Robust perioperative pain management in veterinary medicine is an ethical responsibility and important for reducing time of hospitalization and time to recovery.1,2 Optimally, a multimodal approach, including IV opioids, NSAIDs, and local anesthetics, is used.3 A multimodal analgesic regimen uses agents that provide pain relief by different mechanisms in order to provide additive or synergistic effects and minimize harmful side effects by allowing lower dosages of each individual agent. Though NSAIDs are widely used in veterinary medicine for their anti-inflammatory and analgesic effects,3 their use in many abdominal surgeries is limited due to concerns in patients with hypotension or those undergoing gastrointestinal, hepatobiliary, or renal procedures.4,5 In addition, their potential effects on coagulation also limit their use. Opioids offer the most effective pain relief in critically ill patients but are associated with gastrointestinal ileus and dysmotility,6 which are undesirable in postoperative patients, particularly as early

**OBJECTIVE**

To evaluate the difference in postoperative pain scores of dogs undergoing abdominal surgery receiving surgical incision infiltration of saline or bupivacaine liposomal injectable suspension (BLIS).

**ANIMALS**

40 dogs undergoing exploratory laparotomy.

**METHODS**

Dogs were prospectively enrolled and randomized to receive either BLIS or saline surgical incision infiltration. All dogs received 5.3 mg of BLIS/kg or an equal volume of saline infiltrated in the muscle/fascia, subcutaneous tissue, and intradermal layer during closure. All dogs received a standardized postoperative pain management protocol. Pain assessment was performed at select time points postoperatively by blinded observers with an electronic algometer, short version of the Glasgow Composite Measure Pain Scale (GCMPS), and indirect measures of pain, including systolic blood pressure, heart rate, and serum cortisol levels.

**RESULTS**

At day 0, blood pressure was higher in the saline group (149.6 vs 125.8 mm Hg; \( P = .006 \)). At day 3, GCMPS was lower in the BLIS group (BLIS = 1, saline = 2, \( P = .027 \)), though both average GCMPS scores were low and only 10 dogs were available for day 3 assessments (6 BLIS and 4 saline). No other differences in algometer readings, GCMPS scores, other measured parameters, or need for rescue analgesia were present between BLIS and saline groups at any time point. There was no difference in postoperative incisional infection rate or complications.

**CLINICAL RELEVANCE**

Use of BLIS for exploratory laparotomy did not provide improved pain control over postoperative opioid administration alone. Patients that received BLIS had no increase in short-term complications.

**Keywords:** Nocita, liposomal bupivacaine, analgesia, abdominal surgery, BLIS

**Bupivacaine liposomal injectable suspension does not provide improved pain control in dogs undergoing abdominal surgery**

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enteral nutrition has been shown to have significant benefits in both people and animals including decreased hospitalization time and lower mortality.7–11 Because of these concerns, regional anesthetic techniques such as incisional infiltration with a local anesthetic and the transversus abdominis plane (TAP) block with bupivacaine12–14 are attractive options to reduce postoperative opioid requirements.

Surgical incisional infiltration (SII) with local anesthetics, most commonly bupivacaine, has been shown to be effective for 6 to 7 hours after administration in dogs.15,16 In 2011, a liposomal bupivacaine injectable suspension was approved by the FDA for SII in people. This product consists of aqueous bupivacaine encapsulated in multivesicular liposomes, designed to be gradually released over 72 to 96 hours, and has been evaluated extensively in human medicine with mixed results.17–21 In veterinary medicine, a similar bupivacaine liposome injectable suspension (BLIS; Nocita) is FDA approved for single-dose infiltration into the surgical site to provide local postoperative analgesia for cranial cruciate ligament surgery in dogs and as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.22 Despite its limited approved uses, anecdotally, this product is widely used off-label for many different surgical procedures and soft tissue surgeries, although no studies have reported the efficacy of SII with BLIS for reduction of postoperative pain in dogs undergoing an exploratory laparotomy.

The objective of this study was to compare postoperative pain in dogs undergoing exploratory laparotomy that received SII with saline or BLIS. Postoperative pain was assessed directly via the short form of the Glasgow Composite Measure Pain Scale (GCMPS) and sensory threshold testing (STT) with an algometer (The Prod; TopCat Metrology Ltd) and indirectly via heart rate (HR), systolic indirect blood pressure (BP), blood cortisol concentrations, and need for rescue analgesia. The hypothesis was that dogs receiving BLIS would have lower pain scores via GCMPS, higher quantitative STT, lower HR, lower BP, lower serum cortisol concentrations, and reduced need for rescue analgesia.

