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Randomized, controlled trial of bupivacaine injection to decrease pain after laparoscopic cholecystectomy

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Objectives: To determine if intraoperative instillation of bupivacaine would decrease early postoperative pain after laparoscopic cholecystectomy, if the patients would consequently require less narcotic postoperatively and if such patients would elect to be discharged on the day of operation if given the choice.

Design: Double-blind, randomized, controlled trial.

Setting: A tertiary care hospital in Hamilton, Ont.

Patients: Fifty patients underwent laparoscopic cholecystectomy. Day-surgery patients had the choice of staying overnight for discharge the following day. They were compared with a control group of 47 patients who had laparoscopic cholecystectomy but did not receive bupivacaine.

Intervention: Instillation of 20 mL of 0.5% bupivacaine with epinephrine into laparoscopic cholecystectomy port sites intraoperatively before closure.

Main outcome measures: Visual analogue scale (VAS) pain scores assessed 4 times postoperatively, the choice of patients to leave hospital the same day or to remain in the hospital overnight; the level of postoperative narcotic usage.

Main results: Mean VAS pain scores (range 0 [no pain] to 5 [severe pain]) at less than 2 hours and at 6 hours after surgery were 2.9 and 2.9, respectively, in the bupivacaine group compared with 4.5 and 4.0, respectively, in the control group ($p = 0.001$ and 0.025). VAS scores at 10 hours postoperatively and the next morning did not differ between the groups. More patients in the bupivacaine group elected to go home on the day of surgery ($p = 0.034$). Narcotic usage was not significantly different.

Conclusion: Instillation of bupivacaine into port sites should be standard practice for elective laparoscopic cholecystectomy.

Objectifs : Déterminer si l'instillation peropératoire de bupivacaïne réduirait la douleur postopératoire qui suit immédiatement une cholécystectomie par laparoscopie, si les patients auraient besoin par la suite de moins de stupéfiants après l'intervention et si les patients en question choisiraient de recevoir leur congé le jour de l'intervention s'ils en avaient le choix.

Conception : Étude contrôlée randomisée à double insu.

Contexte : Hôpital de soins tertiaires de Hamilton (Ontario).

Patients : Cinquante patients ont subi une cholécystectomie par laparoscopie. Les patients en chirurgie de jour pouvaient passer la nuit à l'hôpital et obtenir leur congé le lendemain. On les a comparés à un groupe témoin de 47 patients qui ont subi cholécystectomie par laparoscopie mais n'ont pas reçu de bupivacaïne.

Intervention : Instillation de 20 mL de bupivacaïne à 0,5 % avec épinéphrine dans les incisions utilisées pour pratiquer la cholécystectomie par laparoscopie, pendant l'intervention, avant la fermeture de la plaie.

Principales mesures de résultats : Évaluation de la douleur selon l'échelle visuelle analogique (EVA) quatre fois après l'intervention, choix des patients de quitter l'hôpital le jour même ou d'y passer la nuit et taux d'utilisation de stupéfiants après l'intervention.

Principaux résultats : Les évaluations moyennes de la douleur (échelle de 0 [aucune douleur] à 5

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[douleur vive]) à moins de deux heures et à six heures après l'intervention chirurgicale se sont établies à 2,9 et 2,9 respectivement, chez les sujets du groupe qui ont reçu de la bupivacaïne, comparativement à 4,5 et 4,0 respectivement chez ceux du groupe témoin (p = 0,001 et 0,025). Les résultats EVA à 10 heures après intervention et le lendemain matin n'étaient pas différents entre les groupes. Les patients qui ont reçu de la bupivacaïne et qui ont décidé de rentrer chez eux le jour même de l'intervention chirurgicale étaient plus nombreux (p = 0,034). L'utilisation des stupéfiants n'a pas différé de façon significative entre les groupes.

CONCLUSION : L'instillation de bupivacaïne dans les incisions qui ont servi à pratiquer l'intervention devrait constituer une pratique normale dans les cas de cholécystectomie par laparoscopie élective.

Laparoscopic cholecystectomy, having replaced open cholecystectomy as the standard treatment for symptomatic cholelithiasis, is now being performed on an outpatient basis. Compared with patients who undergo open cholecystectomy, patients who have laparoscopic cholecystectomy experience less postoperative pain, use smaller amounts of narcotics for postoperative pain relief and remain in the hospital for a shorter period.[1] However, patients who undergo laparoscopic cholecystectomy still have considerable pain in the immediate postoperative period.

