



# A randomized double blinded study to determine the effectiveness of utilizing intraperitoneal bupivacaine: Does it reduce postoperative opioid use following laparoscopic appendectomy?



Karlin Sevensma<sup>a,\*</sup>, Thomas Schleichert<sup>a</sup>, Caroline Schwickerath<sup>a</sup>, Alan Shoemaker<sup>b</sup>, Clayton Miller<sup>a</sup>

<sup>a</sup> Metro Health University of Michigan Health, 5900 Byron Center, Wyoming, MI, 49519, USA

<sup>b</sup> Biostatistician Calvin College, Grand Rapids, MI, 40506, USA

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## ABSTRACT

**Background:** Improving postoperative pain control may lead to improved outcomes including decreased opioid use, shorter hospital stays, and improved patient satisfaction. This study examined the effects of instilling intraperitoneal bupivacaine following laparoscopic appendectomy.

**Methods:** In this prospective, randomized, double-blinded, placebo-controlled study, patients with appendicitis were randomized to receive either the bupivacaine or normal saline instilled at the appendectomy site prior to close. Postoperative pain scores, opioid doses and length of stay were recorded.

**Results:** Pain scores were lower (mean 2.48 versus 3.8;  $p = 0.014$ ), and postoperative opioid use was lower (mean 7.394 mg versus 16.921 mg;  $p = 0.007$ ) in the bupivacaine group.

**Conclusions:** Instilling bupivacaine at the base of the cecum at the conclusion of laparoscopic appendectomy was associated with reducing postoperative pain scores and in hospital opioid use.

**Statement:** This prospective, randomized, double-blinded, placebo-controlled study enrolled subjects with acute appendicitis undergoing laparoscopic appendectomy. Subjects were randomized to receive either bupivacaine or normal saline intraperitoneally at the close of surgery. In the bupivacaine group, pain scores at 1 h were improved and inpatient postoperative opioid use was less.

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## Introduction

Laparoscopic appendectomy is a commonly performed procedure for patients who present with acute appendicitis. Despite the development of minimally invasive surgery, patients continue to experience postoperative pain that can require the use of opioid medication. Opioids have many deleterious side effects including decreased gut motility, nausea, vomiting, urinary retention, and the potential to develop dependence. The ability to improve a patient's postoperative pain control may lead to improved outcomes including decreased opioid use, shorter hospital stays, and improved patient satisfaction.

Local anesthetic is often infiltrated at incision sites during laparoscopic appendectomy. This practice has been extensively studied in order to identify the optimum method for local

anesthetic infiltration at the incision sites.<sup>1–3</sup> Placement of local anesthetic intraperitoneally at the time of surgery is less common and less well studied. A few studies have evaluated postoperative pain scores using the visual analog scale after instilling intraperitoneal local anesthetic.<sup>4–6</sup> However, results have been variable with respect to opioid use after local anesthetic instillation. One study examined the use of preemptive intraperitoneal anesthetic in patients undergoing laparoscopic appendectomy, wherein 2 mg/kg ropivacaine or normal saline was instilled at initiation of pneumoperitoneum. In this study, opioid use was significantly lower and pain scores were also lower in the ropivacaine group compared to the saline group.<sup>7</sup> Many of the studies examining intraperitoneal local anesthetic use have involved long hospital stays and the use of patient-controlled analgesia, making those studies less applicable to current practice.<sup>4,5,7</sup>

Given the ongoing opioid abuse epidemic, providing appropriate surgical care while delivering more effective postoperative pain control with minimal opiate-based pain medications is an

\* Corresponding author.

E-mail address: [karlin.sevensma@metrogr.org](mailto:karlin.sevensma@metrogr.org) (K. Sevensma).

important topic. The primary aim of this study was to determine the effectiveness of postoperative pain control by using intraperitoneal bupivacaine at the conclusion of laparoscopic appendectomy. We hypothesized that instilling local anesthetic near the cecum following a laparoscopic appendectomy would decrease the amount of opioid medications a patient would require postoperatively. A secondary aim was to determine if postoperative length of stay could be impacted.

## Methods

This study was designed as a prospective, randomized, double-blinded, placebo-controlled study. Prior to starting the study, a power calculation was performed using Satherwaite's *t*-test, which determined the minimum sample size to be 100 patients, with 50 in each arm. Opioid-naïve, adult patients were enrolled upon admission to the hospital with the diagnosis of acute appendicitis and plans for laparoscopic appendectomy. Enrollment occurred over an 18-month period from 2016 through 2017. Patients included in the study were at least 18 years of age and underwent non-elective laparoscopic appendectomy for acute appendicitis. Patients were excluded if they were unable to give consent, non-English speaking, opioid-dependent, or allergic to local anesthetic. Patients with known malignant disease were also excluded.