**Methods**

All study procedures were approved by the University of Georgia Clinical Research Committee, and client informed consent was obtained for each dog prior to enrollment. Dogs undergoing exploratory laparotomy were prospectively enrolled and randomly assigned to receive either BLIS or saline SII. Randomization was performed prior to the start of the study using a randomization website (www.randomization.com). Exclusion criteria included dogs undergoing a caudal abdominal procedure only (e.g., cystotomy) or a laparoscopic procedure; dogs that were aggressive, pregnant, or lactating; dogs with a portosystemic shunt; and dogs with a confirmed septic abdomen. Dogs that were enrolled but later found to have serum cortisol concentrations consistent with hyper- or hypoadrenocorticism were removed from inclusion in cortisol measurements but allowed to remain in the study.

**Anesthesia and surgery**

Prior to anesthesia, baseline GCMPS, STT, HR, and indirect systolic BP were recorded, and whole blood was obtained for cortisol measurements and centrifuged at 2,500 rpm for 10 minutes, with the resulting serum saved in a −80 °C freezer until samples could be tested in batches. Serum cortisol levels were measured using a solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000 XPi; Siemens Medical Solutions USA Inc). All dogs were premedicated with methadone (0.2 mg/kg) and midazolam (0.2 mg/kg) IV or IM, with administration route determined by the attending anesthesiologist. Anesthesia was induced with ketamine (2 mg/kg, IV) and propofol (4 mg/kg, IV, to effect) and maintained with isoflurane in oxygen. No dogs received a TAP block, epidural, or NSAIDs perioperatively. At the time of closure of the abdomen, either BLIS or saline was administered peri-incisionally in 3 layers per manufacturer guidelines.23 In the BLIS group, 5.3 mg of BLIS/kg was diluted 1:1 with 0.9% sterile saline as recommended by the package insert for sufficient volume to inject the entire length of the incision.24 Dogs in the saline group received a volume of 0.9% saline equivalent to that of the diluted BLIS calculated for their weight. Prior to the beginning of the study, all surgeons (American College of Veterinary Surgeons [ACVS] diplomates and ACVS residents under the supervision of an ACVS diplomat) received instructions and watched a video on proper administration of the SII to ensure consistency in treatment. After the body wall closure, 25% of the diluted volume was administered using a 1-inch, 22-gauge needle along the incision under the rectus sheath in a continuous line on both sides of the incision in a moving needle technique. Next, 50% of the volume was administered similarly within the subcutaneous tissues. The remaining volume was administered in a similar manner subcuticularly, without penetrating skin.

**Postoperative care and pain assessment**

Postoperatively, all dogs received 0.2 mg of methadone/kg IV every 6 hours for a minimum of 3 doses with the timing of the first dose at clinician and anesthesiologist discretion, at a maximum of 6 hours after recovery from anesthesia. Additional doses of methadone after 18 hours postoperatively and any doses administered earlier than scheduled were considered rescue analgesia and administered at clinician discretion and on the basis of patient examination. Dogs receiving rescue analgesia remained in the study analysis. Dogs were evaluated at 4 time points postoperatively: 2 to 10 hours, 14 to 24 hours, 36 to 48 hours, and 60 to 72 hours to represent days 0, 1, 2, and 3 postoperatively, respectively. At each time point, GCMPS, STT assessments, HR, and indirect systolic BP were recorded, and blood was obtained for serum cortisol measurements. The GCMPS evaluation was performed by 2 trained observers (LPH and a trained independent observer: KA, SS, JSA, ED, or CC) at each time point, both of whom were blinded to the administered treatment and each other’s GCMPS score. To ensure blind-
ing between observers, 1 observer performed their GCMPS evaluation without the second observer present. Then, the second observer would immediately perform their GCMPS evaluation without the first observer present. Prior to the start of the study, LPH and all independent observers were given in-person instruction on the GCMPS and its use in postoperative patients with a board-certified veterinary surgeon (MLW). All parts of the GCMPS evaluation were used at each time point.

