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ORIGINAL ARTICLE

Pain reduction by continuous intraperitoneal nebulization of ropivacaine during gynecological laparoscopic surgery

Y. Kaufman · L. Ostrovsky · O. Klein · I. Hirsh · R. Auslander · R. Pizov · A. Lissak

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Abstract The objective of this study was to examine the analgesic effect of intraperitoneal nebulization of ropivacaine during gynecological laparoscopic procedures for patients anesthetized with an ultrashort-acting opiate. The study was a double-blinded placebo-controlled randomized trial (Canadian Task Force classification I) and involved 40 patients (20 patients in each arm) undergoing elective gynecological same-day outpatient laparoscopic surgery including unilateral/bilateral salpingo-oophorectomy or unilateral/bilateral ovarian cystectomy at the University Hospital Ambulatory Gynecological Endoscopic Unit. The study group received 10 ml of 1 % ropivacaine, and the control group received 10 ml of sterile water by intraperitoneal nebulization. Vital signs were recorded and summarized. Postoperatively, patients were followed up for 24 h including visual analogue scale (VAS) scores and analgesic usage. Results showed no significant differences between the two groups in terms of patient characteristics and surgical data. There were no significant differences between the groups in postoperative VAS scores at rest at the different time intervals. VAS scores during strain showed significantly decreased pain at the postoperative 2-h interval ($p<0.05$). Postoperative opiate and nonopiate analgesia consumption was similar for both groups. Patients in the study groups required more antiemetic agents compared to the control group patients ($p<0.05$). There were no reported side effects related to ropivacaine. Intraperitoneal nebulization of 100 mg of ropivacaine during gynecological laparoscopy under general anesthesia with an ultrashort-acting opiate does not reduce postoperative pain and it does not reduce postoperative opiate and nonopiate analgesia consumption.

Keywords Pain · Intraperitoneal · Nebulization · Ropivacaine · Gynecology · Laparoscopy · Visual analog scale (VAS) score · Opiates · Remifentanil

Y. Kaufman (✉) · L. Ostrovsky · O. Klein · I. Hirsh · R. Auslander · A. Lissak
Department of Obstetrics and Gynecology,
The Lady Davis Carmel Medical Center,
Technion Institute of Technology Medical School,
7 Michal Street,
Haifa 34362, Israel
e-mail: mdykaufman@013.net.il

R. Pizov
Department of Anesthesiology and Critical Care,
The Lady Davis Carmel Medical Center,
Technion Institute of Technology Medical School,
Haifa, Israel

Background

Laparoscopic surgery has been clearly proven to have significant advantages over open surgery in many aspects including decreased postoperative pain. This has allowed many of the laparoscopic procedures to be performed on an outpatient basis. Pain control and reduction of postoperative nausea and vomiting (PONV) are essential for the patient's well-being and adamant for ambulatory surgery. Good postoperative pain relief has been advocated by the Joint Commission on Accreditation of Healthcare Organizations as a patient's right [1].

Pain during and after laparoscopy is multifactorial. This includes factors related to the procedure such as the type and duration of the procedure; factors related to the CO_2 gas including the total volume, pressure, and humidity of the delivered gas as well as the amount of residual gas within the peritoneum at the end of the procedure; and factors related to the intraoperative anesthetic protocol and the postoperative pain control protocol [2–4]. Improvements in postoperative pain may be achieved by reducing the CO_2 pressure, increasing humidity of the gas, and changing the

intraoperative as well as postoperative use of anesthetics and analgesics.

