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Effects of low pressure pneumoperitoneum and pulmonary recruitment on postoperative pain after laparoscopic cholecystectomy : a prospective, randomized, blinded trial

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Abstract : *Background :* Previous studies have shown that either a low pressure pneumoperitoneum or a pulmonary recruitment maneuver can reduce pain after laparoscopic cholecystectomy. Whether combining those two actions during anesthesia could result in less postoperative pain is yet unknown. We hypothesized that the combination of both could lead to an additional reduction in postoperative pain compared to a low pressure pneumoperitoneum alone. Primary outcome was pain relief during the first 24 hours. Secondary outcomes included total analgesic use, nausea and vomiting, recovery score and length of hospital stay.

Methods : A prospective, randomized controlled, blinded trial was done in 80 electively scheduled patients. Laparoscopic cholecystectomy was performed with low pressure pneumoperitoneum (8-10 mmHg) in all patients. In group 2 a pulmonary recruitment maneuver was done at the end of surgery (insufflation ports open, 30° Trendelenburg position, manual ventilation 2 x 5 seconds at a maximum pressure of 40 cmH_2O); group 1 had no recruitment maneuver. General anesthesia and intra-operative analgesia were standardized. Postoperative pain was measured using the visual analogue scale (VAS) at fixed time points during the first 24 hours. Analgesia at the post anesthetic care unit (PACU) and at ward was also standardized.

Results : Demographics were similar in both groups. After dropout we had 39 and 38 patients in respectively group 1 and 2. There were no significant differences amongst groups in VAS scores during the first 24 hours postoperatively. Secondary outcomes were not significant either.

Conclusion : This study demonstrates that a pulmonary recruitment maneuver does not provide additional analgesia or other advantages in patients already receiving low pressure pneumoperitoneum for laparoscopic cholecystectomy.

Keywords : Low pressure pneumoperitoneum ; Pulmonary recruitment ; Postoperative pain ; Laparoscopic cholecystectomy.

Although laparoscopic cholecystectomy has proven for years to cause less pain and less pulmonary dysfunction compared with small-incision cholecystectomy, it is not a painless procedure. Shoulder pain (referred pain) and upper abdominal pain (visceral and/or abdominal wall pain) are well established causes of postoperative morbidity and are multifactorial. Reducing this pain could still lead to shorter hospitalizations and earlier return to normal activity. Factors that may influence this laparoscopic induced pain include the intra-abdominal pressure, surgical time, volume of insufflated gas, and the volume of the residual gas after the procedure (1,2).

One of the proposed mechanisms of post-laparoscopic pain is peritoneal and diaphragmatic stretching with neuropraxia of the phrenic nerves during gas insufflation. Most likely this is the explanation for the frequently described shoulder tip pain. This stretching could be diminished by a lower intra-abdominal pressure during pneumoperitoneum. The incidence of shoulder tip pain after laparoscopic cholecystectomy is usually reported to be 30-40% (2). Previous studies in laparoscopic

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cholecystectomy surgery have shown that a low pressure pneumoperitoneum (7-10 mmHg) resulted in less postoperative pain (including shoulder tip pain) in comparison to a standard pressure pneumoperitoneum (12-15 mmHg) (3-5). A review and meta-analysis of randomized controlled trials comparing low pressure with standard pressure pneumoperitoneum also demonstrated clear benefits of low pressure pneumoperitoneum in laparoscopic cholecystectomy, including significantly reduced frequency and intensity of postoperative (shoulder tip) pain (6). Although this lower pressure could jeopardize the surgeon's comfort due to an eventual impaired visualization, the technique is proven feasible and safe. It should therefore be considered as part of a multimodal approach to postoperative analgesia (4,6).