Quantitative STT using an algometer was measured by 1 observer (LPH) at each time point. During STT, the tip of the algometer was applied approximately 2 cm lateral to the midpoint of the incision. Pressure was applied until the patient reacted by showing discomfort (flinching, turning toward the tester, or vocalizing), the device was removed, and the highest pressure tolerated by the patient was recorded in Newtons. Preoperatively, STT was performed 3 times and averaged to establish a baseline for the patient and ensure the patient would tolerate STT throughout the study. Patients that did not tolerate STT were removed from inclusion in the study. Thereafter, STT was performed once at each time point. Other data collected included duration of clinical signs associated with the dog's condition preoperatively, surgical procedures performed, surgical time, anesthesia time, anesthetic complications (hypotension and hypothermia), time to first voluntary eating, time until discharge in days, immediate postoperative complications (ie, vomiting, regurgitation, etc), and whether rescue analgesia was required as determined by the overseeing clinician. Hypotension was defined as a mean arterial pressure < 60 mm Hg, diastolic arterial pressure < 40 mm Hg, and/or systolic arterial pressure < 90 mm Hg. Hypothermia was defined as a temperature < 36.67 °C. Anesthesia time was defined as the time from induction until tracheal extubation. Surgical time was defined as the time from the start of the initial incision to completion of skin closure. Patients were discharged on the basis of attending clinician discretion, ensuring no patients were discharged when opioids were still required.

Follow-up was performed at least 1 month postoperatively by means of reviewing medical records and contacting referring veterinarians and/or the owner via telephone. Complications including incisional site inflammation, dehiscence, or infection were recorded.

**Statistical analysis**

All analyses were performed using SAS version 9.4 (SAS Institute Inc), except for the calculation of the intraclass correlation coefficient, which was performed using the irr package in R (version 0.84.1; R Core Team). A significance threshold of 0.05 was used. Two raters recorded GCMPS scores for each dog and time point. The 2 values were averaged prior to analysis.

Linear mixed models were used to compare GCMPS, algometer readings, HR, BP, and cortisol values between groups. Histograms and Q-Q plots of conditional model residuals were examined to evaluate the assumption of normality, and plots of conditional residuals versus predicted values of assessments were examined to evaluate the assumption of homogeneity of variances. Pain scores, algometer readings, and cortisol values all exhibited increasing variability with increasing mean values and were log-transformed prior to analysis. A constant of 1 was added to all pain scores so there were no zero values, which cannot be log-transformed. Each linear mixed model had fixed factors of treatment, time, and a treatment by time interaction and a baseline covariate and a random intercept for each dog. Simple effects of treatment were tested at each time. The Satterthwaite degrees of freedom method and restricted maximum likelihood estimation were used. Normally distributed data are presented as mean ± SD. Nonnormally distributed data are presented as median (IQR).

**Results**

Forty dogs were prospectively enrolled in this study (20 BLIS and 20 saline) on the basis of previous studies. One patient that received BLIS was excluded from cortisol testing due to hypoadrenocorticism. The mean age was 8.6 ± 4.5 years. There were 20 male dogs (3 intact and 17 castrated) and 20 female dogs (3 intact and 17 spayed). The most common dog breed was mixed-breed dog (n = 14 [35%]), followed by German Shepherd Dog (3 [7.5%]), Labrador Retriever (3 [7.5%]), Welsh Corgi (2 [5%]), Miniature Pinscher (2 [5%]), and each of 17 other breeds. There was no difference between groups in age, sex, body condition score, or weight (Table 1).

**Table 1—Demographic data for dogs in the saline group as compared to the bupivacaine liposomal injectable solution (BLIS) group. Values are expressed as mean ± SD.**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (y)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI: 0</td>
<td>9.1 ± 3.8</td>
<td>.535</td>
</tr>
<tr>
<td>FI: 1</td>
<td>8.2 ± 5.1</td>
<td>.770</td>
</tr>
<tr>
<td>MC: 10</td>
<td>5.2 ± 1.4</td>
<td>.420</td>
</tr>
<tr>
<td>FS: 9</td>
<td>24.1 ± 12.7</td>
<td>.367</td>
</tr>
</tbody>
</table>

| Body condition score (1-9) | 5.2 ± 1.4 | 5.6 ± 1.3 | .420 |
| Weight (kg)                | 24.1 ± 12.7| 20.3 ± 13.8| .367 |

MI = Male intact, FS = Female spayed, MC = Male castrated. MI = Male intact.