Postoperative pain is mostly visceral [5]. Pain control is usually done using opiates and opiate derivatives as well as local anesthetics (LA) and nonsteroidal anti-inflammatory drugs. Opiates are effective in pain control but at the price of causing PONV and drowsiness which are counterproductive for outpatient treatment. Reducing the negative effects of the opiates can be done by using short-acting opiates and intraperitoneal local anesthetics during laparoscopy. There are conflicting results regarding the effectiveness of intraperitoneal local anesthetics. Studies on this subject vary in terms of the timing for administration of the local anesthetic in relation to the procedure (i.e., beginning of insufflation, end of insufflation, end of the procedure), location of distribution within the peritoneal cavity, dosage, and the addition of adrenaline, which lowers peak plasma volume of the anesthetic [3]. Previously, we have published a study on continuous intraperitoneal nebulization of ropivacaine throughout gynecological laparoscopic procedures [6]. Ropivacaine pharmacodynamics depend on the method of administration. An animal study has shown that ropivacaine reaches peak concentrations after 1 h from administration, has a half-life of 2 h, and is excreted after approximately 6 h [7]. Our results showed no significant reduction in postoperative pain or in the use of postoperative analgesics. We assumed that residual effects of opiates given during the laparoscopic procedure have a prolonged postoperative effect which might be masking a possible potential pain-decreasing benefit of ropivacaine after surgery. Therefore, we decided to perform a follow-up study using the same technique of intraperitoneal nebulization but with a different anesthetic protocol which is based on ultrashort-acting opiates. Remifentanil is an ultrashort-acting opiate with an onset of action around 1 min and a half-life of 2–3 min which is rapidly eliminated from the body [8].

The objective of our study was to examine the effect of intraperitoneal nebulization of ropivacaine during gynecological laparoscopic procedures under an ultrashort-acting opiate anesthetic protocol on postoperative pain and analgesic consumption.

Methods

The study was a double-blinded placebo-controlled randomized trial approved by the Carmel Medical Center Helsinki Ethics Committee. We included 40 patients (20 patients in each arm), ages 18–70, with an American Society of Anesthesiologists physical status grade I or II, undergoing elective gynecological laparoscopic surgery at our Ambulatory Gynecoendoscopic Unit. All operations were performed by two senior consultants. After signing a consent form, patients who were candidates for a same-day outpatient laparoscopy including unilateral/bilateral salpingo-oophorectomy or unilateral/bilateral ovarian cystectomy randomly received either 10 ml of 1 % ropivacaine to a total of 100 mg (Naropin, 100 mg/10 ml, AstraZeneca, UK) or 10 ml of sterile water. The ampoules were prepared according to a double-blind design with the contents of the ampoules known only to the hospital pharmacy. Patients were randomly assigned to the study and control groups by a computer-generated algorithm.

All patients received the same standard anesthetic technique and standard monitoring including ECG, noninvasive blood pressure, end tidal CO_2, oxygen saturation, and temperature. Anesthesia was induced with a loading dose of remifentanil 1 μg/kg in 10 cc of saline given within a minute. This was followed by propofol 2 mg/kg and droperidol 0.5 mg. Rocuronium 0.6 mg/kg was given to facilitate intubation of the trachea. Anesthesia was maintained with isoflurane at one minimum alveolar concentration, N_2O 60 %, and O_2 40 %. Continuous remifentanil was administered at an initial dose of 0.5 μg/kg/min at the beginning of the procedure and was decreased to 0.2–0.4 μg/kg/min until 5 min before the estimated termination of the operation at which point the remifentanil was stopped. Minute ventilation was controlled and adjusted to keep the end-tidal CO_2 around 40 mmHg.

During laparoscopy, intra-abdominal CO_2 pressure was maintained at 13–15 mmHg throughout filling and maintenance. Nebulization was done using a specially designed nebulizer called Aeroneb Pro® (Aerogen, Ireland) which is an autoclavable Food and Drug Administration-approved device that produces a fine particle aerosol (2.1 μm mass median aerodynamic diameter, 83 % fine particle fraction <5 μm) without heating or degrading medications. The Aeroneb nebulizer can deliver 10 ml of fluid within 30 min regardless of the gas flow. The contents of the blinded ampoule were injected into the Aeroneb reservoir and nebulized along with the CO_2 at a maximal flow rate of 15 l/min. The nebulizer was located proximal to the entry trocar at a distance not exceeding 30 cm to avoid major condensation of the fluid within the tubing. A closed entry

