

Intraperitoneal Versus Interpleural Morphine or Bupivacaine for Pain after Laparoscopic Cholecystectomy

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Background: Opioids can produce peripheral analgesic effects by activation of opioid receptors on sensory nerves. This study was designed (1) to examine a novel route of opioid administration, the intraperitoneal injection; (2) to compare this to interpleural application, and (3) to compare opioid with local anesthetic effects under both conditions.

Methods: At the end of laparoscopic cholecystectomy, 110 patients received the following injections in a double-blind, randomized manner: Group 1 (n = 18) was given intraperitoneal morphine (1 mg in 20 ml saline) and 20 ml intravenous saline. Group 2 (n = 17) received intraperitoneal saline and 1 mg intravenous morphine. Group 3 (n = 15) received 20 ml 0.25% intraperitoneal bupivacaine and intravenous saline. Group 4 (n = 20) received interpleural morphine (1.5 mg in 30 ml saline) and 30 ml intravenous saline. Group 5 (n = 20) received interpleural saline and 1.5 mg intravenous morphine. Group 6 (n = 20) received 30 ml 0.25% interpleural bupivacaine and intravenous saline. Postoperative pain was assessed using a visual analog scale, a numeric rating scale, and the McGill pain questionnaire. Pain localization, supplemental analgesic

consumption, vital signs, and side effects were recorded for 24 h.

Results: Neither intraperitoneal nor interpleural morphine produced significant analgesia after laparoscopic cholecystectomy ($P > 0.05$, Kruskal-Wallis test), whereas interpleural bupivacaine was effective ($P < 0.05$, Kruskal-Wallis test, up to 6 h postoperatively) but not intraperitoneal bupivacaine ($P > 0.05$, Kruskal-Wallis test). Shoulder pain was not prevalent in the majority of patients during the first 6 h. By 24 h, about half of the patients complained of shoulder pain, which was rated "low" by about one-third of all patients. No significant side effects occurred.

Conclusions: Interpleural bupivacaine (0.25%) produces analgesia after laparoscopic cholecystectomy. We attribute the lack of effect of intraperitoneal injections to the small dose and to a rapid dilution within the peritoneal cavity. The fact that interpleural morphine (0.005%) is ineffective may be due to an intact perineurial barrier in the noninflamed pleural cavity, which restricts the transperineurial passage of morphine to opioid receptors on intercostal nerves. (Key words: Analgesics, opioid: morphine. Anesthetic techniques: interpleural; intraperitoneal. Anesthetics, local: bupivacaine. Pain: postoperative. Receptors, opioid: peripheral. Surgery, laparoscopic: cholecystectomy.)

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OPIOID analgesia has been associated with the activation of opioid receptors within the central nervous system. However, recent evidence indicates that potent analgesic effects can be elicited by activation of opioid receptors in peripheral tissues in animals and in humans. Such receptors are localized on peripheral sensory nerves,^{1,2} where they can modulate both afferent^{3,4} and efferent⁵⁻⁷ neuronal functions to eventually result in antinociception.⁸

In humans, peripheral opioid effects have been most extensively studied and convincingly demonstrated after intraarticular administration of morphine.⁹⁻²³ Other modes of administration include the perineural and the interpleural routes, but the results are equivocal.²⁴⁻²⁶ The current study was designed to (1) examine the efficacy of intraperitoneal injection of opioids, (2)

compare this to interpleural administration, and (3) compare opioid with local anesthetic effects under both conditions.

Materials and Methods

Patients

The project was approved by the institutional review board of the Klinikum Grosshadern, Ludwig-Maximilians-University, Munich, and written informed consent was obtained from each patient before surgery. One hundred ten inpatients undergoing elective laparoscopic cholecystectomy for cholelithiasis were studied. The surgery was performed using standard techniques as described.²⁷ The criteria for exclusion from the study were ASA physical status 3 or greater or a history of pleuritis in part 2 of the study. All patients received clorazepate dipotassium (a benzodiazepine, 20 mg orally per patient) 1 h before surgery. Anesthesia was induced with thiopental (3–5 mg/kg), fentanyl (1.5 µg/kg), and succinylcholine (1 mg/kg) and was maintained with oxygen/nitrous oxide, isoflurane (0.6–1.5%), vecuronium (0.1–0.15 mg/kg), and supplemental fentanyl (maximum 3 µg/kg). End-expiratory P_{CO_2} was monitored and maintained at approximately 35 mmHg throughout the procedure.

