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A double-blinded evaluation of intraperitoneal bupivacaine vs saline for the reduction of postoperative pain and nausea after laparoscopic cholecystectomy

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Abstract

Background: Intraperitoneal local anesthesia has been reported to reduce postoperative pain after laparoscopy for gynecologic procedures that do not require a great deal of dissection or manipulation of viscera. This study was performed to determine the efficacy of intraperitoneal bupivacaine in laparoscopic cholecystectomy (LC).

Methods: Fifty-five patients were evaluable in this randomized, double-blind, placebo-controlled study. Twenty-six patients received bupivacaine (0.1%) and 29 patients received placebo (saline). Prior to any dissection of the gallbladder, the surgeon irrigated 100 ml of experimental solution under the right hemidiaphragm, over Glisson's capsule, over the gallbladder serosa, and into the subhepatic space. The operation was then performed as usual. Postoperatively, analgesic medication usage, nausea, vomiting, and pain scores were determined during hospitalization. A questionnaire was given to each patient upon discharge from the hospital in order to continue monitoring medications and pain for the first 48 h at home.

Results: Postoperative pain was reduced significantly ($P < 0.05$) in the patients who received bupivacaine, but the effect was modest and observable only during the first 6 h after surgery. Despite this difference, there was no significant reduction in the amount of analgesic medication used by the patients who received bupivacaine, nor was there any reduction in nausea, vomiting, or shoulder pain when queried specifically.

Conclusions: Intraperitoneal bupivacaine offered a detectable, albeit subtle benefit to patients undergoing LC. However, the effect was transient and had little impact upon the patient's convalescence.

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Local anesthetics block the generation and propagation of action potentials in nerve and other excitable tissues in a reversible manner [8], probably at the level of the passive sodium channels [10, 21]. The uses of local anesthetics are numerous in all areas of medicine, extending from local application for minor procedures such as central venous catheter placement and wound repair [9, 25], intracavitary instillation for analgesia after injuries or minor surgery [17, 19, 25, 30], infiltration for nerve block for regional procedures [5], and even for abdominal surgery such as hernia repair [13] and cesarean section [6]. Recently, the intraoperative use of local anesthesia during laparoscopy has generated interest. With the established trend for surgery of ever-increasing complexity to be done on an outpatient basis, more laparoscopic intraabdominal surgery will be done with brief hospitalizations, using local or regional anesthesia with sedation as an adjunct or alternative to general anesthesia. This may be accomplished by reducing postoperative pain to the point that narcotic analgesics are not required.

Laparoscopic cholecystectomy (LC) has become an accepted standard of care for symptomatic cholelithiasis [11, 27, 29, 31]. The laparoscopic procedure has decreased the morbidity associated with cholecystectomy, especially as experience has accrued [11, 31]. Patients who undergo laparoscopic cholecystectomy have shorter hospital stays, use less parenteral narcotics for pain control, and have a shorter period of convalescence before returning to work [27]. Nevertheless, it would be desirable to decrease patients' postoperative discomfort further and create an even smoother transition back to normal activity. Performance of LC as a routine outpatient procedure would

be advantageous, both for the patient and for the economics of health-care delivery. Improved patient selection, improvements in technique such as minimizing bile leaks and other complications [18, 24], and improvements in anesthesia and postoperative pain control are all contributory. Intraperitoneal local anesthesia may be a part of the solution.