Table 1 Patient characteristics

	Control (n=20)	Study (n=20)	p value
Mean age (SD, 95 % CI)	47 (16.2, 23–77)	45.7 (13.4, 25–69)	0.79
Body mass index	26.5 (5.2, 19.5–43.7)	26.3 (7.2, 16.9–43.7)	0.90

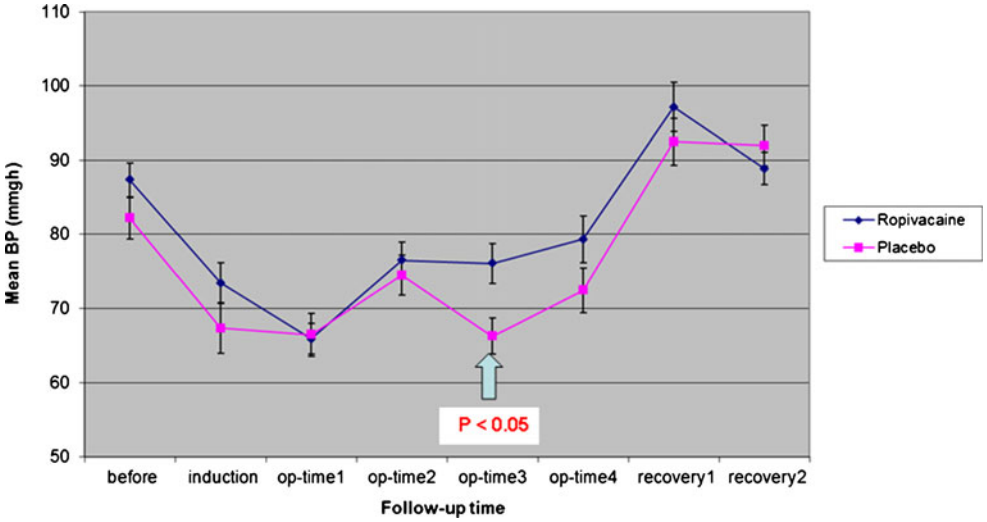

Fig. 1 Mean arterial blood pressure (MAP) during surgery presented as mean and SE

technique was used. Insufflation of CO_2 through the nebulizer system delivered ropivacaine or sterile water into the peritoneal cavity. Mean arterial blood pressure (MAP) and heart rate were recorded before surgery, during induction, and at time intervals during the procedure and at the recovery unit. Intraoperative pain was evaluated by changes in MAP and heart rate. Surgery duration and blood loss were recorded at the end of the procedure. Following the procedure, visual analog scale (VAS) scoring was used to assess pain severity at rest and during strain (cough). This was done in the recovery room postoperatively at 30 min, 1 h, and 2 h from completion of surgery. Intravenous morphine 0.05 mg/kg was administered when the VAS score exceeded 4. Additional doses of morphine were given till the VAS score dropped below 4. Patients with shivers were given 15 mg of IV pethidine. Nausea and vomiting were treated with IV 4 mg ondansetron.

After discharge, patients were interviewed at home by phone at 6 h and 24 h after surgery for VAS scores. Patients were asked whether they required analgesia. The type, dosage, and frequency of analgesic consumption were recorded.

Statistical analysis was performed by using the SPSS 15 software. The continuous variables were presented by mean ± std or median, as appropriate. The categorical variables were presented in percentages.

Comparisons between the two groups regarding patient characteristics and surgical data were done by using independent *t* test or Mann–Whitney, as appropriate, for the continuous variables. Chi-square test was performed for the categorical variables.

The VAS score analysis comparing the two groups at each point of time was done by using the nonparametric Mann–Whitney test with Bonferroni correction for multiple statistical comparisons. A p value <0.05 was determined as statistically significant.

