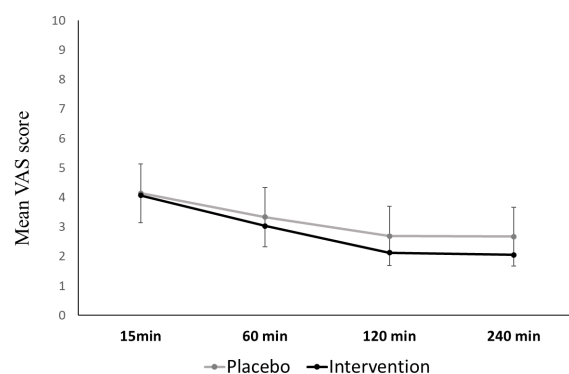
Fig. 3. Mean visual analogue scores for pain at 15, 60, 120 and 240 minutes after laparoscopic tubal ligation. Data are shown in mean (standard deviation). Significant test was done with independent sample *t*-test.

4. Discussion

This randomised placebo-controlled trial showed that intraperitoneal instillation of 112.5 mg of ropivacaine over the ligated tubes during LTL did not significantly improve the post-operative pain score.

The pain-relief mechanisms mediated by intraperitoneal local analgesia are unclear, but the blockage of free afferent

nerve endings in the peritoneum could play a potential role [35]. However, the effectiveness of intraperitoneal local analgesia varies with the procedure [17]. Despite there being six times more randomised controlled trials in laparoscopic cholecystectomy, the evidence for intraperitoneal local analgesia during gynaecological and gastric laparoscopy appears to be stronger [18]. Unfortunately, the available data from trials focusing on pain relief after LTL were not only scarce but also conflicting in nature [19, 22, 24, 25, 37, 38]. For example, intraperitoneal analgesia, whether alone or in combination with other local analgesia, was found to be an effective and safe method to manage post-operative pain after LTL in some reports [19, 22, 25, 37], while others have found no benefit from this route [24, 38]. A reason for the failure of intraperitoneal local analgesia to reduce post-operative pain could be that these local analgesics may work better for local incisional pain rather than for visceral pain [39].

In the present study, intraperitoneal administration of 112.5 mg of ropivacaine did not improve the pain score between 15 minutes and 2 hours post-operatively. However, a possible significant improvement may have been possible 2 hours post-LTL. In a recent systematic review and meta-analysis of instilled intraperitoneal ropivacaine during laparoscopic cholecystectomy, concentrations as low as 0.25–1.5% were reported to lead to a significant reduction in the pain score measured with visual analogue pain score between 6–9 and 9–24 hours post-operatively [40]. The selected time point to assess pain was six hours, a reflection of the long-lasting effects of local analgesia [41]. Unfortunately, it was not possible to observe our patients beyond six hours as the local protocol guideline advises allowance of discharge within four hours after uncomplicated day-surgery LTL procedures. Moreover, pain management during pelvic laparoscopy was supposedly to be more successful than that during laparoscopic cholecystectomy [9]. The negative outcome of intraperitoneal instillation from our trial could also be attributed to the time of intraperitoneal local anaesthetic instillation. Although there is inadequate evidence to conclusively determine the best timing to instill local analgesia intraperitoneally [42], some studies have observed a successful pain control when local analgesia is applied before tissue trauma [43, 44] rather than at the end of the surgery Finally, we acknowledge that the dose of ropivacaine and/or the sample size may have been inadequate to produce a significant effect between 15 minutes and 4 hours post-operatively. The administered dose was selected based on two reasons. We chose 112.5 mg not only to facilitate drug preparation (15 mL of 0.75% ropivacaine and 5 mL of 0.75% ropivacaine under port side skin incision), but also because Labaille *et al.* [34] reported potential serum toxicity in 2 out of 19 patients with 150 mg of intraperitoneal ropivacaine, although clinical toxicity was not observed. Though a significant reduction in pain score after LTL was observed with the intraperitoneal administration of 150–200 mg of ropivacaine [25, 26], care must be taken before a administering higher doses. There-

fore, further trials are required to determine the safest, most effective, and lowest dose of intraperitoneal ropivacaine to reduce pain after LTL.

5. Conclusions

This randomised placebo-controlled trial showed that instillation of 112.5 mg of ropivacaine intraperitoneally during LTL did not significantly improve the post-operative pain score. However, further research is needed to confirm whether the dose of ropivacaine used and the observation time were appropriate.

Abbreviations

ASA, American Society of Anesthesiologist; LTL, laparoscopic tubal ligation; PACU, Post-Anesthesia Care Unit.

Author contributions

JMKA, ASA, NAMA and SZO conceived and designed the experiments. JMKA, SSB, SRKB, performed the experiments. JMKA, SNSJHZ, NR and MH analyzed the data. SSB, SRKB, SNSJHZ, NR and NAMA contributed reagents and materials. JMKA, ASA, MH and SZO wrote the paper.

Ethics approval and consent to participate

Written informed consent was obtained from all participants. This study was registered and approved by the Ministry of Health Research and Ethics Committee (MREC) of the National Medical Research Register and the Clinical Research Centre (NMRR), Malaysia (NMRR-09-601-3897).

Conflict of interest

The authors declare no conflict of interest.

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