Residual intra-abdominal gas on the other hand causes postoperative pain by longer exposure to carbon dioxide dissolution, intra-abdominal acidosis and consequent peritoneal irritation. This could be prevented by maximal evacuation of the gas at the end of laparoscopic surgery. One way to do this is a simple pulmonary recruitment maneuver. Previous clinical trials have shown that the administration of pulmonary recruitment maneuvers to a maximum pressure of 40-60cmH_2O was effective in reducing postoperative pain after laparoscopic surgery by mechanically increasing intraperitoneal pressure to facilitate the elimination of residual carbon dioxide (CO_2) (7-11). However, even with the necessary precautions, a recruitment maneuver may have important side effects such as pulmonary barotrauma or hemodynamic instability. Therefore, it is not feasible in all patients.

Whether combining the low pressure pneumoperitoneum during laparoscopic cholecystectomy and a pulmonary recruitment maneuver at the end of surgery could result in less postoperative pain is yet unknown. We hypothesized that the combination of both interventions could lead to an additional reduction in postoperative pain in patients after laparoscopic cholecystectomy in comparison with patients with whom only a low pressure pneumoperitoneum was used.

Methods

The regional medical ethics committee of the AZ Groeninge Hospital of Kortrijk, Belgium approved this prospective, randomized controlled, blinded, monocentric trial on 31 March 2015 (chairman Doubel P., MD, internal reference: AZGS 2014160). Written informed consent was obtained from all participants. Randomization to one of the two parallel groups was done beforehand by an investigator using the following website: www.randomization.com. Group allocation was indicated on a sheet of paper that was kept in a numbered opaque envelope and only available to the anesthetic investigator. All patients were blinded to group allocation. The two performing surgeons were not blinded because the recruitment maneuver had to be done before the end of surgery. However, all nurses at the PACU and at ward who obtained the VAS scores and other clinical findings and who administered analgesic medication were blinded.

We included 80 electively scheduled ASA categories 1 and 2 patients undergoing laparoscopic cholecystectomy for gall stone disease. Exclusion criteria were: refusal to give consent, (suspected) cholecystitis, age under 18 years, Body Mass Index above 35, ASA classification above 2, intolerance or allergy to analgesics used in the protocol, and pregnancy. All patients were operated by the same two abdominal surgeons using standard techniques. Open cut-down was performed at the umbilicus, and carbon dioxide insufflation was started and maintained at a rate of 3 L/min. After placement of the first operative port, the intra-abdominal pressure was immediately lowered from 14 mmHg to 8 mmHg. Laparoscopic cholecystectomy was performed with a low pressure pneumoperitoneum (8-10 mmHg) in all patients. In group 2 (intervention group) a pulmonary recruitment maneuver was performed at the end of the surgical procedure. To do so, the patient was placed in 30° Trendelenburg position, the operative ports (trocars) were fully open to allow CO_2 escape, and two manual pulmonary inflations to a maximum pressure of 40 cmH_2O were given by the investigating anesthesiologist; each positive-pressure inflation was held for 5 seconds. Group 1 (control group) had no recruitment maneuver.

Induction and maintenance of general anesthesia were standardized. Each patient received propofol 2 mg/kg, sufentanil 0.15 µg/kg. Muscle relaxation was obtained with atracurium 0.5 mg/kg at the induction of anesthesia. After endotracheal intubation all patients were ventilated with an oxygen/air mixture and anesthesia was maintained with inhaled sevoflurane (1 to 1.5 MAC). Intraoperative analgesics were also standardized: by the end of surgery all patients had received 1 gram of paracetamol and 75 milligrams of diclofenac intravenously. If considered necessary one milliliter of glycopyrrolate 0.5 mg/ml-neostigmine 2.5 mg/ml was administered to reverse residual neuromuscular blockade at the end of surgery.

