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Liposomal Bupivacaine Injection for Analgesia During Minimally Invasive Supracervical Hysterectomy

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ABSTRACT

Objective: To evaluate the efficacy of intracervical injection of liposomal bupivacaine for postoperative pain control among women undergoing minimally invasive supracervical hysterectomy.

Methods: A randomized double-blinded placebo-controlled trial of intracervical injection of combination liposomal bupivacaine and bupivacaine for postoperative pain among patients undergoing laparoscopic and robotic supracervical hysterectomy. Patients were enrolled between October 1, 2018 and April 30, 2019. The primary outcome was pain at 12 hours postoperatively using a numeric rating scale from zero to 10. Pain scores were also recorded pre-operatively, immediately postoperatively, at 12, 24, and 48 hours postoperatively. The secondary outcome was the number of patients who required opioid analgesic medications up to 48 hours postoperatively.

Results: Sixty participants were randomized into the control (n = 30) and intervention (n = 30) groups. Pain scores were 1 and 1.75 (p = 0.89) immediately postoperatively, 3 and 3.5 (p = 0.85) at 12 hours, 3.5 and 5 (p = 0.22) at 24 hours, and 2.75 and 4 (p = 0.18) at 48 hours for the control and intervention groups, respectively. Within the first 24 hours, 10 patients in the control and 14 patients in the intervention group used narcotics (p = 0.37). From the 24 to 48 hours window, 6 and 8 patients in the control and intervention groups used narcotics (p = 0.74), respectively.

Conclusion: There was no statistically significant difference in pain scores between patients receiving combination liposomal bupivacaine and bupivacaine intracervical block and those receiving placebo in the first 48 hours after surgery. There was no difference in analgesic use between the two study groups.

Key Words: Supracervical hysterectomy, Liposomal bupivacaine, Intracervical injection, Postoperative pain.

INTRODUCTION

More than 600,000 hysterectomies are performed annually in the United States, with the majority performed for benign indications. Among these, the proportion performed abdominally and vaginally is decreasing, whereas laparoscopic and robot-assisted laparoscopic hysterectomies are increasing.[1] Postoperative pain control for patients undergoing these procedures is important given its impact on their experiences and recoveries.

Because of the opioid epidemic in the United States, there has been a focus on decreasing the number of opioids prescribed by physicians. As of 2014, 2 million Americans suffered from substance abuse disorders involving prescription medications.[2] The mainstay of pain control after surgery has been opioids, both in the hospital setting and at home. While patients who undergo minimally invasive surgery tend to take fewer opioids, any opioid exposure can potentiate abuse disorder. This further demonstrates the need for alternative postoperative pain management techniques.

Bupivacaine has a long history of use in the surgical setting, and its efficacy, when administered perioperatively via wound infiltration for acute postoperative surgical pain, is well established.[3] A novel formulation of bupivacaine, i.e., liposome bupivacaine, has been developed to address the need for long-acting local anesthetics that can be administered in a single dose. Liposomal bupivacaine is believed to be effective for up to 72 hrs.[4]

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Paracervical and intracervical injections are used for procedures that require cervical manipulation in various obstetrical and minor gynecological procedures. One study showed that during office hysteroscopy, paracervical block with lidocaine was superior to nonsteroidal anti-inflammatory drugs, topical anesthetics, and misoprostol in decreasing pain during and after the procedure.[5]

Recently published data highlighted the impact of bupivacaine used in major procedures like hysterectomies. One study found that a paracervical block with 00.5% bupivacaine immediately before starting a laparoscopic hysterectomy decreased one-hour postoperative pain scores when compared to a placebo.[6] Similarly, another study found that paracervical block using 00.5% bupivacaine in women undergoing total laparoscopic hysterectomies reduced postoperative pain scores by 25% and reduced opioid consumption by 47% in the first hour postoperatively when compared to placebo injection with saline.[7]