The most common surgeries performed were splenectomy (n = 11), gastropexy (11), and liver biopsy (11). Other procedures performed included liver lobectomy (n = 4), cholecystectomy (4), enterotomy (4), diaphragmatic herniorrhaphy (3), gastroscopy (2), and 1 of each of prostatic omentalization, nephrectomy, partial nephrectomy, intestinal resection and anastomosis, colopexy, ovarioectomy, ovariohysterectomy, and ureterotomy, with 26 of 40 (65%) dogs undergoing > 1 surgical procedure within 1 anesthetic episode. Of the baseline assessments performed at day – 1, no significant differences were
noted between the BLIS and saline groups. There was no difference in number of procedures, surgery time, anesthesia time, hypotension, or hypothermia intraoperatively between groups. There was no difference between groups in postoperative gastrointestinal complications including vomiting/regurgitation, anorexia, and diarrhea \( (P = .752) \). Regarding time to first voluntary ingestion of food, there was no difference between groups, with saline dogs eating 0.78 ± 0.81 days postoperatively as compared to BLIS dogs eating 0.81 ± 0.54 days postoperatively \( (P = .883) \). No difference was present in length of postoperative hospitalization between groups, with saline dogs hospitalized for 2.05 ± 1.35 days and BLIS patients hospitalized for 2.2 ± 0.77 days \( (P = .670) \). Rescue analgesia was required in 6 of 40 (15%) dogs, including 4 in the BLIS group and 2 in the saline group, which was not different between groups \( (P = .661; \text{Figure 1}) \). Follow-up at 30 days postoperatively was available in 34 of 40 (85%) dogs. One of 17 dogs in the BLIS group and 0 of 17 dogs in the saline group had surgical site infection and dehiscence of the surgical incision \( (P = 1.000) \).

**Direct pain assessments**

Pain assessment data were available for all dogs preoperatively and at days 0 and 1, 30 dogs (17 BLIS and 13 saline) at day 2, and 10 dogs (6 BLIS and 4 saline) at day 3. Direct pain assessment data are available (Table 2). GCMPS score was significantly lower in the BLIS group at day 3 \( (P = .027; \text{Figure 2}) \). The median pain score in the saline group was 2 (2 to 3; \( n = 4 \)) and in the BLIS group was 1 (0 to 3; 6). The GCMPS score was not significantly different between groups at any other time point. Additionally, the mean and median GCMPS scores at all time points in both groups were lower than the intervention threshold established in previous studies.27 The inter-rater reliability for the 159 paired scores from 2 raters was good \( (r = .752) \). Regarding agreement between raters was \(-0.16\), and the limits of agreement established in previous studies.27 The mean difference for the 159 paired scores from 2 raters was good \( (0.89; 95\% \text{ CI}, 0.85 \text{ to } 0.92) \). The mean difference between raters was \(-0.16\), and the limits of agreement were \(-2.4 \text{ to } 2.1\). There were no differences in STT tolerance between groups at any time point (Figure 3).

![Figure 1](image-url)  
**Figure 1**—Kaplan Meier plot showing time in hours to rescue analgesia administration from the time of tracheal extubation. No difference was present between groups regarding administration of rescue analgesia \( (P = .661) \).