Findings

Our results show no significant differences between the two groups in terms of patient characteristics and surgical data

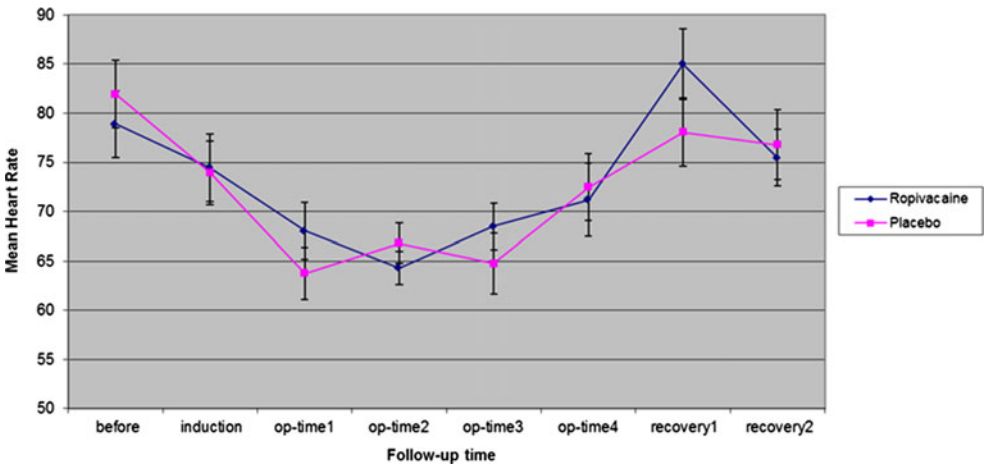

Fig. 2 Heart rate (HR) during surgery presented as mean and SE

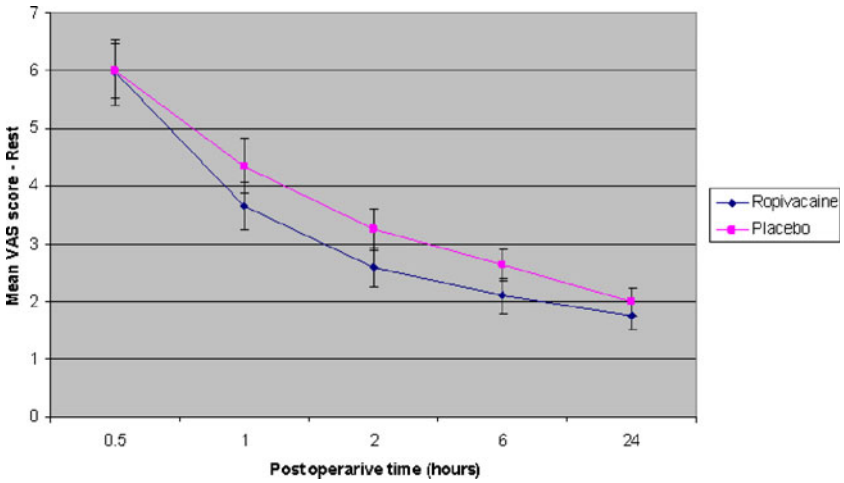

Fig. 3 Visceral visual analog scale (VAS) scores at rest during 24 postoperative hours

(Table 1). This includes mean age, BMI, surgery duration, blood loss, number and size of trocars, total insufflated gas, and type of procedure.

There were no significant differences between the groups at each time interval in terms of mean arterial blood pressure except for operating time interval 3 ($p<0.05$, Fig. 1). No significant changes were found between the groups in terms of heart rate (Fig. 2).

There were no significant differences between the groups in postoperative VAS scores at rest at the different time intervals (Fig. 3). Analysis of VAS scores during strain (cough) showed significantly decreased pain between study and control groups at the postoperative 2-h interval in favor of the study group patients ($p<0.05$, Fig. 4).

Postoperative opiate and nonopiate analgesia consumption was similar for both groups (p=n.s., Table 2). Patients in the study groups required more antiemetics compared to the control group patients ($p<0.05$).

There were no reported side effects related to ropivacaine and no intraoperative or postoperative complications for any of the patients in both the study and control groups (Table 3).