Patients to be enrolled into the study underwent informed consent and were provided informational documents and contact information. An envelope randomization scheme was used to assign patients to the bupivacaine group or to the saline group. The operating room circulating nurse was the only individual privy to which solution was administered. The remainder of the operating room personnel was blinded to the agent used. Patients were randomized to receive either 20 mL of 0.5% bupivacaine without epinephrine (100 mg dose) or 20 mL normal saline instilled at the appendectomy site after all irrigation and aspiration of intraperitoneal fluid was completed and prior to evacuating pneumoperitoneum.

Ten surgeons participated in this study. All of the surgeons used a three port laparoscopic appendectomy technique. All of the surgeons infiltrated local anesthetic into the skin and deep tissues at each of the port sites.

Following surgery, pain scores were recorded at regular intervals by nursing staff according to standard hospital protocol. The pain scores at 1 h, 2 h, 4 h, and 12 h (as applicable) were recorded. Some patients were discharged prior to the 12-h pain score, and thus pain scores from all 4 intervals were not available for every patient. Postoperative length of stay was calculated as time from incision closure to time of discharge in minutes. Time of discharge was recorded in the medical record as the time the patient left the hospital. Patients were discharged from the hospital with a prescription for hydrocodone 5mg/acetaminophen 325 mg tablets. The patients were seen in follow up by their surgeons. Their records were reviewed to examine return visits to the emergency department within the first 24 h after surgery.

The amount of opioid medication administered preoperatively and postoperatively was abstracted from the medication administration record and recorded separately for each patient. The amount of opioid was converted to equivalent intravenous morphine sulfate doses in milligrams (mg), which allowed for a standardized comparison. Calculations regarding post-operative opioid doses were performed between the bupivacaine and control groups, then a separate calculation was performed with pre-operative opioid as a covariate.

Operative time in minutes was used as a surrogate for anesthetic dose. Another covariate analysis was performed to determine the effect of operative time on any differences between the two groups.

Group differences regarding categorical variables were compared using a Chi-square test, and continuous variables were compared using ANOVA. We considered P values of less than 0.05 statistically significant. The study proposal was submitted to the institutional review board at Metro Health University of Michigan Health prior to initiation of the study and was approved. Ongoing approval for the study was obtained as needed over the course of the data collection period.

## Results

One hundred and one patients were enrolled in the study with fifty-three patients randomized to the bupivacaine group and forty-eight randomized to the saline group. No significant differences were found between the two groups in regards to sex, race, body mass index, procedure time, estimated blood loss and pre-operative opioid use. There were no complications associated with instilling intraperitoneal bupivacaine at the time of surgery. There were no return visits to the emergency department at the study hospital within 24 h of discharge in either group. Pain scores at 1 h were found to be significantly improved in the bupivacaine versus the saline group (mean 2.48 vs 3.8;  $p = 0.014$ ). Pain scores were found to be improved, but not significantly, in the bupivacaine versus the saline group at 2 h (mean 3.54 vs 4.18;  $p = 0.251$ ), at 4 h (mean 3.54 vs 4.44;  $p = 0.106$ ) and at 12 h (mean 3.20 vs 3.74;  $p = 0.436$ ). Postoperative length of stay was found to be significantly improved in the bupivacaine versus the saline group (mean 683.2 min vs 1372 min;  $p = 0.023$ ). Postoperative opioid converted to milligrams of intravenous morphine sulfate equivalents was found to be significantly improved in the bupivacaine versus the saline group (mean 7.394 mg vs 16.921 mg;  $p = 0.007$ ) (Table 1).

Due to the unequal distribution of patients with perforated appendicitis between the bupivacaine group and the saline group, a subset analysis was performed to ensure that the necessarily longer hospital stays and potential for greater post-operative pain in patients with perforated appendicitis did not skew the results of the study. Again, no significant differences were found between the two groups in regards to sex, race, body mass index, procedure time, estimated blood loss and pre-operative opioid use. This subset analysis of non-perforated appendicitis had fifty-two patients in the bupivacaine group and thirty-nine patients in the saline group. Post-operative pain scores at 1 h were found to be significantly improved in the bupivacaine group versus the saline group (mean 2.51 vs. 4.09,  $p = 0.006$ .) Post-operative pain scores at 2 h, 4 h and 12 h were found to be less in the bupivacaine group but not significantly so. Post-operative opioid use was significantly less in the bupivacaine group than in the saline group (6.703 vs. 12.987;  $p = 0.006$ .) Post-operative length of stay was also less in the bupivacaine group, but this was no longer significant (658.90 vs 794.62;  $p = 0.0229$ ) (Table 2.)

Two covariate analyses were undertaken to account for the effects of pre-operative opioid use and also to account for operative time. Operative time in this case was offered as a surrogate for anesthetic dose. With procedure times as a covariate, analysis of covariance showed that pain scores at 1 h ( $p = 0.007$ ) and post-operative opioid use ( $p = 0.007$ ) were significantly different between the two groups. The addition of pre-operative opioid as a covariate did not change the findings between the groups. The difference between the pre-operative opioid use was also not significant between the bupivacaine and saline groups.