Recently, the use of liposomal bupivacaine was used to examine pain control after posterior vaginal surgery.[8] Results demonstrated no difference in pain scores among women who received an injection of liposomal bupivacaine intraoperatively vs. placebo on postoperative days 1, 3, and 7.[8] There was also no difference in postoperative opioid use between the groups.[8]

Data on liposomal bupivacaine use during hysterectomy is scant. One study shows that postoperative day 3 pain scores after laparoscopic and robotic hysterectomies were decreased with port site injection of liposomal bupivacaine vs. 0.25% bupivacaine alone.[3]

Given the success of intracervical bupivacaine and liposomal bupivacaine port site injection in reducing postoperative pain after hysterectomy, intracervical liposomal bupivacaine may reduce pain and opioid use. The main objective of this study was to evaluate the efficacy of intracervical injection of liposomal bupivacaine in postoperative pain control among patients undergoing minimally invasive supracervical hysterectomy. Identifying effective ways to decrease postoperative pain can decrease the need for supplemental opioid pain medications, lead to fewer opioid-related adverse events, and promote a better recovery experience for patients.

MATERIALS AND METHODS

We performed a randomized double-blind placebo-controlled study of women who underwent a minimally invasive (robot-assisted or laparoscopic) supracervical hysterectomy. Intracervical injection with either a combination of liposomal bupivacaine and bupivacaine or placebo injection was given at the time of uterine manipulator insertion, and postoperative pain scores, as well as opioid consumption, were accessed thereafter.

Women between 35 – 75 years of age who were scheduled for a minimally invasive (robot-assisted or laparoscopic) supracervical hysterectomy were considered for the study. Patients had to have the ability to provide informed consent, adhere to the study visit schedule, and complete all study assessments and language-specific questionnaires.

Women were excluded if they used any of the following medications within a specified time before surgery: opioids, selective serotonin reuptake inhibitors, tricyclic antidepressant, gabapentin, or pregabalin within three days of surgery; or use of acetaminophen within 24 hours of surgery. Patients with comorbidities known to cause chronic pain, such as rheumatoid arthritis or chronic neuropathic pain were excluded. Patients undergoing additional surgical procedures at the time of the supracervical hysterectomy were excluded. Chronic users of analgesic medications were also excluded, including patients taking opioid medications for more than 14 days in the last three months, or nonopioid pain medications more than five times per week.

Additional exclusion criteria included current use of systemic gluco-corticosteroids or use of glucocorticoids within one month of enrollment into this study; history of hepatitis (other than hepatitis A); history of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past two years; failure of the presurgical drug and alcohol screen; history of hypersensitivity or idiosyncratic reactions to amide type local anesthetics, opioids, or propofol; administration of an investigational drug within 30 days prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study; uncontrolled anxiety, schizophrenia, or other psychiatric disorder that could interfere with study assessments or compliance; significant medical conditions or laboratory results that indicated an increased vulnerability to study drug and procedures, and expose subjects to an unreasonable risk; any clinically significant event or condition uncovered during the surgery that might render the subject medically unstable or complicate the subject's postoperative course (e.g., excessive

bleeding, acute sepsis); and an incision length greater than 3 cm.

After obtaining informed consent, participants were randomly assigned to the intervention or placebo arm. Randomization was carried out utilizing a computer-based statistical program, statistical package for the social sciences (SPSS) version 24, that generated patient assignment to each arm in a block size of 10 for a total of 60 patients. The pharmacy packaged each investigational medication as per assignment in amber plastic bags that were available for pick up by the study personnel and given to the resident physician for injection before the procedure. The placebo consisted of injecting 20 mL of sodium chloride 00.9%. The interventional arm consisted of 10 mL of 0.25% bupivacaine HCL mixed with (133 mg) 10 mL of liposomal bupivacaine injection suspension.