Protocols

The test solutions were drawn into two coded syringes by a nurse and given to the investigators, who did not know their contents. The patients were randomly allocated to the groups.

Part 1. At the conclusion of surgery but before the laparoscope was removed, one of the test solutions was sprayed intraperitoneally onto the gallbladder bed (5 ml) and onto the subphrenic surface of the liver (15 ml) via a special catheter by use of an air pressure-driven apparatus (Tissomat, Immuno, Vienna, Austria) to achieve a homogeneous distribution of the solution in the desired areas: group 1 ($n = 18$) received intraperitoneal morphine (1 mg in 20 ml of normal saline) and intravenous normal saline (20 ml). To control for possible central effects due to systemic absorption of morphine, group 2 ($n = 17$) received intraperitoneal saline (20 ml) and intravenous morphine (1 mg in 20 ml saline). Group 3 ($n = 15$) received 0.25% intraperitoneal bupivacaine (20 ml) and intravenous saline (20 ml). Thereafter, anesthesia was terminated.

Part 2. After removal of the laparoscope, the effects of muscle relaxants were reversed, and patients were

allowed to breathe spontaneously while general anesthesia was maintained. While supine and in 30° reverse Trendelenburg's position, an interpleural catheter (Braun, Melsungen, Germany) was placed in the right midaxillary line above the fifth rib using a modification of the originally described technique.²⁸ The catheter was advanced 5 cm toward the shoulder, and the following test solutions were injected: Group 4 ($n = 20$) received interpleural morphine (1.5 mg in 30 ml saline) and intravenous saline (30 ml). Group 5 ($n = 20$) received interpleural saline (30 ml) and intravenous morphine (1.5 mg in 30 ml saline). Group 6 ($n = 20$) received 0.25% interpleural bupivacaine (30 ml) and intravenous saline (30 ml). Thereafter, the interpleural catheter was removed, and general anesthesia was terminated. All doses were chosen based on our previous studies investigating peripheral analgesic actions of opioids in humans.^{9,10,25}

Assessment of Pain, Vital Signs, and Side Effects

Postoperative pain was assessed using a 100-mm visual analog scale (VAS), a numeric rating scale (NRS) ranging from 1 to 100, and a German version of the McGill pain questionnaire (MPQ).^{29,30} Patients were asked about the location of pain (shoulder, incision, and/or intraabdominal). These assessments were made hourly for the first 6 h and once after 24 h. Supplemental analgesic medication was available upon request and was recorded at the above intervals. The following drugs were used: intravenous metamizol (a nonsteroidal antiinflammatory analgesic) and intravenous piritramide (an opioid agonist) during the first 3 h in the recovery room, and intramuscular tramadol (an opioid agonist and monoamine reuptake-inhibitor) thereafter on the surgical wards. Heart rate (HR), blood pressure (BP), and side effects (pruritus, urinary retention, nausea) were recorded. Sedation was assessed using a five-point scale consisting of the descriptors "awake, oriented," "awake, disoriented," "arousable upon command," "arousable upon painful stimuli," and "not arousable."

Data Analysis

To score the VAS, the distance (mm) from the "no pain" end to the mark provided by the patient was measured. The MPQ was scored as described previously.³¹ The number of words chosen (NWC) and the total pain rating index (PRI(t)) are given. Each patient's total consumption of supplemental analgesics in 24 h was calculated. Comparisons between groups and *post*