Discussion

The efficacy of intraperitoneal administration of LA for pain relief after laparoscopic surgery has been a subject of many studies. Interpretation of overall results in a meta-analysis is difficult due to the large heterogeneity in methodology. Studies differ with regard to the type of LA, dosage, method and timing of administration, intraoperative and postoperative pain control protocol, and follow-up parameters. Long-acting local anesthetics have been shown to be efficient for postoperative pain relief in different types of laparoscopic procedures such as cholecystectomy [9] and appendectomy [10]. There are several studies showing conflicting results on the effect of LA instillation following gynecological laparoscopic procedures [10–16].

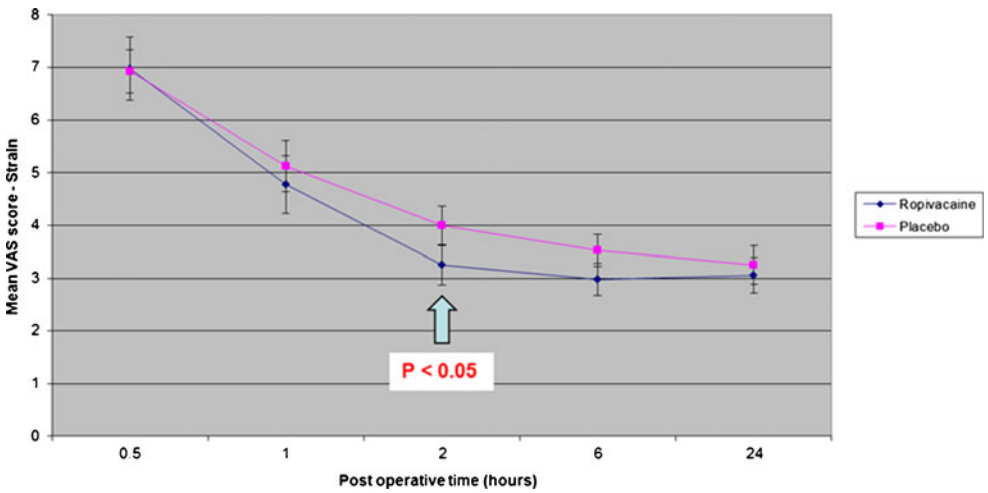

Fig. 4 Visceral visual analog scale (VAS) scores at cough during 24 postoperative hours

Table 2 Surgical data

	Control (n=20)	Study (n=20)	p value
Mean surgery duration (SD, 95 % CI)	56.4 (27.6, 30–135)	56.5 (25.5, 30-110)	0.95
Mean blood loss (SD, 95 % CI)	32.8	36.4	0.11
Trocars (×1, ×2, ×3)			
5 mm	10, 9, 1	14, 6, 0	0.33
10–12 mm	1, 19	0, 20	>0.99
Mean gas insufflation (l), (SD, 95 % CI)	109 (74.2, 36–319)	100 (57.4, 30–289)	0.97
Procedure, total (%)			
Ovarian cystectomy	10 (50)	8 (40)	
Unilateral salpingo-oopherectomy (left/right)	1 (5)	4 (20)	
Bilateral salpingo-oophorectomy (left/right)	9 (45)	8 (40)	
Total	20 (100)	20 (100)	0.461

Timing of administration is of importance. In a meta-analysis on the use of intraperitoneal LA during laparoscopic cholecystectomy, Kahokehr and colleagues have shown that for most studies, the LA was administered at the end of laparoscopy [9]. They advocate that LA should be given just before exsufflation of the gas from the pneumoperitoneum. Other studies argue for the importance of administration from the beginning of the procedure in order to gain a potential preemptive analgesic effect. Coughlin and colleagues performed a meta-analysis of studies comparing preemptive intraperitoneal administration of LA with postoperative instillation [17]. They showed that preemptive administration significantly reduces pain following laparoscopy. Another study showed that postoperative pain and anesthetic consumption were significantly reduced when bupivacaine was instilled prior to CO_2 insufflation as compared to following creation of pneumoperitoneum [18]. The authors concluded this difference can be attributed to the preemptive analgesia effect.