The gynecologic surgeon and the patient were blinded and were unaware of whether the syringe used for the injection contained the study drug or placebo. However, the pharmacy was not blinded. One of two minimally invasive gynecologic surgery fellows performed the injection either alone or along with a resident physician. For all cervical injections patients received 10 ml at the 3 o'clock location and 10 ml at the 9 o'clock location. A short video on how to perform the injection was reviewed before injection to diminish differences in injection technique.

The severity of pain at rest was assessed pre-operatively in the holding area, on arrival to the postanesthesia care unit (PACU), and 12, 24, and 48 hours postoperatively using a numeric rating scale (NRS) with the primary outcome being the 12 hour time point. A score of 0 meant no pain and 10 meant the worst possible pain. Pain scores were obtained by directly asking the patient to rate their pain while still in the PACU and the patients were called at home for the remaining pain scores.

When the patients were at home, they completed a pain medication diary that was provided before discharge. In the diary, patients recorded their pain medication usage (opioid) for 48 hours postoperatively. The patients then brought the diary to their two-week postoperative visit and/or mailed it for assessment. For each returned diary, a 25 dollar gift card was provided. If diaries were not returned, then postoperative pain medication usage was obtained from the patient via phone call. Phone calls were conducted by a research assistant who was also blinded.

The sample size for our study was based on the results from a double-blinded randomized controlled trial comparing postoperative pain scores among patients who received a paracervical block using bupivacaine vs placebo.[6] Assuming their 60-minute time point with a mean of 5.9 and a standard deviation of 3.0, we would have with 80% power, and $\alpha = 0.05$, to detect a difference in NRS of 2.36, given a sample size of 21 subjects per group.

RESULTS

Between October 1, 2018 and April 30, 2019, we screened 70 patients and consented 60. Ten patients either met one of the exclusion criteria listed above or chose not to participate. Complete postoperative pain scores were collected for 58 out of the 60 patients. Two patients did not have complete pain scores recorded for all time points. All surgeries were performed by one of four high-volume gynecologists who each have more than five years of experience in practice.

There were no significant differences between the women in the control group and the intervention groups in regard to age, uterine size, and surgical time. The body mass index (BMI) for the control group and intervention group was 29.7 and 27 respectively ($p = .0421$) (**Table 1**).

Baseline pre-operative pain values were 0 for all patients in the study. The immediate postoperative pain scores were 1.0 and 1.75 ($p = .89$), for the control and intervention groups, respectively. Follow up pain scores were 3.0 and

Table 1.
Clinical and Demographic Characteristics of Women in the Control and Intervention Groups

	Placebo	Bupivacaine/Liposomal bupivacaine	*P* Value
N	30	30	
Age	47 (44 – 50)	45.5 (43 – 49)	0.5023
Body Mass Index	29.65 (26.4 – 33.4)	27 (24.6 – 31.2)	0.0421
Uterine size (gram)	170 (100 – 273.7)	218.5 (110 – 389)	0.3029
Operative Time (min)	180 (120 – 240)	167.5 (110 – 239)	0.8517

Table 2.
Pain Scores at Pre-operative, Immediate Post-operative, 12, 24, and 48 Hours (Range of Responses)

	Placebo	Bupivacaine/Liposomal bupivacaine	*P* Value
Pre-operative	0 (0 – 0)	0 (0 – 0)	0.9595
Postoperatve	1 (0 – 5)	1.75 (0 – 4)	0.8881
12	3 (2 – 6.5)	3.5 (1.5 – 6.25)	0.8526
24	3.5 (2 – 6)	5 (3 – 6)	0.2227
48	2.75 (1.5 – 4.75)	4 (2.5 – 5)	0.1873

3.5 (p = .85) at 12 hours, 3.5 and 5.0 (p = .22) at 24 hours, and 2.75 and 4.0 (p = .18) at 48 hours (**Table 2**). None of the differences in pain scores were statistically significant.