Table 1. Demographic Characteristics of Patients Receiving Intraperitoneal Morphine (Group 1), Saline (Group 2), or Bupivacaine (Group 3) and of Patients Receiving Interpleural Morphine (Group 4), Saline (Group 5), or Bupivacaine (Group 6)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
n	18	17	15	20	20	20
Sex (m/f)	5/13	4/13	4/11	3/17	3/17	5/15
Age (yr)	45.3 ± 3.4	54.0 ± 3.3	47.7 ± 2.9	47.6 ± 2.9	44.9 ± 3.1	49.9 ± 2.5
Weight (kg)	76.5 ± 3.4	69.7 ± 2.6	70.3 ± 2.8	74.9 ± 3.6	67.5 ± 3.2	73.0 ± 3.2
Height (cm)	170 ± 2	166 ± 2	166 ± 2	167 ± 2	163 ± 2	169 ± 2
Surgery						
Duration (min)	85 ± 6	70 ± 6	63 ± 4	63 ± 5	73 ± 6	67 ± 3

Values are mean ± SEM.

boc testing were performed using the Kruskal-Wallis and Dunn tests, respectively. For multiple comparisons, the significance level was corrected according to Bonferroni.³²

Results

Part 1

There were no significant differences in patient demographics (table 1), vital signs, pain location, or any of the pain scores (fig. 1) between groups. Neither intraoperative (group 1, 0.24 ± 0.06 mg; group 2, 0.26 ± 0.04 mg; group 3, 0.24 ± 0.06 mg fentanyl) nor postoperative supplemental analgesic consumption (fig. 2) was significantly different. Forty-three of 50 patients did not complain of shoulder pain up to 6 h

after surgery. Shoulder pain was rated "low" by five patients and "moderate" by two patients. At 24 h, 24 patients reported shoulder pain, which was rated "low" by 16, "moderate" by 2, and "severe" by 6 patients. These patients were equally distributed among the groups. During the first hour, four patients were arousable upon verbal command, and two were disoriented. By 3 h, all patients were awake and oriented. None of the above-mentioned side effects were reported in any group.

Part 2

There were no significant differences in patient demographics (table 1), vital signs, or location of pain between groups. Pain scores were not different between groups 4 and 5 (fig. 3). All pain scores were

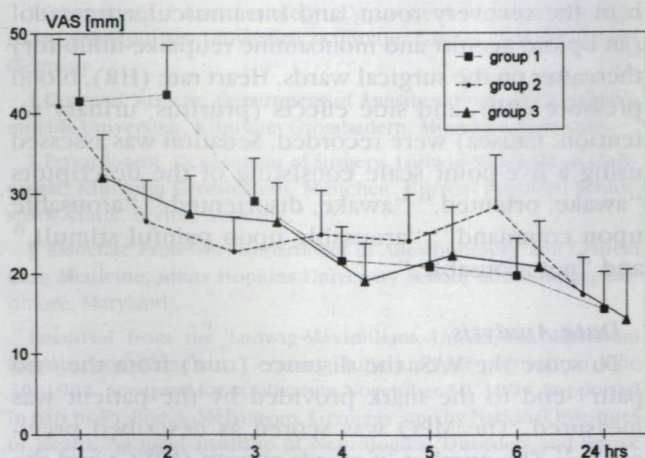


Fig. 1. Pain scores as determined by the visual analog scale in patients receiving intraperitoneal morphine (group 1, squares), saline (group 2, circles), or bupivacaine (group 3, triangles). Mean ± SEM is given.

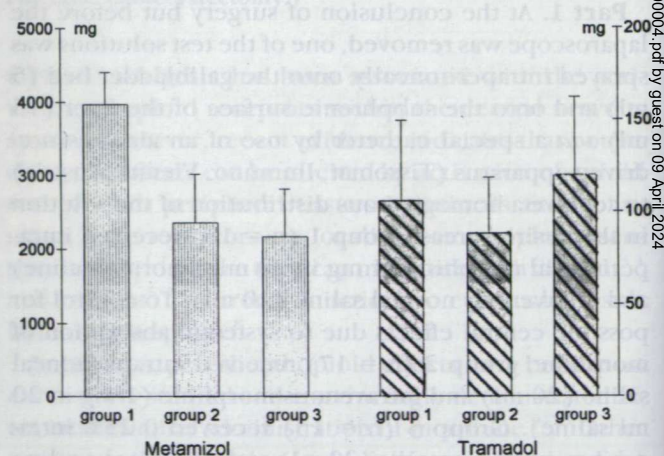


Fig. 2. Supplemental consumption of metamizol (open bars) and tramadol (hatched bars) in patients receiving intraperitoneal morphine (group 1), saline (group 2), or bupivacaine (group 3). Mean ± SEM is given.