Widespread use of intraperitoneal local anesthesia for laparoscopic procedures in gynecologic surgery has been reported previously [2–4, 20]. Those studies used a local anesthetic agent to reduce postoperative pain and nausea after diagnostic laparoscopy [20] or after tubal ligation [2–4]. Both procedures involve minimal dissection compared to the complexity of many laparoscopic general surgery procedures now being performed. Following diagnostic laparoscopy, Narchi and associates reported a reduction in postoperative scapular pain in 63% of patients who received either 80 ml 0.5% lidocaine or 80 ml 0.125% bupivacaine infiltrated into the right supradiaphragmatic area [20]. Baram et al. reported a significant reduction in postoperative pain in a saline-controlled study for patients who received 5 ml of 1% etidocaine following laparoscopic tubal ligation [2]. Their treated patients also had nonsignificant decreases in nausea and vomiting, as well as slightly smaller antiemetic and analgesic requirements than did the control group. Bordahl et al. reported a significant reduction in analgesic use by patients who received 25–50 mg bupivacaine (5 mg/ml) applied directly to the fallopian tubes during intravenous sedation, compared to patients who received general anesthesia alone for the same procedure [4].

Despite the possible efficacy of adjunctive local anesthesia for analgesia following gynecologic laparoscopy, there are few data concerning the use of local anesthesia for laparoscopic general surgical procedures, and specifically LC. A randomized, double-blind, case-control study was performed to determine the value of intraperitoneal local anesthesia, in addition to standard general anesthesia, for reduction of pain and nausea after LC. Our specific hypothesis was that intraperitoneal bupivacaine, administered under direct vision to the undersurface of the right hemidiaphragm, over Glisson's capsule, into Calot's triangle, and the subhepatic space of Morison, would reduce postoperative pain and nausea. Patients were expected, as primary-outcome measures, to use less narcotic and non-narcotic analgesic medication, report less pain, and experience less nausea and vomiting.

Patients and methods

The study was approved by the Committee on Human Rights in Research of Cornell University Medical College. Patients were enrolled if they were aged 18–80 years and were undergoing an elective LC for chronic calculous cholecystitis with or without intraoperative cholangiography. Patients were excluded for acute cholecystitis or if exploration of the common bile duct was planned. No patients were excluded for medical reasons.

The LC was performed by one of ten surgeons. Prior to the operation, only the scrub nurse was informed as to what substance would be used by the surgeon. Two 60-ml syringes, each filled with 50 ml of either normal saline or 50 ml 0.1% bupivacaine in saline, were placed on the operative field. The surgeon performed the LC as usual. Access to the peritoneal cavity by Veress needle or Hasson trocar was at the discretion of the operating surgeon, as was the decision to convert to open cholecystectomy. If subhepatic adhesions were present, preliminary dissection was undertaken so that the study medication could be delivered freely to the intended location. Just prior to any dissection of the cystic duct, cystic artery, or gallbladder, 100 ml of solution was irrigated under the right hemidiaphragm, over Glisson's capsule, and into the subhepatic space including the serosa of the gallbladder. The substance was then left in the operative bed and suctioned out in increments as needed for visualization during the course of the operation.

A standard, balanced anesthetic was used. After surgery, no constraints were placed on the ordering of analgesic medication by the surgeon or anesthesiologist, but antiemetics were not prescribed. As it happened, all patients received either parenteral morphine or meperidine, followed by conversion to oral combinations of codeine or a codeine congener with acetaminophen. No patients received nonsteroidal antiinflammatory drugs (including aspirin) at any time.

Postoperatively, the patient was seen by a trained data collector who recorded the analgesic use of the patient from the hospital record and asked the patient a standardized set of questions which included: On a scale of 0–10, what number would you rate your pain where 0 represents no pain and 10 represents the worst pain you have ever experienced? Are you nauseous? Have you vomited? Do you have any shoulder pain? What number would you rate your shoulder pain on the same 0–10 scale? The hospital record was reviewed for the duration of surgery and hospitalization, and for the occurrence of a bile spill or "excessive" bleeding (>50 ml) during surgery. Negligible bile spillage during performance of intraoperative cholangiography was not considered a bile spill for the purpose of the study.

The patient was then given a questionnaire with the pain questions represented as a visual analog scale and asked to record any medications taken while at home. The questionnaire covered the first 2 days the patient was at home. The patient was asked to mail the questionnaire back to our institution promptly after the 2nd day. Analgesic use was then converted to equivalent doses of subcutaneous morphine for purposes of data analysis, based on published pharmacologic equivalents (Table 1) [2, 14, 22, 23].