Postoperative pain was measured using the visual analogue scale (VAS) score at fixed time points during 24 hours: on arrival at the post anesthetic care unit (PACU), and at 1, 6, 12, 18 and 24 hours postoperatively. Analgesia at the PACU and at the ward was standardized; 1 gram of paracetamol IV maximum every 6 hours, 75 milligrams of diclofenac IV maximum every 12 hours, and only in case of inadequate analgesia (VAS score above 4) 100 milligrams of tramadol IV maximum every 6 hours was associated. In case of severe postoperative pain and only at the PACU patients received rescue intravenous morphine sulphate titrated per 1 milligram and with a maximum of 5 milligrams per hour. Postoperative nausea and vomiting were assessed and treated in a standard way with 50 milligrams of alizapride IV maximum every 6 hours and/or 4 milligrams of ondansetron IV maximum every 8 hours.

The primary endpoint of our study was pain relief during the first 24 hours postoperatively. Secondary endpoints included total analgesic use during the first 24 hours, incidence of nausea and vomiting during the first 24 hours, quality of recovery after 48 hours based on a validated questionnaire, and the length of hospital stay.

The quality of recovery (QoR) after anesthesia is an important measure of the early postoperative health status of patients. Based on extensive clinical and research experience with the 40-item QoR-40 questionnaire, important items were selected by Stark *et al.* to create a shorter version, the postoperative 15-item patient-rated QoR-15 (13,14). It incorporates five dimensions of health : patient support, comfort, emotions, physical independence and pain, with a score ranging from 0 (poorest) to 150 (best possible). This QoR-15 form was evaluated and had an excellent validity, reliability, clinical acceptability and feasibility (13). Figure 1 shows the QoR-15 questionnaire we used in our trial; we phoned all patients 48 hours postoperatively and went through the list together to obtain their recovery score.

Sample size calculation and statistical analyses were executed using SAS 9.4, SAS Institute Inc., Cary, NC, USA. The primary endpoint of the study was pain relief during the first 24 hours, as quantified by the visual analogue scale (VAS 0 : no pain, VAS 10: worst conceivable pain, round numbers). Group sample sizes of 37 and 37 were calculated to achieve 80% power to detect a difference in VAS score of 1.0 point between both groups with estimated group standard deviations of 1.5 and at a significance level (alpha) of 0.05 using a two-sided two-sample *t*-test.

QoR-15 Patient Survey
Date: _ _ / _ _ / _ _ Study #: _____

PART A
How have you been feeling in the last 48 hours?
(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily
2. Been able to enjoy food
3. Feeling rested
4. Have had a good sleep
5. Able to look after personal toilet and hygiene unaided
6. Able to communicate with family or friends
7. Getting support from hospital doctors and nurses
8. Able to return to work or usual home activities
9. Feeling comfortable and in control
10. Having a feeling of general well-being

PART B
Have you had any of the following in the last 48 hours?
(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain
12. Severe pain
13. Nausea or vomiting
14. Feeling worried or anxious
15. Feeling sad or depressed

Fig. 1. — Postoperative quality of recovery (QoR-15) score.

Data are presented as frequencies for categorical variables and as mean ± standard deviation or median with interquartile range for continuous variables, as appropriate. Baseline patient demographics and outcomes were compared between the two groups using the Fisher's exact test (for 2 x 2 tables) for categorical variables, and the unpaired *t*-test or Wilcoxon rank sum test for continuous variables. A more complex linear mixed model (repeated measures ANOVA) was performed to evaluate the effect of time and group on the VAS scores and the possible interaction between time and group, adjusted for age, sex, tramadol consumption and morphine consumption.

Results

Between May 2015 and June 2016, 80 suitable consecutive patients were randomized and allocated to one of our study groups. Figure 2 shows a CONSORT flow diagram of patient recruitment. Baseline demographics including age, sex ratio, weight and height were similar amongst both groups (Table 1). In one patient belonging to group 1 a standard pressure pneumoperitoneum was required to optimize surgical visualization, and moreover this patient had an unexpected cholecystitis on laparoscopic image. Two patients in group 2 also needed a standard pressure pneumoperitoneum for technical reasons ; one also had an unexpected cholecystitis and in the other patient there was an iatrogenic liver bleeding that required better visualization for repair. These three patients were excluded for statistical analyses.