Pain occurring immediately after laparoscopic surgery may be ameliorated by instillation of a local anesthetic agent into port sites before closure. Decreases in postoperative pain after infiltration of local anesthetics into operative wounds have been observed among patients who undergo herniorrhaphy and gynecologic procedures.[2–4] For patients who undergo groin procedures, injection of a local anesthetic to block the ilioinguinal nerve has been reported to result in less postoperative pain than that experienced by patients who received no local anesthetic.[5–7] Postoperative catheter infusion of bupivacaine into the subcostal incision during open cholecystectomy has been shown to decrease atelectasis, improve pulmonary function and reduce narcotic usage.[8,9] Continuous postoperative infusion of a local anesthetic agent into abdominal wounds has reduced both postoperative pain and narcotic requirements.[10,11]

Local anesthetic agents are widely used, have a good safety profile and are available in long-acting preparations. They provide the benefit of anesthesia without the systemic side effects that may result from use of enterally or parenterally administered drugs. Bupivacaine has a half-life of 2.7 to 3.5 hours and has been reported to provide pain control for an average of 6 hours.[12] The length of anesthesia varies with drug concentration, method of application and the use of vasoconstrictors. If epinephrine is added to a bupivacaine preparation, absorption of the bupivacaine is slowed, which allows a larger dose to be used and prolongs its effect by approximately one third.[13] For small wounds, the margin of safety of the bupivacaine dose needed for anesthesia is wide. At the upper limit of 2.5 mg of bupivacaine per kg of body weight, 100 mg of the drug can be used safely in a patient with a lean body mass of 40 kg (total body weight, 70 kg).

At our centre, we observed that patients often reported pain at the port sites after laparoscopic cholecystectomy. However, on some services, patients received a postoperative injection of bupivacaine, and these patients reported less pain. This observation led us to design a randomized, controlled, double-blind study to test the following hypotheses: patients who undergo laparoscopic cholecystectomy and receive an instillation of bupivacaine into the port sites before closure will have less pain in the immediate postoperative period; patients who receive bupivacaine will require a smaller amount of narcotic medication postoperatively; and patients who receive bupivacaine will elect to be discharged on the day of surgery if given the choice.

PATIENTS AND METHODS

After approval of the study by the Research Committee at St. Joseph's Hospital, Hamilton, Ont., patients scheduled to undergo elective laparoscopic cholecystectomy at the institution between March 1995 and June 1996 were invited to participate. All patients gave informed consent and met the following criteria: ultrasonographic proof of gallstones or sludge; age greater than 16 years; a single, planned elective procedure; and eligibility for a standard anesthesia protocol developed by the anesthesia department.

Patients who declined to participate were rare: 2 patients did not continue after randomization, stating that it was too much of a nuisance; 25 early patients were excluded because pain scores were inappropriately culled from charts before review. This problem was later remedied. The estimate of sample size was 40 patients in each arm; with 50 patients the power to detect the observed difference was greater than 90% for the first interval.

Patients were excluded from the study intraoperatively or postoperatively for the following reasons: lack of compliance in completing pain assessments, placement of a drain intraoperatively, the presence of acute pancreatitis, prolonged hospitalization to facilitate endoscopy, repair of incidental umbilical hernia during the laparoscopic cholecystectomy and documented recent narcotic abuse. Patients were screened for eligibility to undergo anesthesia. Enrolled patients participated in preoperative practice sessions that trained them in the use of the visual analogue scale

(VAS) for pain employed in the study. The VAS scores ranged from 0 (no pain) to 5 (severe pain).

No patient received preoperative or postoperative sedation. Induction of anesthesia was achieved with propofol, vecuronium bromide and fentanyl citrate and was maintained by nitrous oxide and isoflurane. Anesthesia was reversed with physostigmine and either glycopyrrolate or atropine.

Pneumoperitoneum was produced by insufflation of carbon dioxide with a Veress needle. A 12-mm subxiphoid port, a 10-mm umbilical port, and 2 5-mm ports were established in the right abdominal wall. The resected gallbladder was delivered through the subxiphoid port. After delivery of the gallbladder, the attending surgeon left the operating room to remain blinded to bupivacaine administration. The surgical resident then chose an envelope containing randomly generated instructions to instill or not to instill bupivacaine before closing the port sites. Patients who received the drug were given 20 mL of 0.5% bupivacaine (100 mg) with epinephrine (1:200 000): 6 mL was infiltrated through the abdominal wall around each of the midline port sites, and 4 mL was administered in a similar fashion at the lateral port sites.

Patients were cared for in the postanesthesia care unit (PACU) according to a standard study protocol. They were given 2 to 4 mg of morphine on demand for pain control in the PACU and were transferred to the short-stay unit about 2 hours postoperatively. Just before transfer, patients were assessed by PACU nurses using the VAS for pain. Additional VAS scores were obtained by nurses on the short-stay unit at 6 and 10 hours postoperatively and the following morning. For patients who elected to go home on the day of surgery, use of the VAS was reviewed, and the patients were asked to complete the remaining score sheets at home and return them to the surgeon's office at the follow-up visit 2 weeks postoperatively.

