

PAIN

Intraperitoneal nebulization of ropivacaine for pain control after laparoscopic cholecystectomy: a double-blind, randomized, placebo-controlled trial

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Editor's key points

- Optimization of analgesia with minimal side effects is a goal of perioperative pain management.
- Existing local anaesthetics may be delivered in a novel to maximize analgesic benefit.
- This study investigates the effects of intraperitoneal nebulization of ropivacaine on postoperative recovery.
- Peri-operative intraperitoneal ropivacaine provided better analgesia and reduced opioid consumption compared with placebo.
- Further studies are needed to investigate the optimum timing and safety of this technique.

Background. Intraperitoneal local anaesthetic nebulization is a relatively novel approach to pain management after laparoscopic surgery. This randomized, double-blind, placebo-controlled trial evaluated the effects of intraperitoneal ropivacaine nebulization on pain control after laparoscopic cholecystectomy.

Methods. Patients undergoing laparoscopic cholecystectomy were randomized to receive intraperitoneal nebulization of ropivacaine 1% (3 ml) before surgical dissection and normal saline 3 ml at the end of surgery (preoperative nebulization group); intraperitoneal nebulization of normal saline 3 ml before surgical dissection and ropivacaine 1% (3 ml) at the end of surgery (postoperative nebulization group); or intraperitoneal nebulization of normal saline 3 ml before surgical dissection and at the end of surgery (placebo group). Intraperitoneal nebulization of ropivacaine or saline was performed using the Aeroneb Pro[®] device. Anaesthetic and surgical techniques were standardized. The degree of pain on deep breath or movement, incidence of shoulder pain, morphine consumption, and postoperative nausea and vomiting were collected in the post-anaesthesia care unit and at 6, 24, and 48 h after surgery.

Results. Compared with placebo, ropivacaine nebulization significantly reduced postoperative pain (–33%; Cohen's *d* 0.64), referred shoulder pain (absolute reduction –98%), morphine requirements (–41% to –56% Cohen's *d* 1.16), and time to unassisted walking (up to –44% Cohen's *d* 0.9) ($P < 0.01$). There were no differences in pain scores between ropivacaine nebulization groups.

Conclusions. Ropivacaine nebulization before or after surgery reduced postoperative pain and referred shoulder pain after laparoscopic cholecystectomy. Furthermore, ropivacaine nebulization reduced morphine requirements and allowed earlier mobility.

Keywords: acute pain, regional techniques; anaesthetic techniques, insufflation; anaesthetic techniques, regional; analgesics, postoperative; local anaesthetics, ropivacaine

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Pain after laparoscopic surgery has been associated with surgical manipulations, including intraperitoneal insufflation of carbon dioxide (CO₂), resulting in peritoneal stretching, diaphragmatic irritation, changes in intra-abdominal pH, and retention of the insufflated gas in the abdominal cavity after surgery.¹ These effects may result in the irritation of

peritoneal nerves causing visceral and shoulder pain, as commonly reported after laparoscopic procedures. Intraperitoneal local anaesthetic instillation can provide pain relief after laparoscopic surgery, but local anaesthetic distribution may not always be uniform throughout the peritoneal surface.^{2–5}

Intraperitoneal local anaesthetic nebulization is a relatively novel method for pain control after laparoscopic surgery.^{4,6} This approach should provide uniform dispersion of local anaesthetic particles throughout the peritoneal cavity.⁷⁻⁹ However, the analgesic effectiveness of intraperitoneal local anaesthetic nebulization may depend upon the nebulization device and the delivery mode. Alkhamesi and colleagues⁶ reported that nebulization of bupivacaine using a custom-made device significantly reduced pain after laparoscopic cholecystectomy. Compared with intraperitoneal ropivacaine instillation, nebulization of ropivacaine using a high-frequency vibrating membrane nebulizer (Aeroneb Pro[®], Aerogen, Galway, Ireland) reduced shoulder pain and the time to unassisted walking after laparoscopic cholecystectomy.⁴ In contrast, Zimmer and colleagues¹⁰ did not find significant differences in pain or analgesic consumption after bupivacaine nebulization using the Insuflow[®] device.