Table 2 shows the results regarding the primary study endpoint; there were no differences in median

Table 1

Demographics of both groups

	Group 1 (n=40)	Group 2 (n=40)	p-value
Age (years) *	51.3 ± 14.4	49.9 ± 15.6	0.677
Sex ratio M:F **	6:34	11:29	0.274
Weight (kg) *	72.4 ± 12.4	77.5 ± 13.5	0.085
Height (cm) *	167.6 ± 7.9	170.2 ± 8.2	0.152
BMI (kg/m²) *	25.7 ± 3.3	26.7 ± 3.9	0.244

Data are presented as mean ± standard deviation*, or frequency **

Table 2

VAS scores at different time points in both groups

	Group 1	n	Group 2	n	p-value
VAS on arrival @ PACU	0 (2)	39	0 (3)	38	0.623
VAS 1h postoperative	4 (3)	39	4 (3)	38	0.419
VAS 6h postoperative	2 (3)	39	2 (3)	38	0.451
VAS 12h postoperative	1 (2)	37	1 (2)	36	0.764
VAS 18h postoperative	2 (2)	37	2 (3)	35	0.734
VAS 24h postoperative	1 (3)	27	1 (3)	27	0.340

Data are presented as median (interquartile range)

Table 3

Secondary outcomes in both groups

	Group 1 (n=39)	Group 2 (n=38)	p-value
Total tramadol consumption (number of 100mg gifts) *	1 (1)	1 (1)	0.833
Total morphine consumption (number of 1mg gifts) *	0 (0)	0 (1)	0.213
Recovery score (0-150) **	125 ± 15	128 ± 11	0.368
PONV @PACU ***	13	9	0.451
PONV @ward ***	3	5	0.481
Length of hospital stay (hours) *	25.5 (7.5)	26.2 (5.4)	0.608

Data are presented as median (interquartile range)*, mean ± standard deviation**, or frequency***

VAS scores between the two groups at different times during the first 24 hours postoperatively. There were no statistically significant differences between the VAS scores at different time points. The time-dependency seen in this table shows a sudden jump from median value '0' on arrival at the PACU to '4' at 1 hour postoperatively in both groups; this could be due to the fact that most patients were still drowsy with residual anesthetic effects on arrival at the PACU. Later in time, both groups show similar VAS score time-profile. The number of observations gradually diminished in time since some patients already returned home before 24 hours postoperatively; this trend is also similar in both groups.

The linear mixed model for repeated measures (ANOVA) involving other covariates tried to explain the variation in VAS score over time. This model

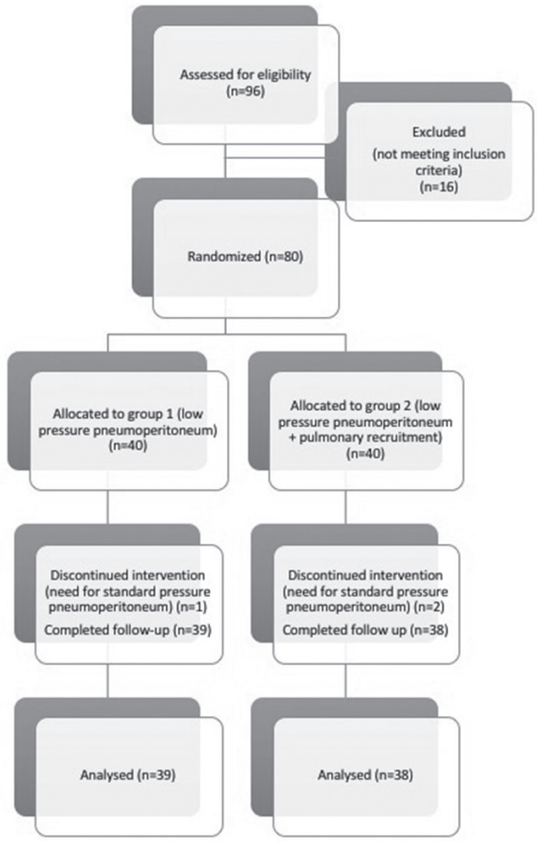

Fig. 2. — CONSORT flow diagram.

