British Journal of Anaesthesia **110** (5): 800–6 (2013)
Advance Access publication 4 January 2013 · doi:10.1093/bja/aes495

BJA

PAIN

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

P. M. Ingelmo[1]*, M. Bucciero[1], M. Somaini[1], E. Sahillioğlu[2], A. Garbagnati[1], A. Charton[3], V. Rossini[1], V. Sacchi[1], M. Scardilli[4], A. Lometti[4], G. P. Joshi[5], R. Fumagalli[1] and P. Diemunsch[3]

[1] First Service of Anaesthesia and Intensive Care, San Gerardo Hospital, Monza, Milan Bicocca University, Italy
[2] Department of Anaesthesia and Intensive Care, Anadolu Medical Center, Kocaeli, Turkey
[3] Service d'Anesthésiologie–Réanimation Chirurgicale, CHU de Hautepierre, and EA 3072, Faculté de Médecine, Strasbourg, France
[4] Second Service of Surgery, San Gerardo Hospital, Monza, Italy
[5] Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

* Corresponding author: U.O. Anestesia e Rianimazione I, Ospedale San Gerardo di Monza, Via Pergolesi 33, 20900 Monza. Italy.
E-mail: pabloingelmo@libero.it

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

Accepted for publication: 21 October 2012

Pain after laparoscopic surgery has been associated with surgical manipulations, including intraperitoneal insufflation of carbon dioxide (CO_2), 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 colleagues[6] 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 colleagues[10] 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 antiepileptic 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 CO_2 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

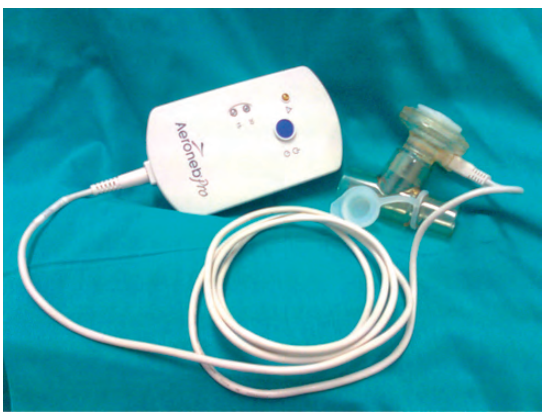

Fig 1 Aeroneb Pro® device.