Data were collected and analyzed using a microcomputer (Macintosh LC, Apple Computer, Cupertino, CA) and commercial software (Excel 4.0, Microsoft, Inc., Redmond, WA; StatView 4.0.2, Abacus Concepts, Inc., Berkeley, CA). Differences in mean values were compared by an unpaired two-tailed *t*-test, or by a chi-square test using Fisher's exact test, as appropriate. Differences in pain scores and analgesic doses over time within groups were compared with a one-way analysis of variance (ANOVA). Differences in analgesic doses and pain scores over time between groups were compared with a two-way ANOVA without repeated measures. Statistical significance was determined at an alpha of 0.05.

Table 1. Analgesic medication conversion into equivalents of subcutaneous morphine

Medication	Equivalents of subcutaneous morphine (mg)
Meperidine, 75 mg IM	10
Morphine, 5 mg IV	15
Oral medications	
Acetamenophen 325 mg with oxycodone 5 mg	5
Acetamenophen 500 mg with hydrocodone 5 mg	5
Acetamenophen 325 mg with codeine 30 mg	3
Acetamenophen, 650 mg	2

Table 2. Demographic and operative variables

Variable	Bupivacaine	Saline	*P* value
Age (years)	42.1 ± 3.1	47.0 ± 2.8	0.17
Duration of operation (min)	106.8 ± 6.6	134.5 ± 8.3	0.01*
Length of hospital stay (days)	1.9 ± 0.3	2.2 ± 0.5	0.61
Bile spill during operation	2 of 26	2 of 29	0.17

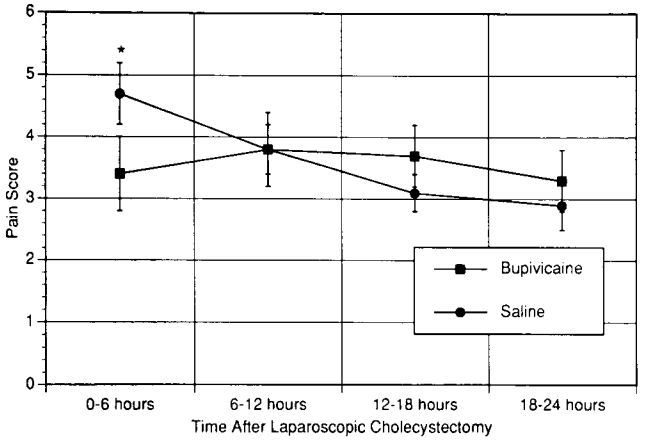

Fig. 1. Pain scores are depicted at 6-h intervals for the bupivacaine and saline groups. Pain scores were significantly higher in the saline group compared to bupivacaine in the first 6 h, and higher during that period compared to later periods within the saline group.

Table 3. Incidence of shoulder pain, nausea, and vomiting in the first 24 h

Variable	Bupivacaine (n = 26)	Saline (n = 29)	*P* value
Shoulder pain	7	9	0.77
Nausea	7	8	0.99
Vomiting	5	7	0.75

Table 4. Equivalent analgesic medication used over the first 24 h post-operatively[a]

Time after operation (h)	Bupivacaine	Saline	*P* value
0–6	13.4 ± 2.2	10.0 ± 1.8	0.24
6–12	4.3 ± 1.1	4.9 ± 1.0	0.68
12–18	2.2 ± 0.7	2.0 ± 0.7	0.84
18–24	1.8 ± 0.7	0.5 ± 0.4	0.08
Total medication used (24)	21.7 ± 3.0	17.4 ± 2.1	0.25

[a] Equivalent to mg subcutaneous morphine.

Table 5. Equivalent analgesic medication used over the second and third 24-h postoperative periods[a]

Time after operation (h)	Bupivacaine	Saline	*P* value
24–48	5.5 ± 2.0	5.9 ± 1.8	0.89
48–72	3.7 ± 1.2	2.8 ± 0.9	0.55

[a] Equivalent to mg subcutaneous morphine.