showed that tramadol, morphine and timing of tramadol consumption were the variables explaining most of the variation. There was no effect of group and no interaction between time and group, meaning that there was no significant difference in VAS score over time between both groups. The effect on VAS scores was probably due to analgesic use and not to the pulmonary recruitment maneuver.

Secondary outcomes, including total analgesic use, recovery score at 48 hours postoperatively, postoperative nausea and vomiting at the PACU and at ward, and length of hospital stay, were not significantly different amongst the two groups either (Table 3).

There were no harms or unintended effects in either group.

Discussion

In our trial, the addition of a pulmonary recruitment maneuver did not result in lower pain scores during the first 24 hours postoperatively in patients receiving a low pressure pneumoperitoneum for laparoscopic cholecystectomy. To our know-

ledge, this was the first trial combining those two actions in an attempt to obtain a cumulative reduction in postoperative pain.

This primary outcome result could be due to already low VAS scores in patients receiving low pressure pneumoperitoneum. Hence, it could be more difficult to significantly lower the pain scores even more with an additional maneuver intra-operatively. A systematic review and meta-analysis by Hua *et al.* clearly demonstrated that low pressure compared with standard pressure pneumoperitoneum reduced the incidence of shoulder pain (20% *vs* 38%, respectively) and also pain intensity on the VAS was significantly lower (6). Although this lower pressure could cause impaired visualization, the technique is proven feasible and safe, and it should be considered as part of a multimodal approach to postoperative analgesia (4,6). Therefore, we used the low pressure pneumoperitoneum in all patients, which may be considered as a limitation since we had no group of patients receiving standard pressure pneumoperitoneum.

For safety reasons, mainly to avoid barotrauma, we used positive pressure inflations to a maximum of 40 cmH_2O during pulmonary recruitment. A randomized controlled trial by Ryu *et al.* in gynecologic laparoscopy showed that a low pressure pulmonary recruitment maneuver, using 40 cmH_2O, was as effective for removal of residual gas as a high pressure maneuver using 60 cmH_2O (12). The findings of this article, published in 2017 after our patient inclusion was completed, also support the use of 40 cmH_2O in our study protocol.

Bile spillage during laparoscopic cholecystectomy was previously shown to be associated with more rapid resolution of the pneumoperitoneum and would not cause increased postoperative pain or slower recovery (2). This might be related to subsequent lavage with displacement of subphrenic carbon dioxide. In our study, we analyzed some extra data and found no significant differences between the two groups with respect to bile spillage, operating time or extra doses of sufentanil given during surgery. The finding that there was no difference in operating time was in turn in agreement with the meta-analysis of RCT's by Hua *et al.*(6).

We do not believe that longer follow-up of pain scores would have made any difference, since pain is to be expected the worse in our time window of the first 24 hours postoperatively.

In conclusion we found no statistically significant differences amongst both groups in VAS scores at several time points during the first 24 hours postoperatively.

This study demonstrates that performing a pulmonary recruitment maneuver in patients undergoing laparoscopic cholecystectomy with a low pressure pneumoperitoneum does not improve postoperative analgesia.

This could be due to the beneficial effects of low pressure insufflation in all patients, which makes it more difficult to get a clinical important reduction in pain score. However, using a low pressure pneumoperitoneum for laparoscopic surgery is not feasible in all patients. Therefore, further research to determine the exact role and modalities of pulmonary recruitment maneuvers is necessary.

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