All patients received intramuscular injections of meperidine or took acetaminophen with 30 mg of codeine orally as requested at 4-hour intervals postoperatively, along with diphenhydramine administered intramuscularly or orally.

The operative control sheet was included in the chart in the event that it needed to be referenced. However, neither the PACU nor ward nurses knew that the information was available. The patients were thoroughly blinded to the intervention as was the surgeon. Attending surgeons made rounds on the afternoon of surgery and offered patients the option of being discharged that day or remaining in the hospital overnight.

Pain assessments were standardized to occur before the patient left the PACU and at standard times on the ward, coincident with medication administration time. Total narcotic dosage taken in the PACU and the short-stay unit, and the day of hospital discharge for the patients who received bupivacaine were compared with those variables for patients who received no local anesthesia. Statistical techniques used were Student's t-test and the χ^2 test. Narcotics given in the PACU were measured in milligrams of morphine; those given in the short-stay unit were measured in milligrams of meperidine. Codeine amounts were recorded according to standard equivalent values in meperidine. Patients were expected to experience the greatest effect of the bupivacaine shortly postoperatively, so the PACU data were analysed separately from the ward data to detect any early differences between groups. Differences were considered significant at a probability level less than 0.05.

Results

Fifty patients (41 women, 9 men; mean [and SD] age 45.8 [13.8] years; mean weight 77.7 [21.7] kg) received bupivacaine. The control group comprised 47 patients (40 women, 7 men; mean age 46.0 [15.7] years; mean weight 78.7 [16.2] kg). The patients in the 2 groups were similar with respect to age, weight and sex distribution.

No postoperative complications were noted in either group during hospitalization or at the 2-week follow-up visit. For the 4 pain-assessment times, mean scores on the VAS ranged from 2.7 to 2.9 for the bupivacaine group and from 2.8 to 4.5 for the control group (Table I). Compared with patients who received no local anesthetic agent, patients given bupivacaine experienced a 36% reduction in pain while in the PACU (less than 2 hours postoperatively) (p = 0.001), a 28% reduction 6 hours postoperatively (p = 0.025), a 20% reduction 10 hours postoperatively (p = 0.142) and a 4% reduction (p = 0.819) the next morning. Therefore, bupivacaine provided a significant reduction in pain during the first 6 hours after surgery.

There were no significant differences between the groups in the total

Table I

Mean (and SD) Visual Analogue Scale (VAS) Pain Scores* Postoperatively for Patients Given Bupivacaine Compared With Those Not Receiving Bupivacaine (Control)

Postop assessment time, h	Bupivacaine group	Control group	Difference, %	p value
< 2	2.9 (2.2)	4.5 (2.3)	36	0.001
6	2.9 (2.2)	4.0 (2.4)	28	0.025
10	2.7 (1.8)	3.4 (2.4)	20	0.142
Next morning	2.7 (2.0)	2.8 (2.4)	4	0.819

*Range from 0 (no pain) to 5 (severe pain)

dosages of narcotics given in either the PACU or the short-stay unit. Significantly more patients in the bupivacaine group than in the control group chose to go home on the evening of their operation (Table II). Thus, two thirds of the patients who received bupivacaine were discharged on the day of surgery, whereas fewer than half of the patients in the control group went home then. Overall, however, patients who chose same-day discharge did not have significantly lower pain scores than those who elected to be discharged the next day (Table III).

Discussion

Controversy exists about the principal source of pain after minor laparoscopic procedures. Some clinicians maintain that the placement of trocars through the abdominal wall is the primary source. Others believe that most pain arises from the intraperitoneal dissection,[14,15] although intraperitoneal irrigation with local anesthetic agents has failed to show a benefit that would support this theory. Preincisional injection of 0.5% bupivacaine (32 mL) at port sites was found ineffective in one study, but pain was not measured until 5 hours postoperatively.[14] The effects of bupivacaine may be very diminished by that time, and the advantages of the agent in providing pain control immediately after surgery may be hidden by late assessments of pain. Therefore, in this study we evaluated pain while patients were still in the PACU and at 4 other postoperative times.

The effect of an injection of bupivacaine on postoperative pain can best be measured in the absence of residual activity of the general anesthetic agents given. It is unlikely that the administration of bupivacaine would affect nausea or vomiting. Patients experiencing less pain may be less likely to be nauseated and vomit, but the difference between groups in this regard was expected to be small. We used a standard protocol of short-acting induction agents and inhalation maintenance anesthetic agents to ensure that anesthesia was minimal at the end of the procedure. Preoperative and postoperative sedation, which might also have affected the pain-score measurements, was specifically avoided.