We designed this randomized, double-blind, placebo-controlled, single-centre trial to evaluate the efficacy of intraperitoneal ropivacaine nebulization with the Aeroneb Pro[®] system on pain control after laparoscopic cholecystectomy. In addition, we also assessed the effect of the timing (preoperative vs postoperative) of ropivacaine nebulization.

Methods

This study was approved by the San Gerardo Hospital ethics committee (Ref 271 of 24/04/2008 Gen Dir. Dr GA Spata) and registered with the Clinical Trial (NCT 01247857). After obtaining written consent, we enrolled 90 adult patients, ASA physical status I–III undergoing elective laparoscopic cholecystectomy. Patients were excluded if they had a clinical diagnosis of acute pancreatitis, acute preoperative pain other than biliary colic, chronic pain treatment or anti-epileptic therapy, history of alcohol or drug addiction, severe hepatic or renal impairment, allergy to the study drugs, cognitive impairment or communication problems, or were pregnant or lactating.

On the day of surgery, a research assistant not involved with patient care confirmed patient eligibility and written consent. An anaesthesia nurse not involved in the study received from the research assistant a sealed opaque envelope containing patient allocation and instructions for the solution preparation. The anaesthesia nurse filled two 5 ml transparent syringes with 3 ml of ropivacaine 1% (30 mg) and 3 ml of normal saline. The research assistant was not allowed to enter the operating theatre until the study solutions were being prepared to maintain blinding. In case of an emergency possibly related to the study drugs, the nurse was authorized to disclose the contents of the syringe to the anaesthesiologist of the case (not involved with the study) and to the research assistant.

Patients were randomized using a computer-generated randomization list to receive peritoneal nebulization of ropivacaine before surgery (preoperative nebulization group), peritoneal nebulization of ropivacaine after surgery (postoperative nebulization group), or peritoneal nebulization of

saline (control group). Patients in the preoperative nebulization group received intraperitoneal nebulization of ropivacaine 1% (3 ml) (30 mg) before the start of the gall bladder dissection and intraperitoneal nebulization of normal saline 3 ml at the end of surgery just before the deflation of pneumoperitoneum. Patients in the postoperative nebulization group received intraperitoneal nebulization of normal saline 3 ml before the start of the gall bladder dissection and intraperitoneal nebulization of ropivacaine 1% (3 ml) (30 mg) at the end of surgery just before the deflation of pneumoperitoneum. Patients in the placebo group received intraperitoneal nebulization of normal saline 3 ml before the start of the gall bladder dissection and at the end of surgery just before the deflation of pneumoperitoneum.

Intraperitoneal nebulization of ropivacaine or saline was performed using the Aeroneb Pro[®] device. The nebulization unit was placed in series between the insufflator and the insufflation tubing. Ropivacaine or saline was carried to the abdominal cavity by the insufflation gas through a 200 cm tubing connected to the umbilical port by the lower trocar's outlet (Fig. 1). The initial ropivacaine or normal saline nebulization was initiated simultaneously with gas insufflation through the umbilical port, while the other ports were being inserted. Nebulization after surgery was performed just before the withdrawal of the ports. Nebulization was terminated once the nebulizer chamber was empty (usually within 5–6 min).

Laparoscopic cholecystectomy was performed according to the standard surgical and anaesthesia protocols. A classical four-port surgical technique that consisted of placement of a 12 mm port via the umbilical incision, a 10 mm port in the epigastric area, and two 5 mm ports on the right side of the abdomen was used for all patients. Pneumoperitoneum was achieved using non-humidified and non-heated CO₂ with the intra-abdominal pressure maintained around 14 mm Hg.