Data regarding the use of alternative analgesia was only recorded by 39 patients out of the 60 patients. Thirteen control patients and 15 intervention arm patients used opioids postoperatively (**Table 3**). Within the first 24 hours, 10 patients in the control and 14 patients in the intervention group used opioids. Between 24 and 48 hours, 6 and 8 patients in the control and intervention groups used opioids, respectively. These differences were not statistically significant.

DISCUSSION

The current study expands upon the scant literature on the topic of liposomal bupivacaine use in patients undergoing minimally invasive supracervical hysterectomy. We found no significant difference in postoperative pain scores between the control and the intervention arms at any of the time points analyzed.

Data on the impact of intraperitoneal local anesthetic injection on pain scores for women undergoing gynecologic surgery are conflicting. However, a 2021 systematic review and meta-analysis analyzing the use of local anesthetic on postoperative pain after laparoscopic gynecologic procedures found that intraperitoneal injection of local analgesia significantly reduced pain at 6-hours after surgery.[9] Nevertheless, the methods of administering intraperitoneal analgesia varied widely between the studies, including installation, nebulization, spray, and pelvic administration through drains. None of the studies included intracervical injection of analgesia. This speaks to the importance of future studies investigating various methods and sites of injection of local analgesia to determine possible beneficial pain-reducing techniques.

Information regarding the secondary outcome, alternative postoperative pain medications, was only collected for 39 of the 60 study participants which limits the analysis of this outcome. However, a substantial number of those participants did not use opioids. Thirteen individuals in the control group and 15 in the intervention group used opioids. However, approximately 50% of patients in each group were given a prescription for opioids that was neither filled nor used. This adds to the large amount of data stating that minimally invasive surgical techniques lead to decreased opioid use when compared to abdominal hysterectomy, as well as the need to modify opioid prescribing practices.

This study had many strengths, one of which was obtaining pain scores up to 48-hours after surgery, which was not assessed in the study by Radtke et al.[6] That study followed 41 patients after a total laparoscopic hysterectomy at 30- and 60-minutes and reported pain scores of 5.7 vs 3.2, and 5.9 vs 2.3 (control vs bupivacaine paracervical block respectively). Their findings were statically significant and are important for pain management in the

Table 3.
Use of Opioids during the Postoperative Period

	Placebo	Bupivacaine/Liposomal bupivacaine	*P* Value
Opioid Use	13 (56.5%)	15 (60.0%)	1.0000
Within 24 hours	10 (45.5%)	14 (60.9%)	0.3762
24 – 48 hours	6 (27.3%)	8 (34.8%)	0.7494

hospital during the recovery period. However, the benefit to using longer pain score time frames, as in our study, is that the results can potentially impact pain management while patients are at home.

Another strength was the completeness of the follow-up. We were able to call and record complete pain scores for 58 out of 60 patients up to 48 hours postoperatively. There were no adverse effects noted by the patients at the given timed intervals.

One of the limitations of the study was only 39 out of 60 patients completely filled their pain diaries limiting our secondary outcome assessment. We were only able to comment on the use of opioid medication, but could not evaluate possible dosage differences between the two groups.

An additional limitation of the study was the statistically significant difference in BMI between the control and intervention arms of the study after randomization. The BMI difference between the groups was small (average of 29.65 in the control group and 27 in the intervention group), which brings into question the clinical significance of this finding.

Cervical injection in this study was performed by resident physicians under the guidance of a minimally invasive gynecologic surgery fellow or the fellow alone. While this design technique was pragmatic, it serves as a limitation of the study. Injections were performed by various providers with different levels of training. Everyone who performed the injection watched a video demonstrating the proper technique, but this does not ensure uniformity among injections.

Although this study did not show a statistically significant benefit to the use of intracervical injection of liposomal bupivacaine, it does reinforce the finding that the minimally invasive approach is associated with low postoperative pain scores and minimal use of opioids. Many patients reported that they did not use opioids. Moving forward we hope to continue to investigate patients' postoperative pain experiences, understand their expectations of care, educate our patients on postsurgical pain, and continue to investigate effective pain management techniques.

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