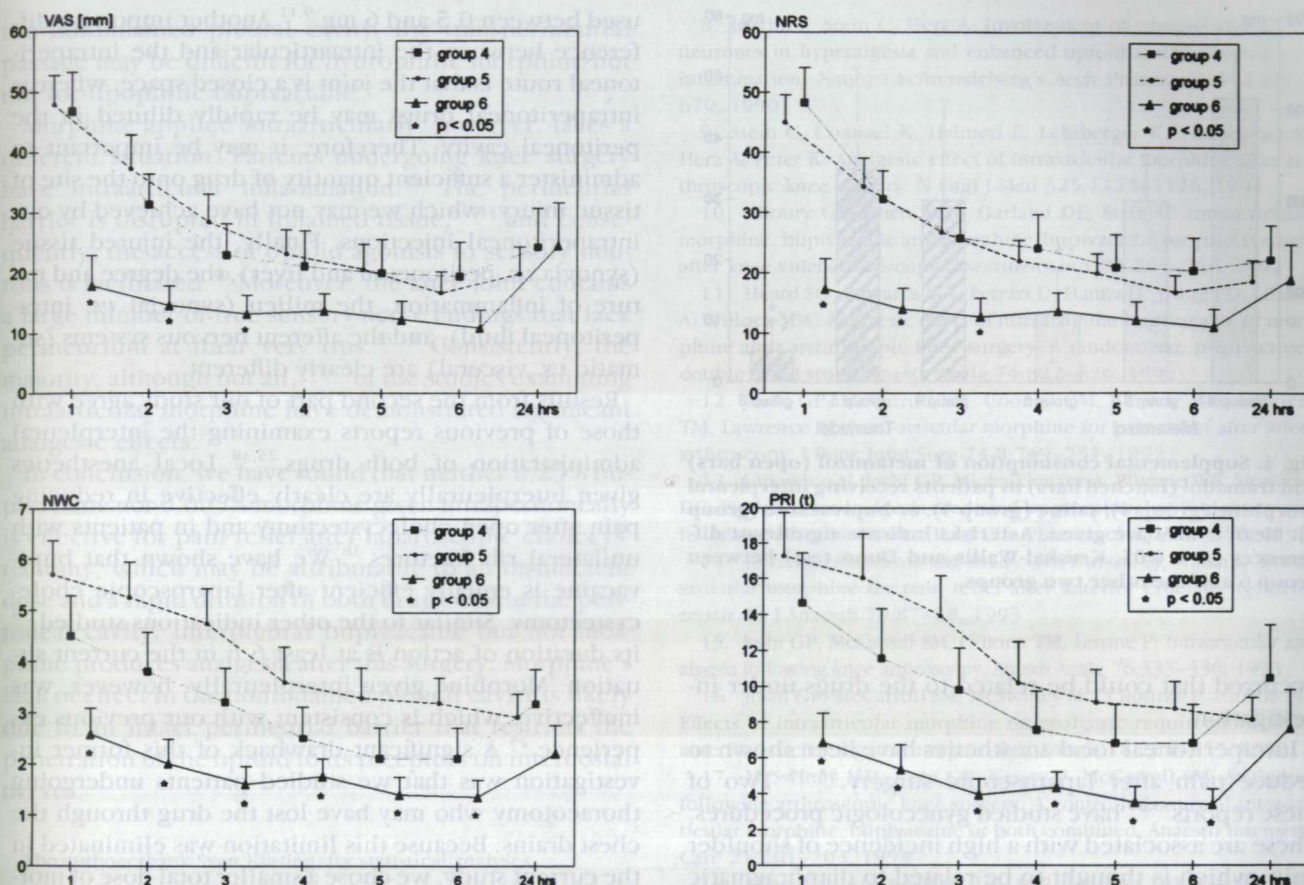


Fig. 3. Pain scores as described by the visual analog scale, numeric rating scale, number of words chosen, and total pain rating index³¹ in patients receiving interpleural morphine (group 4, squares), saline (group 5, circles), or bupivacaine (group 6, triangles). Mean \pm SEM are given. Asterisks indicate significant differences ($P < 0.05$, Kruskal-Wallis and Dunn test) between group 6 and the other two groups.