Results

Ninety-one patients were approached for possible participation, of whom 75 patients agreed to participate after informed consent. Fifty-five patients were evaluable, with the other 20 patients excluded as follows: 17 procedures were converted to an open cholecystectomy, 1 patient experienced a postoperative stroke, 1 patient experienced a suspected intraoperative pulmonary embolism and received 36 mg morphine postoperatively, and 1 patient did not receive the study drug.

There were 26 patients in the bupivacaine group (BUPIV) and 29 patients in the saline group (SALINE). The mean patient age was not significant between groups (Table 2), nor were there differences in the mean length of hospital stay, intraoperative bile spills, or the incidence of hemorrhage (none in either group). However, the duration of operation was significantly longer ($P < 0.05$) for the SALINE group.

Pain scores revealed a significant decrease ($P < 0.05$) over time in the SALINE group, with a mean pain score of 4.7 ± 0.5 at 0–6 h and a mean pain score of 2.9 ± 0.4 at 18–24 h postop (Fig. 1). In contrast, there was no change in pain scores in the BUPIV group over time ($P = 0.91$). However, pain scores in the BUPIV and SALINE group revealed a significant difference ($P < 0.05$) between the two groups at 0–6 h.

Shoulder pain was too mild in both groups for pain scores to be quantitated. Therefore, shoulder pain was noted as either present or not present (Table 3). Seven patients experienced shoulder pain in the BUPIV group whereas nine patients experienced shoulder pain in the SALINE group ($P = 0.77$). Nausea and vomiting were present in both groups in nearly equivalent incidences, and were likewise not statistically different. The periodic and total analgesic requirements expressed as subcutaneous morphine equivalents are shown in Table 4. Mean total analgesic use during the first 24 h postoperatively in the BUPIV group was 21.7 ± 3.0 mg, compared to 17.4 ± 2.1 mg in the SALINE group ($P = 0.24$). Eighteen patients in each group received an immediate dose of intravenous or subcutaneous morphine (range, 4–8 mg) in the postanesthesia care unit (PACU). Ten patients in the BUPIV group and eight patients in the SALINE group received that early dose of morphine, but afterward required no other analgesic medication.

Table 5 shows the mean medication use in the second and third 24-h periods. There was no difference in medication use between the groups for either time interval. Pain scores were unevaluable due to a standard error that exceeded the possible range of pain scores [12] due to the high frequency of pain scores of zero in the second and third 24-h time periods.

Discussion

The data indicate that intraperitoneal bupivacaine offers little adjunctive benefit for patients undergoing

laparoscopic cholecystectomy. Although patients in the SALINE group had significantly higher pain scores in the first 6 h after surgery, the difference was small and did not cause an increase in analgesic medication requirements for the group. Similarly, there was no reduction in nausea, vomiting, or shoulder pain in the BUPIV group as compared with the SALINE group. Thus, although an effect of bupivacaine was detectable, it was of insufficient magnitude to impact patient comfort or the duration of hospital stay. This may be because pain from the procedure is minimal and generally well tolerated by most patients. In the event that LC becomes widely performed as an outpatient procedure, oral medication provided after a brief period of postprocedure observation should suffice, as analgesic requirements diminish markedly after the first 6 h.

The use of bupivacaine for intracavitary anesthesia is not new [1, 26, 28, 30]. Because of its long duration of action, bupivacaine is an excellent choice for reducing postoperative pain. Intrapleural instillation of bupivacaine for analgesia after upper abdominal surgery produces peak blood levels within 20 min to a degree that is variable among individual patients but consistent across studies [26, 30]. However, the absorption of bupivacaine from the peritoneum is less well quantified. Spielman et al. [28] found that 100 mg bupivacaine (in 20 ml saline) sprayed directly on the fallopian tubes during tubal ligation resulted in a mean blood bupivacaine concentration of 0.44 ± 0.15 μg/ml (range, 0.22–0.77 μg/ml; convulsive level, 2.3–5.5 μg/ml) [16, 28]. Thus, it could be argued that more bupivacaine could be delivered safely for procedures such as LC. However, the effect of bupivacaine in the present study did not result in a reduction in analgesic use. It is difficult to predict if an increased dose might result in a decrease in medication use, as overall levels of postoperative pain were moderate.