Patients were premedicated with diazepam 5–7 mg, 30 min before surgery. General anaesthesia was induced with



Fig 1 Aeroneb Pro[®] device.

propofol 2–3 mg kg⁻¹ i.v. and tracheal intubation was facilitated with cisatracurium 0.15 mg kg⁻¹ i.v. Anaesthesia was maintained with sevoflurane 1.5–2.5% end-tidal concentration titrated to maintain state entropy values between 45 and 60 (Entropy sensor™, M-ENTROPY™ module, GE Healthcare, Helsinki, Finland), fentanyl boluses 1–2 µg kg⁻¹ titrated to maintain non-invasive mean arterial pressure and heart rate $\pm 20\%$ of basal values, and cisatracurium 0.03 mg kg⁻¹ titrated to maintain a train-of-four (TOF) count of 1–2, and also according to clinical needs. Ventilation was controlled to maintain end-tidal CO₂ between 4.5 and 5.5 kPa. After tracheal intubation, an orogastric tube and an oesophageal temperature probe were placed. The operating theatre temperature was set at 20°C and patients were kept warm using the forced warm-air device and warmed i.v. solutions. At the end of surgery, residual muscle paralysis was reversed with neostigmine 0.05 mg kg⁻¹ and atropine 0.02 mg kg⁻¹, and tracheal extubation was performed once clinical signs were observed and a TOF ratio of 0.9 was achieved.

All patients received dexamethasone 4 mg i.v. after the induction of anaesthesia and ondansetron 4 mg i.v. at the end of surgery for postoperative nausea and vomiting (PONV) prophylaxis. Paracetamol 15 mg kg⁻¹ i.v. was infused during surgery and then every 6 h for 48 h, postoperatively. In addition, each portal site was infiltrated with ropivacaine 0.3% 3 ml after the completion of the surgery. Patients complaining of pain in the post-anaesthesia care unit (PACU) received morphine 3 mg i.v. boluses until the visual analogue scale (VAS) score was <30 mm (where 0 mm represented 'no pain' and 100 mm represented 'worst possible pain'). This was followed by the initiation of i.v. patient-controlled analgesia (i.v.-PCA), morphine 1 mg bolus with a lockout time of 5 min. Patients were encouraged to ambulate as soon as possible. Patients were hospitalized for up to 48 h as part of our routine practice.

Data collected included patient age, gender, weight and BMI, intraoperative opioid use, duration of surgery, residual volume in the nebulization unit (post-nebulization volume), indirect signs of local anaesthetic toxicity (intraoperative arrhythmias, burst suppression on entropy monitor, and delayed awakening), patient temperature in the PACU, and duration of PACU stay. The intensity of pain on deep breathing, coughing, or movement (dynamic pain) was assessed using a 100 mm VAS. Data on pain intensity, the proportion of patients with significant pain (dynamic VAS ≥ 30 mm), proportion of patients with significant shoulder pain (VAS ≥ 30 mm), morphine consumption, and the proportion of patients with PONV were collected in the PACU and at 6, 24, and 48 h after surgery. The research assistants involved in data collection, and nurses and doctors taking care of the patients were unaware of the study group assignment.

Statistical analysis

The primary endpoint of the study was the pain intensity after surgery and sample size calculations were based on two

assumptions. First, in a previous study involving intraperitoneal local anaesthetic nebulization⁶ and in a pilot study in our institution, the response within each subject group was normally distributed with a pain numeric scale (0–10) with a standard deviation (SD) of 2 points. Assuming a true difference between nebulization and control pain score means of 1.5 points, 29 experimental subjects and 29 control subjects would be needed to reject the null hypothesis that the pain score means of the experimental and control groups are equal with a probability (power) of 0.8. The type I error probability associated with this test of the null hypothesis was 0.05.

Secondly, data from a pilot study in our institution indicate that 80% of patients undergoing elective laparoscopic cholecystectomy complained of significant pain (dynamic VAS ≥ 30 mm) during the first 24 h after an elective laparoscopic cholecystectomy. If the true incidence of significant pain during the first 24 h after surgery for subjects receiving nebulization is 40% (net reduction 50%), we need to study 29 subjects per group to be able to reject the null hypothesis that the proportion of patients complaining from significant pain after surgery receiving nebulization or placebo are equal with the probability (power) of 0.9. The type I error probability associated with this test of the null hypothesis is 0.05. We used an uncorrected χ^2 statistic to evaluate this null hypothesis. We enrolled 30 patients in each group to allow for possible protocol violations.