less in group 6 (interpleural bupivacaine) than in groups 4 or 5 between 1 and 6 h postoperatively (fig. 3). The differences were significant ($P < 0.05$) between 1 and 3 h as determined by VAS and NRS and between 1 and 6 h as determined by NWC and PRI(t). The intraoperative dose of fentanyl was not different between groups (group 4, 0.22 ± 0.01 ; group 5, 0.25 ± 0.02 ; group 6, 0.23 ± 0.02 mg). The supplemental consumption of metamizol and tramadol was significantly less ($P < 0.05$) in group 6 than in groups 4 or 5 (fig. 4). Fifty-three of 60 patients did not complain of shoulder pain up to 6 h after surgery. Shoulder pain was rated "low" by three, "moderate" by one, and "severe" by two patients. At 24 h, 23 patients reported shoulder pain, which was rated "low" by 14, "moderate" by 5, and "severe" by 2 patients. These patients were equally distributed among the groups. During

the first hour, 16 patients were awake and disoriented. By 4 h, all patients were awake and oriented. None of the above-mentioned side effects were reported in any group.

Discussion

This study shows that neither intraperitoneal nor interpleural morphine (0.005%) in the doses studied produces significant analgesia after laparoscopic cholecystectomy, whereas 0.25% interpleural bupivacaine is effective but not 0.25% intraperitoneal bupivacaine. Shoulder pain was not prevalent in the majority of patients during the first 6 h. By 24 h, about half of the patients complained of shoulder pain, which was rated "low" by about one-third of all patients. No side effects

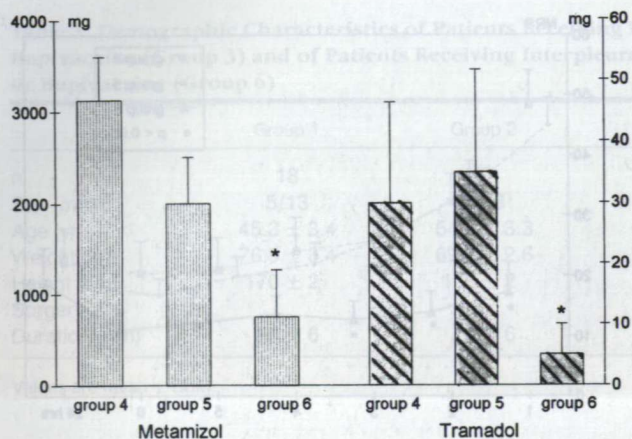


Fig. 4. Supplemental consumption of metamizol (open bars) and tramadol (hatched bars) in patients receiving interpleural morphine (group 4), saline (group 5), or bupivacaine (group 6). Mean \pm SEM are given. Asterisks indicate significant differences ($P < 0.05$, Kruskal-Wallis and Dunn test) between group 6 and the other two groups.

occurred that could be related to the drugs under investigation.

Intraperitoneal local anesthetics have been shown to reduce pain after laparoscopic surgery.³³⁻³⁵ Two of these reports^{33,34} have studied gynecologic procedures. These are associated with a high incidence of shoulder pain, which is thought to be related to diaphragmatic irritation by intraperitoneal carbon dioxide. Accordingly, we monitored the localization of pain and, in anticipation, injected drugs into the subdiaphragmatic area. However, we found a low incidence of shoulder pain in all treatment groups. Therefore, we may have failed to detect effects of intraperitoneal bupivacaine due to a lower intensity or different characteristics of pain after laparoscopic cholecystectomy.