The dosage of bupivacaine used in this study was selected to match that used in the gynecologic study of Narchi et al. [20], so that direct comparisons might be made. The bupivacaine was instilled early during the operation to duplicate additionally the conditions of that study. Early instillation has the potential advantage of sufficient time for onset of action before emergence from anesthesia, as the latent period for bupivacaine is prolonged. It is possible that later instillation might have achieved higher peak blood levels if no medication was aspirated from the peritoneal cavity during surgery, but it is also possible that saline irrigant used during surgery and aspirated incompletely before instillation might dilute drug instilled later below an effective concentration or disperse it from the operative field, that clotted blood in the field might also interfere with dispersion of the drug, or that local peritoneal irritation from spillage of bile might reduce the analgesic effect of a given dose, as is the case when local infiltrative anesthetics are used for incision and drainage of a subcutaneous abscess. The reasons why efficacy is different in gynecologic laparoscopy as compared with LC are a matter of speculation. Possible reasons for the lack of effect in cholecystectomy include the greater extent of dissection (especially compared to diagnostic laparoscopy), the greater amount of traction used upon the gallbladder and adjacent viscera (especially the liver) compared to the gynecologic organs, or irritation of the diaphragm from blood or bile. However, the latter possibility is discounted by our observations.

Possible differences in medication use may have been masked by the sometimes-reflexive administration of morphine in the postanesthesia care unit. Ten and eight patients in the BUPIV and SALINE groups, respectively, received morphine in the immediate aftermath of surgery, but afterward required no other analgesic medication. It is possible that the patients required only minimal medication for pain relief, but also that the initial dose of morphine was given without an assessment of need. It is notable that in the SALINE group, three patients required no analgesic medication whatsoever.

The objective indicator of postoperative pain was analgesic use. The conversion scale to equivalents of subcutaneous morphine employed in this study was conservative, according to published conversions [14, 22, 23]. Had we chosen a more liberal conversion factor (i.e., to have ascribed greater analgesic potency to intravenous morphine and oral codeine congeners), our results would not have differed. Similarly, a more conservative estimate of analgesic potency made no qualitative change.

Because the study was double-blind and neither the patient nor the data collector knew the nature of the substance given, bias in recording the pain scores is unlikely. Moreover, the visual analogue scale and 11-point rating scale (0–10) employed in this study have been validated and correlated previously in independent assessments of different types of pain [7, 15]. However, pain perception is an area of potential discrepancy because of individual differences in the interpretation of what is painful. When an individual is asked to score a subjective sensation, there is variability and potential for misinterpretation of the results.

In developing additional approaches to intraperitoneal local anesthesia for general surgical laparoscopy, it may be useful to reconsider both the choice of drug and its dosage. Lidocaine and etidocaine may be useful when applied to membranous tissues [2]. While an excellent local anesthetic when injected into tissue, bupivacaine may be less well absorbed across membranes, and may be an irritant to tissues. Also, the timing of drug delivery may require modification. If a shorter-acting agent is to be used, periodic administration may be necessary to maintain a therapeutic level of analgesia.

Conclusion

Intraperitoneal bupivacaine offered a detectable, albeit subtle benefit to patients undergoing LC. Postoperative pain was significantly reduced in the patients who received bupivacaine, but only for the first 6 h. However, postoperative analgesic medication require-

ments were not significantly different. The presence of nausea, vomiting, and shoulder pain were also not significantly different between the two groups.

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