Because this study evaluated the effect of intraperitoneal ropivacaine nebulization on pain intensity after laparoscopic cholecystectomy, conversion to an open technique was considered as protocol violation and these patients were excluded from further analysis. However, the excluded patients received the same anaesthesia and analgesia protocol and evaluations until their hospital discharge for the safety analysis.

Continuous data (age, weight, BMI, temperature, opioids use during surgery, post-nebulization volume, duration of surgery, PACU stay, static and dynamic pain scores, and morphine requirements) are presented as range, mean (SD), and 95% confidence interval and analysed with analysis of variance (ANOVA) or the Mann–Whitney *U*-test as appropriate. Data regarding patient gender, ASA physical status, number of patients with significant postoperative pain, patients with significant shoulder pain, patients receiving postoperative morphine, and patients with PONV are presented as frequency, percentage, and absolute risk reduction and analysed with the χ^2 test or Fisher's exact test as appropriate.

An effect size is the difference between two means divided by the SD of the two conditions. The division by the SD enables the comparison of effect sizes across experiments and is used to interpret changes in the health status. To evaluate the relative impact of ropivacaine nebulization on pain control, morphine consumption, and walking time, we estimated the effect size of each intervention through Cohen's *d* test.¹¹

Statistical comparisons were accomplished with Microsoft Excel 97 (Microsoft Inc., Redmond, WA, USA), EPI INFO, version 2004 [EpiInfo 3.2.2, Center for Disease Control and Prevention (CDC), Atlanta, GA, USA], and SPSS software