Our current study is a follow-up to two previous studies that were published by our group [6, 19]. All three studies analyzed the effect of continuous nebulization of local anesthetics throughout the laparoscopic procedure, from initiation of CO_2 insufflation. To the best of our knowledge, our studies are the only ones using nebulization instead on instillation of a LA for gynecological laparoscopic procedures. Our first study showed that nebulization of lidocaine significantly decreased postoperative pain but for a limited duration [19]. For the second study, we opted to use a long-acting LA [6]. We chose ropivacaine since it has previously been shown to have a good effect with less toxicity when compared to bupivacaine [20]. The results of our second study showed no significant decrease in postoperative pain or analgesic consumption. The intraoperative anesthetic protocol included fentanyl, a long-acting opiate which can have a prolonged postoperative effect. We concluded that the potential benefit of ropivacaine might be masked by the use of fentanyl. Therefore, we decided to perform our current follow-up study using a different anesthetic protocol which includes remifentanil, a short-acting opiate, instead of fentanyl and to discontinue its administration 5 min prior to termination of surgery. Our decision to nebulize 100 mg of ropivacaine, the same dose that was used during the second study, was based on a study by Labaille and colleagues [21]. They performed a study during which ropivacaine was instilled at the start and end of laparoscopic cholecystectomy. They showed that administering a total dose of 100 mg gives similar results in terms of postoperative analgesic effect, morphine consumption, and side effects when compared to 300 mg of ropivacaine. But patients receiving the larger dose had significantly elevated plasma concentrations of ropivacaine, and for some of the patients, the level exceeded 4 μg/ml, which is the limit for potential toxicity. Based on this study, we decided to maintain a total dosage of 100 mg ropivacaine for the follow-up study.

Nebulization of a LA is intended for equal distribution within the peritoneal cavity in order to overcome pain that is transmitted not only from the surgical site but also from other areas of the peritoneum. It is possible that when nebulizing 100 mg of ropivacaine, the total amount of LA that reaches the surgical site is insufficient. Therefore, when remifentanil is discontinued before the end of the procedure, the patient feels

Table 3 Postoperative analgesia (opiate and nonopiate) and antiemetic consumption

	Study (n=20)	Control (n=20)	p value
Opiate consumption	17 (85 %)	18 (90 %)	0.99
Nonopiate analgesia consumption	14 (70 %)	15 (75 %)	0.72
Antiemetic consumption	11 (55 %)	17 (85 %)	**<0.05**

Bold show less antiemetic consumption within the study group pateints than control group patients

pain from the surgical site. As a result, postoperative morphine consumption is relatively high, further masking potential analgesic effects of ropivacaine at later postoperative time intervals.

Our results showed a no significant decrease in postoperative pain after nebulization of ropivacaine. Furthermore, most patients, in both study and control groups, required morphine and ondansetron after surgery.

Unfortunately, there are no other studies for comparison that used nebulization of a long-acting LA during gynecological laparoscopy. Nevertheless, nebulization of a long-acting LA did decrease postoperative pain following laparoscopic cholecystectomy [22].

Further studies are needed to conclude whether nebulization of LA can decrease postoperative pain. A follow-up study should possibly include a higher dose of long-acting LA while monitoring blood levels. Adrenaline can be used to decrease systemic absorption of ropivacaine by half [7]. An addition of intraperitoneal fentanyl can also be beneficial. Most importantly, nebulization should be done using a nebulizing device that is guaranteed to deliver the total amount of substance without losing some of medication along the tubing.

Conclusion

In summary, our current and previous studies show that intraperitoneal nebulization of 100 mg of ropivacaine or lidocaine during gynecological laparoscopy, under ultrashort- and short-acting opiates, does not significantly reduce postoperative pain.

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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