We found a large variation in pain scores at each of the assessment times. Aside from individual differences in pain perception, several other patient or technical factors may have affected the scores. First, patients who suffer from chronic pain may report pain that is unrelated to their surgical procedure. If such patients rely on narcotic medications preoperatively, they may have an increased tolerance to analgesic agents and may feel more intense pain in response to a given stimulus. Second, the bupivacaine was infiltrated in a standard fashion after the ports were removed. However, ports are often inserted obliquely through the abdominal wall. Therefore, instillation of bupivacaine alongside the ports before their removal rather than afterward may have facilitated more direct delivery of the drug to the tissues traumatized by port insertion. Third, in some patients the epigastric incision had to be widened for intact removal of the gallbladder, and this widening may have resulted in higher pain scores. Fourth, given that the entire thickness of the abdominal wall was infused with bupivacaine, a larger volume of the agent with a weaker concentration may have been more uniformly effective.

Despite the large variation in pain scores, we did detect significant differences in mean pain scores between the bupivacaine and control groups at the first 2 assessment times, which spanned a period of 6 hours. Although we expected the effect of the local anesthetic to diminish after this time, there was no increase in pain scores at the third pain assessment in the patients who received bupivacaine. For the control group, pain scores peaked immediately after the surgical procedure and then declined to a level comparable to that for the bupivacaine group by the third assessment. Therefore, the main effect of bupivacaine in this study seems to have been amelioration of the pain peak occurring immediately after the procedure. On average, patients given bupivacaine were as free of pain within 2 hours after surgery as they were at discharge, either on the day of surgery or the next morn-

Table II

Time of Discharge Chosen by Bupivacaine and Control Groups of Patients

Discharge time	Bupivacaine group, no. (and %)	Control group, no. (and %)
Same day	33 (66)	20 (43)*
Next day	17 (34)	27 (57)*

*$p = 0.034$ compared with bupivacaine group by the χ^2 test.

Table III

Mean (and SD) VAS Pain Scores in Relation to the Time of Discharge for Bupivacaine and Control Groups of Patients

Postop assessment time, h	Time of discharge			
	Bupivacaine group		Control group	
	Same day	Next day	Same day	Next day
< 2	2.5 (2.2)	3.4 (2.2)	4.5 (2.3)	4.5 (2.4)
6	2.6 (2.2)	3.4 (2.1)	3.2 (2.3)	4.5 (2.3)
10	2.7 (1.9)	2.7 (1.6)	3.2 (2.7)	3.6 (2.7)
Next morning	2.8 (2.2)	2.6 (1.6)	2.8 (2.5)	2.8 (2.5)

ing. The difference between the groups has important implications for institutions in which performance of laparoscopic cholecystectomy as an ambulatory procedure is encouraged.

We found no appreciable difference in narcotic use between the control and bupivacaine groups. Given the significant differences in mean pain scores between the 2 groups at the first 2 assessment times, this finding was unexpected. However, a trend toward lower pain scores in the absence of significant differences in narcotic requirements has been observed in several previous investigations,[4,14–16] and this trend occurred regardless of whether patients were given patient-controlled analgesia or were asked by a nurse whether they needed a pain-relieving medication. If there is a threshold of pain beneath which pain medication is not generally required, it has not been consistently achieved in laparoscopic cholecystectomy.

More patients in the bupivacaine group than in the control group chose to go home on the day of surgery. However, patients who chose same-day discharge did not uniformly have significantly lower pain scores than those who stayed in hospital overnight, although there was a nonsignificant association between lower pain scores and same-day discharge. Many factors (for example, availability of family members and transportation) influence patients' decisions about the timing of discharge. These factors should have been randomly distributed between the 2 groups in this study, allowing the extent of postoperative pain to be the deciding factor in this determination. Perhaps a larger number of patients would be required to show a significant relation between amount of pain and patient-selected length of hospital stay.

If laparoscopic cholecystectomy is to be a routine ambulatory surgery procedure, the pain experienced by patients immediately after the procedure must be addressed. Our study showed that injection of bupivacaine into the port sites at closure diminishes the peak of pain occurring immediately after surgery. Any reduction in such pain is clinically relevant, particularly if it is statistically significant. Whether the lower pain scores translated into increased patient functionality is questionable. However, at whatever level they functioned they did so more comfortably and were more inclined to spend the remainder of the day at home instead of in the hospital. This simple, inexpensive, effective technique thus improves the postoperative in-hospital course. We advocate its use in all elective laparoscopic cholecystectomies.

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