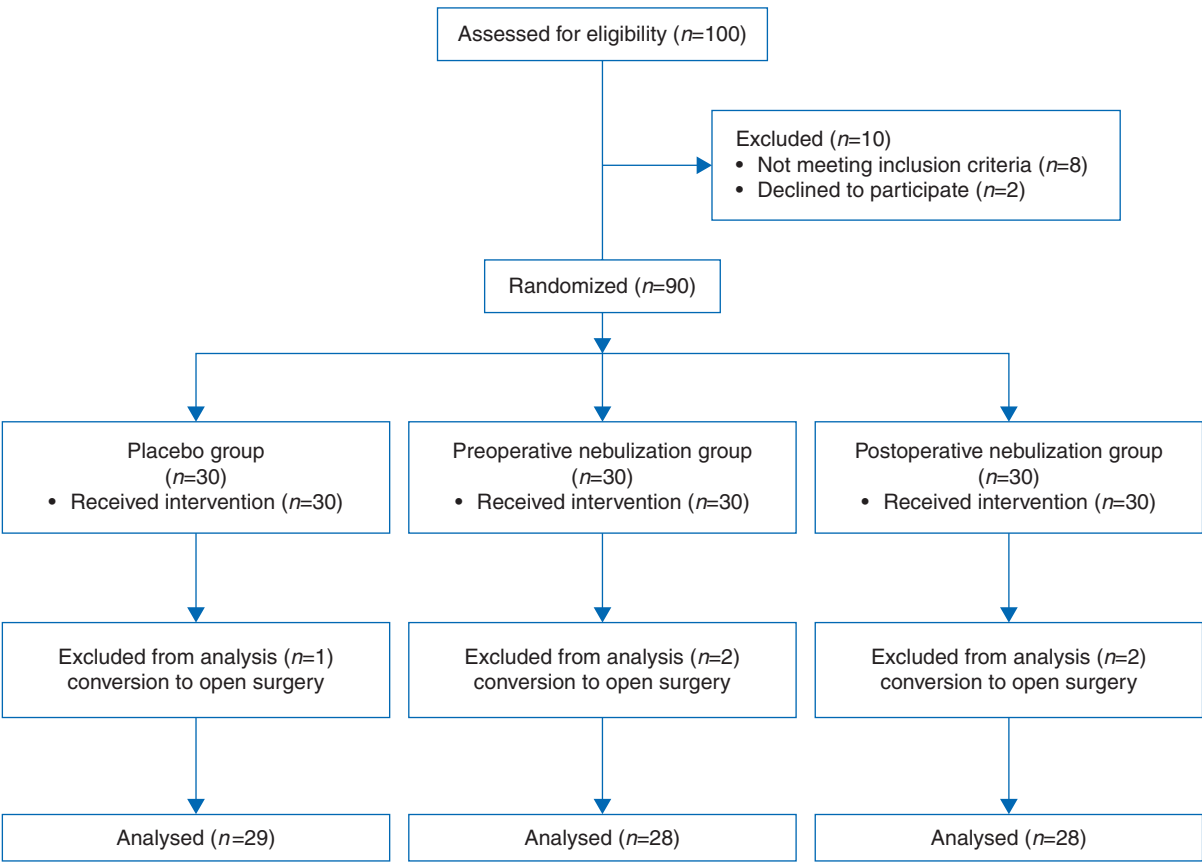


Fig 2 Flow diagram showing participants in this trial study.

Table 1 Patient's clinical characteristics in the three groups. Data are median (range), mean (SD), or the number of patients. There are no differences between the groups

	Placebo (n=29)	Preoperative nebulization (n=28)	Postoperative nebulization (n=28)
Age (yr)	61 (25–70)	48 (29–70)	54 (30–70)
Weight (kg)	70 (15)	70 (16)	71 (11)
Sex (female/male)	16/13	17/11	17/11
BMI (kg m ⁻²)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)
Duration of surgery (min)	55 (38)	50 (24)	46 (32)
Intraoperative fentanyl (μg)	128 (59)	106 (41)	123 (40)
Post-nebulization volume (ml)	0.02 (0.2)	0.06 (0.1)	0.02 (0.06)
Temperature after surgery (°C)	36.2 (0.3)	36.2 (0.5)	36.2 (0.3)
Post-anaesthesia care unit stay (min)	35 (30)	30 (15)	29 (13)

(version 13, Chicago, IL, USA). A *P*-value <0.05 was considered to be statistically significant.

Results

Ninety patients were enrolled, and 85 were included in the data analysis. Two patients in the preoperative nebulization group, two patients in the postoperative nebulization group,

and one patient in the placebo group were excluded because of a conversion to open surgery (Fig. 2). There were no significant differences among the groups with respect to age, weight, gender, BMI, duration of surgery, intraoperative opioid use, post-nebulization volume, temperature after surgery, and time to PACU discharge (Table 1).

At every evaluation after discharge from the PACU, patients in the placebo group reported higher pain scores

Table 2 Dynamic pain (pain on deep breathing or coughing) (VAS-D) after laparoscopic cholecystectomy. Data are mean (SD) and 95% CI of VAS-D in mm on a 100 mm scale. * $P < 0.01$ when compared with the ropivacaine nebulization groups for ANOVA. PACU, post-anaesthesia care unit

	Placebo (n=29)	Preoperative nebulization (n=28)	Postoperative nebulization (n=28)
VAS-D PACU	52 (26), 95% CI 42–61	40 (29), 95% CI 29–51	47 (22), 95% CI 39–55
VAS-D 6 h	38 (14)*, 95% CI 33–43	24 (15), 95% CI 18–30	29 (13), 95% CI 24–34
VAS-D 24 h	29 (17)*, 95% CI 23–35	16 (15), 95% CI 10–22	20 (12), 95% CI 16–24
VAS-D 48 h	18 (15)*, 95% CI 12–23	8 (13), 95% CI 3–13	13 (15), 95% CI 7–19

Table 3 Cumulative morphine consumption (mg) after surgery. Data are mean (SD) and 95% CI for cumulative morphine consumption (mg) after surgery. * $P < 0.01$ for ANOVA when compared with the ropivacaine nebulization groups. # $P < 0.01$ for the Fisher exact test between preoperative and postoperative nebulization of ropivacaine. PACU, post-anaesthesia care unit