## Discussion

In this study of intraperitoneal bupivacaine use during laparoscopic appendectomy, postoperative pain scores at 1 h and

**Table 1**

	Saline Group (N = 48)	Bupivacaine Group (N = 53)	P-value
Sex			
Female	26	21	0.166
Male	22	32	
Race			
Black	0	2	0.376
Hispanic/Latino	1	2	
Caucasian	47	1	
Unknown	0	48	
BMI	30	28.6	0.305
Procedure Time (minutes)	46.3	47.7	0.694
Pre-op opioid dose	9.4	6.7	0.110
EBL	11	13.3	0.423
Number perforated	9	1	0.006
Complications	0	0	N/A
Length of stay (minutes)	1372	683	0.023
Post-operative opioid (IV morphine equivalent)	16.9	7.4	0.007
Pain score 1 h	3.8	2.5	0.014
Pain score 2 h	4.2	3.5	0.251
Pain score 4 h	4.4	3.5	0.106
Pain score 12 h	3.7	3.2	0.436

postoperative opioid use were significantly improved in the bupivacaine group when compared to the saline group. There was a trend toward improvement in postoperative pain scores at all other postoperative times, however, these data points were not statistically significant. This finding is in line with the known duration of action of bupivacaine, which has a peak effect at 30–45 min and lasts between four and 8 h.<sup>8</sup>

Past work on this topic analyzed instillation of local anesthetic at the start of the operation, whereas this study looked at instilling local anesthetic at the end of the procedure. Evidence suggests that both methods are effective, though presently it is uncertain which one is most effective. Similarly, several long-acting local anesthetics have been tried as intraperitoneal agents, and the most effective one has yet to be determined. It has been demonstrated, however, that instilling local anesthesia during laparoscopic appendectomy does benefit the patient in terms of a measurable reduction in postoperative pain scores and decreased opioid use.<sup>4–7</sup> Kim et al. found that intravenous lidocaine injection was as effective at reducing post-operative pain as intraperitoneal administration.<sup>4</sup> This raises the question of whether intraperitoneal local anesthetic is effective because of its local effects or because it is absorbed systemically. Further research could be done to help maximize the benefits of intraperitoneal local anesthetic by comparing various local anesthetic agents and the timing at which they are administered, as well as the effectiveness of concomitant skin, deep tissue and intravenous local anesthetic administration.

One of the limitations of this study is that anesthesia was not standardized among the patients, and intraoperative opioids, if any, were not standardized. A larger study may be able to better compensate for differences in anesthesia requirements. A second limitation of this study is the lack of standardization in the type and quantity of local anesthetic infiltrated at the incision sites, though all surgeons involved in the study infiltrated local anesthetic at

each port site. Additionally, the location of the port sites was not standardized between surgeons. Lastly, pain after discharge was not recorded, nor was opioid use at home. These components of postoperative care would be interesting to examine with future research, as this would determine whether or not intraperitoneal local anesthetic has an impact on outpatient and overall opioid requirements.

Additionally, the saline group contained nine patients with perforated appendicitis, and the bupivacaine group contained only one. This presented a concern when comparing both postoperative opioid use and length of stay, since patients with perforated appendicitis typically have more pain and stay in the hospital longer than those with non-perforated appendicitis. The subset analysis of patients with non-perforated appendicitis showed improvement in pain scores at 1 h and decreased postoperative opioid use, and those results remained statistically significant in the bupivacaine versus the saline group. Postoperative length of stay remained improved, however, was no longer statistically significant. Further research with a larger sample size or an even distribution of perforated appendicitis may be able to more accurately determine the effect of intraperitoneal bupivacaine on length of stay in both perforated and non-perforated appendicitis. Based upon these data, length of stay is not affected by the use of intraperitoneal bupivacaine.

Instilling bupivacaine at the conclusion of laparoscopic appendectomy has a statistically significant effect on reducing both postoperative pain scores and postoperative opioid use in the hospital. There may be an impact on postoperative length of stay, though that was not conclusively shown in this study. There were no complications identified in association with the practice. These findings support the value of liberal local anesthetic use at the time of surgery for the purposes of postoperative pain control. Decreasing postoperative opioid use by placing bupivacaine

**Table 2**

Subset analysis, non-perforated appendicitis.

	Saline Group (N = 43)	Bupivacaine Group (N = 52)	P-value
Length of stay (minutes)	794.62	658.90	0.229
Post-operative opioid (IV morphine equivalent)	12.987	6.703	0.006
Pain score 1 h	4.09	2.51	0.006
Pain score 2 h	4.44	3.60	0.162
Pain score 4 h	4.68	3.50	0.053
Pain score 12 h	4.47	3.26	0.117

intraperitoneally may also have ramifications for society, as the medical community is attempting to minimize the amount of opioid used. Decreasing pain after a major operation may increase patient satisfaction with the procedure and improve the experience of interfacing with the medical profession. This study did not measure patient satisfaction scores, but this could be evaluated in future studies. Based upon the available data, instilling bupivacaine at the appendiceal base at the conclusion of laparoscopic appendectomy can be considered beneficial.

### Conflicts of interest

The authors declare no conflict of interest.

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