Another important consideration is the amount of drug delivered to the surgical site. Chundrigar *et al.*³⁵ successfully applied 20 ml 0.25% bupivacaine onto the gallbladder bed, whereas we injected only 5 ml onto the gallbladder bed and 15 ml into the right subdiaphragmatic area. Other studies that found no analgesic effects of intraperitoneal local anesthetics after open³⁶ or laparoscopic³⁷ cholecystectomy also have attributed their findings to insufficient dosage. Our failure to detect analgesic effects of either intraperitoneal bupivacaine or intraperitoneal morphine may have similar reasons. Thus, in the current study, we applied only 0.25 mg morphine onto the surgical site, whereas previous studies examining intraarticular injections have

used between 0.5 and 6 mg.^{9,11} Another important difference between the intraarticular and the intraperitoneal route is that the joint is a closed space, whereas intraperitoneal drugs may be rapidly diluted in the peritoneal cavity. Therefore, it may be important to administer a sufficient quantity of drug onto the site of tissue injury, which we may not have achieved by our intraperitoneal injections. Finally, the injured tissue (synovia *vs.* peritoneum and liver), the degree and nature of inflammation, the milieu (synovial *vs.* intraperitoneal fluid), and the afferent nervous systems (somatic *vs.* visceral) are clearly different.

Results from the second part of our study agree with those of previous reports examining the interpleural administration of both drugs.^{25,38} Local anesthetics given interpleurally are clearly effective in reducing pain after open cholecystectomy and in patients with unilateral rib fractures.³⁸ We have shown that bupivacaine is equally efficient after laparoscopic cholecystectomy. Similar to the other indications studied,³⁸ its duration of action is at least 6 h in the current situation. Morphine given interpleurally, however, was ineffective, which is consistent with our previous experience.²⁵ A significant drawback of this former investigation was that we studied patients undergoing thoracotomy who may have lost the drug through the chest drains. Because this limitation was eliminated in the current study, we chose a smaller total dose of morphine (1.5 mg *vs.* 2.5 mg in²⁵), which was aimed at yielding the same concentration as that in our intraperitoneal solution. Compared to our previous studies of intraarticular injections, however, the current amount of morphine is still three times the smallest effective intraarticular dose (0.5 mg⁹). Thus, it is unlikely that the current lack of effect is exclusively attributable to the dose.

An additional issue that has to be considered is that morphine's access to opioid receptors may be restricted in the pleural cavity. Peripheral antinociceptive effects of opioid agonists are brought about by an interaction with opioid receptors located on peripheral sensory nerves.^{1,2,8} Accordingly, we hypothesized that interpleural morphine may activate opioid receptors on intercostal nerves. However, in the absence of inflammation, such neuronal receptors are not easily accessible because the intact perineurium significantly impedes the penetration of macromolecules.³⁹ In particular, tight intercellular contacts at the innermost layer of the perineurium act as a diffusion barrier for hydrophilic substances such as morphine.^{40,41} Thus, in

the noninflamed pleural cavity, the transperineurial passage may be difficult for hydrophilic morphine but not for lipophilic bupivacaine.

Morphine applied intraarticularly, however, faces a different situation. Patients undergoing knee surgery have intraarticular inflammation.⁴² The perineurial barrier is disrupted in inflamed tissue,^{40,41} and consequently, the access of opioid agonists to sensory neurons is facilitated.³⁹ Moreover, the knee joint contains a large number of free sensory nerve endings that lack perineurium at their very tips.^{43,44} Consistently, the majority, although not all,⁴⁵⁻⁴⁷ of the studies examining intraarticular morphine have demonstrated significant analgesic effects.⁹⁻²³

In conclusion, we have found that neither 0.25% bupivacaine nor 0.005% morphine given intraperitoneally is effective for pain relief after laparoscopic cholecystectomy, which may be attributable to an insufficient dose and a rapid dilution of both drugs within the peritoneal cavity. Interpleural bupivacaine but not morphine produces analgesia after this surgery. Morphine's lack of effect in the noninflamed pleural cavity is likely due to an intact perineurial barrier that restricts the penetration of the opioid to its receptors on intercostal nerves.

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