	Placebo (n=29)	Preoperative nebulization (n=28)	Postoperative nebulization (n=28)
PACU	8 (4)*, 95% CI 7–9	4 (4), 95% CI 3–5	4 (3), 95% CI 3–5
6 h	13 (6)*, 95% CI 11–15	7 (6), 95% CI 5–9	8 (5), 95% CI 6–10
24 h	21 (9)*, 95% CI 17–24	10 (9), 95% CI 7–13	13 (7), 95% CI 11–16
48 h	27 (11)*, 95% CI 23–31	12 (15)#, 95% CI 6–18	16 (8), 95% CI 13–19

compared with those in the preoperative and postoperative ropivacaine nebulization groups (Table 2). Nebulization of ropivacaine before or after surgery produced the same effect sizes on postoperative pain at 24 h (Cohen's d 0.64, large decrease –33% of dynamic VAS). Fewer patients receiving ropivacaine nebulization (preoperative and postoperative) presented a dynamic VAS score ≥ 30 mm at 6 h (absolute reduction –29%, 95% CI –50 to –7; $P=0.01$) and at 24 h (absolute reduction –27%, 95% CI –46 to –9; $P<0.01$) after surgery when compared with those receiving saline nebulization.

All patients receiving placebo complained of significant shoulder pain after surgery compared with one (4%) patient in the postoperative nebulization group and no patients in the preoperative nebulization group (absolute reduction –98%, 95% CI –101 to –94).

Patients receiving ropivacaine nebulization consumed significantly less morphine than those in the placebo group (Table 3). Over the 48 h postoperative period, ropivacaine nebulization produced a larger reduction in morphine consumption (preoperative nebulization 56% reduction, Cohen's d 1.16; postoperative nebulization 41% reduction, Cohen's d 1.16). On the first postoperative day, 26 patients receiving placebo used morphine compared with 20 patients in the postoperative nebulization group (absolute reduction –29%, 95% CI –59 to 1; $P=0.07$) and 16 patients in the preoperative nebulization group (absolute reduction –42%, 95% CI –67 to –17; $P<0.01$). On the second postoperative day, 22 patients in the placebo group and 19 patients in the postoperative nebulization group required morphine (absolute reduction –10%, 95% CI –39 to –19; $P=0.35$) compared with eight patients receiving preoperative nebulization (absolute reduction –47%, 95% CI –70 to –25; $P<0.01$).

Ropivacaine nebulization was associated with earlier mobility. Patients receiving placebo walked without assistance 18 (SD 9) h after surgery, those in the postoperative nebulization group at 12 (SD 10) h (Cohen's d 0.64 'medium effect', –33%), and those in the preoperative group at 10 (9) h after awakening (Cohen's d 0.9 'large effect', –44%) ($P<0.01$). Seven patients (24%) in the control group were able to stand and walk without assistance within 12 h after surgery compared with 17 patients (61%) receiving postoperative nebulization (absolute difference 37%, 95% CI 13–60; $P<0.01$) and 18 patients (64%) receiving preoperative nebulization (absolute difference 40%, 95% CI 16–63, $P<0.01$).

There were no significant differences between the groups in the length of hospital stay. Patients of all groups were discharged 1.9 (SD 0.5) days after surgery ($P=0.66$).

There were no significant differences in the proportion of patients with PONV. One patient (3.6%) in each of the ropivacaine nebulization groups vomited after surgery compared with no patients in the control group ($P=0.59$). No patients exhibited signs of local anaesthetic toxicity (intraoperative arrhythmias, burst suppression on entropy monitor, delayed awakening) or other adverse effects associated with local anaesthetic administration during or after surgery.

Discussion

The main finding of this study is that, compared with placebo, ropivacaine nebulization (either preoperative or postoperative) using the Aeroneb Pro® device significantly reduced postoperative pain, referred shoulder pain, morphine requirements, and time to unassisted walking after laparoscopic cholecystectomy.

However, there were no differences in pain scores between the preoperative and postoperative ropivacaine nebulization groups. Patients receiving preoperative nebulization of ropivacaine consumed significantly less morphine than those in the postoperative ropivacaine nebulization group.

The primary aim of this study was to evaluate the analgesic efficacy of ropivacaine nebulization in patients undergoing laparoscopic cholecystectomy. Additionally, we assessed if this approach is superior when performed before or after surgery. However, this study did not evaluate the pre-emptive or preventative effects of ropivacaine nebulization. This would have required the assessment of analgesic efficacy beyond the duration of action of the topical ropivacaine.¹²

Bucciero and colleagues⁴ suggested that ropivacaine nebulization reduced shoulder pain and unassisted walking time when compared with ropivacaine instillation and humidified gas. The present results confirmed the effects of a lower dose of nebulized ropivacaine on pain control when compared with humidified gas alone, without the use of local anaesthetic instillation.

The nebulization system used in this study consists of a commercially available high-frequency vibrating mesh nebulizer, which is reusable and easy to assemble, can be placed in series with the insufflation tubing, and does not need a separate tubing, injection system, or driving gas. It allows simultaneous and efficient delivery of the local anaesthetic while the surgical procedure is being performed.⁸ Because the particle size generated by the Aeroneb[®] device is small (mass median diameter <5 µm), it can be presumed that the local anaesthetic would spread uniformly throughout the peritoneal surface.^{13 14} Although the exact mechanism of action is not fully understood, it is probably through the effects of the local anaesthetic on peritoneal nerve endings, which may involve local and systemic modulation of the inflammatory process.^{15 16}

Studies evaluating intraperitoneal local anaesthetic nebulization for pain relief after laparoscopic cholecystectomy have used different types of nebulization devices. Alkhamesi and colleagues⁶ studied the effects of nebulization of bupivacaine 50 mg after surgery. They used a custom-made cumbersome device with a separate source of gas to transport the nebulized solution in the abdominal cavity. Zimmer and colleagues used the Insuflow device, which is a hot evaporation-based nebulizer. It is not surprising that these authors did not observe any analgesic benefits from nebulizing bupivacaine 0.5% (10 ml), because hot evaporation enables only evaporation of the solvent (e.g. water) and not of the solute (e.g. local anaesthetic), thus making the device inefficient in delivering the local anaesthetic into the peritoneal cavity.⁸ This suggests that studies evaluating the effects of peritoneal nebulization should use a device suitable to deliver the local anaesthetic such as the one used in this study.

Although we did not observe symptoms related to local anaesthetic toxicity, the study was not powered to evaluate the safety of the method. Nevertheless, a recent animal study¹⁷ describing the pharmacokinetics of nebulized

ropivacaine 3 mg kg⁻¹ found that the maximal ropivacaine plasma concentrations were within safe values. In addition, the total amount of ropivacaine used in this study (30 mg for nebulization plus 36 mg for the infiltration of the four surgical ports) is far below the maximum dose for infiltration anaesthesia in an adult patient (3 mg kg⁻¹ or 200 mg of plain solution).¹⁸ We, therefore, did not measure the plasma concentrations of ropivacaine.

One of the limitations of the nebulization technique is that the small size of droplets creates a 'foggy' environment, which may interfere with the surgeon's vision. Thus, continuous local anaesthetic nebulization throughout the surgical duration is not clinically feasible. Therefore, we performed the initial nebulization through the central port during the insertion of the other ones, and the second nebulization just before exsufflation of the pneumoperitoneum.

We choose 30 mg of ropivacaine based upon previous reports and upon the time taken by surgeons for port placement (Aeroneb Pro can deliver 3 ml of solution in 5–6 min). Although superior analgesia may be obtained by larger doses of local anaesthetics, this would require a longer nebulization time, which may delay the start of surgery. Future studies should include a dose-finding analysis, the evaluation of the pharmacokinetics profile of different doses of ropivacaine, and the impact on the surgeon's vision of different nebulization times.

Another criticism of this study could be that we studied patients undergoing laparoscopic cholecystectomy on an inpatient basis. Unfortunately, the day surgery regime is not a standard practice for patients undergoing laparoscopic cholecystectomy in our institution. However, hospitalization allowed the use of i.v.-PCA morphine for rescue analgesia and to obtain a more precise assessment of opioid consumption.

In conclusion, compared with placebo, ropivacaine nebulization before or after surgery reduced postoperative pain and referred shoulder pain after laparoscopic cholecystectomy. Furthermore, ropivacaine nebulization reduced morphine requirements and allowed earlier mobility.

Declaration of interest

None declared.

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