**Table 2**—Objective pain assessment data reported as mean ± SD or median (IQR). Day –1 represents the preoperative time point, and days 0, 1, 2, and 3 represent 2 to 10 hours, 14 to 24 hours, 36 to 48 hours, and 60 to 72 hours postoperatively, respectively. Mean difference is given as BLIS value minus saline value. Estimated difference is given as BLIS value minus saline value and is adjusted for baseline and missing values.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Time point</th>
<th>Saline (95% CI)</th>
<th>BLIS (95% CI)</th>
<th>Mean difference (95% CI)</th>
<th>Estimated difference (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCMPS</td>
<td>–1</td>
<td>0 (0 to 2)</td>
<td>1 (0 to 1)</td>
<td>–0.2 (–1.4 to 1.0)</td>
<td>–0.2 (–1.4 to 1.0)</td>
<td>.687</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2 (1 to 3)</td>
<td>4 (1 to 6)</td>
<td>–2.8 (–7.2 to 1.6)</td>
<td>–2.8 (–7.2 to 1.6)</td>
<td>.360</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2 (1 to 4)</td>
<td>3 (1 to 4)</td>
<td>–0.5 (–1.8 to 0.8)</td>
<td>–0.5 (–1.8 to 0.8)</td>
<td>.525</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (0 to 4)</td>
<td>1 (0 to 3)</td>
<td>–5.2 (–10.0 to 0.0)</td>
<td>–5.2 (–10.0 to 0.0)</td>
<td>.023</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2 (2 to 3)</td>
<td>1 (0 to 3)</td>
<td>–2.9 (–8.0 to 2.2)</td>
<td>–2.9 (–8.0 to 2.2)</td>
<td>.249</td>
</tr>
<tr>
<td>Sensory threshold</td>
<td>–1</td>
<td>0 ± 2.5</td>
<td>0 ± 2.5</td>
<td>–0.2 (–2.5 to 2.1)</td>
<td>–0.2 (–2.5 to 2.1)</td>
<td>.525</td>
</tr>
<tr>
<td>testing (N)</td>
<td>0</td>
<td>0 ± 2.5</td>
<td>0 ± 2.5</td>
<td>–0.2 (–2.5 to 2.1)</td>
<td>–0.2 (–2.5 to 2.1)</td>
<td>.525</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5 ± 2.5</td>
<td>5 ± 2.5</td>
<td>–0.2 (–2.5 to 2.1)</td>
<td>–0.2 (–2.5 to 2.1)</td>
<td>.525</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5 ± 2.1</td>
<td>5 ± 2.6</td>
<td>–0.4 (–3.2 to 2.5)</td>
<td>–0.4 (–3.2 to 2.5)</td>
<td>.164</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5 ± 1.9</td>
<td>3 ± 1.3</td>
<td>–2.6 (–5.4 to 0.2)</td>
<td>–2.6 (–5.4 to 0.2)</td>
<td>.049</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>–1</td>
<td>144 ± 20.7</td>
<td>136 ± 21.5</td>
<td>–8.0 (–21.5 to 5.6)</td>
<td>–8.0 (–21.5 to 5.6)</td>
<td>.321</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>0</td>
<td>149 ± 28.1</td>
<td>125 ± 25.8</td>
<td>–23.9 (–41.1 to 6.6)</td>
<td>–23 (–39 to 7)</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>143 ± 24.8</td>
<td>127 ± 28.7</td>
<td>–16.5 (–33.6 to 0.7)</td>
<td>–16 (–31 to 0)</td>
<td>.057</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>139 ± 16.6</td>
<td>128 ± 21.1</td>
<td>–11.5 (–26.1 to 3.1)</td>
<td>–10 (–28 to 8)</td>
<td>.272</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>125 ± 24.7</td>
<td>134 ± 8.9</td>
<td>9.5 (–15.3 to 34.3)</td>
<td>18 (–10 to 47)</td>
<td>.210</td>
</tr>
<tr>
<td>Heart rate</td>
<td>–1</td>
<td>117 ± 21.1</td>
<td>112 ± 30.0</td>
<td>–5.0 (–21.1 to 12.1)</td>
<td>–5.0 (–21.1 to 12.1)</td>
<td>.552</td>
</tr>
<tr>
<td>(beats/min)</td>
<td>0</td>
<td>108 ± 21.4</td>
<td>99 ± 29.6</td>
<td>–8.8 (–25.3 to 7.8)</td>
<td>–8 (–24 to 8)</td>
<td>.327</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>111 ± 24.5</td>
<td>104 ± 29.7</td>
<td>–7.5 (–24.9 to 9.9)</td>
<td>–7 (–23 to 9)</td>
<td>.408</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>116 ± 22.0</td>
<td>95 ± 21.5</td>
<td>–21.5 (–37.8 to 5.1)</td>
<td>–13 (–31 to 5)</td>
<td>.161</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>109 ± 31.2</td>
<td>105 ± 26.9</td>
<td>–3.5 (–46.0 to 39.0)</td>
<td>9 (–19 to 37)</td>
<td>.525</td>
</tr>
<tr>
<td>Serum cortisol</td>
<td>–1</td>
<td>4 ± 2.7</td>
<td>4 ± 2.1</td>
<td>–0.2 (–1.8 to 1.4)</td>
<td>–0.2 (–1.8 to 1.4)</td>
<td>.321</td>
</tr>
<tr>
<td>(g/dL)</td>
<td>0</td>
<td>11 ± 7.9</td>
<td>9 ± 7.3</td>
<td>–2.6 (–8.3 to 3.1)</td>
<td>–2.6 (–8.3 to 3.1)</td>
<td>.321</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4 ± 2.4</td>
<td>3 ± 2.6</td>
<td>–1.0 (–2.0 to 0.0)</td>
<td>–1.0 (–2.0 to 0.0)</td>
<td>.321</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 ± 2.4</td>
<td>3 ± 2.5</td>
<td>–0.9 (–2.0 to 0.2)</td>
<td>–0.9 (–2.0 to 0.2)</td>
<td>.321</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2.9 ± 2.1</td>
<td>2.8 ± 1.6</td>
<td>–0.1 (–2.8 to 2.6)</td>
<td>–0.1 (–2.8 to 2.6)</td>
<td>.321</td>
</tr>
</tbody>
</table>

GCMPS = Glasgow Composite Measure Pain Scale. Bolded \( P \) values indicate significance.
Indirect pain assessments

There was no difference between the saline and BLIS groups regarding indirect assessment of pain (serum cortisol, BP, and HR) at any time point, except for BP on day 0 (23.9 [6.6 to 41.1] mm Hg lower in the BLIS group than the saline group; \( P = .006 \); Figure 3), which was the first assessment between 2 and 10 hours postoperatively. An increase in serum cortisol concentration was identified in both the saline and BLIS groups at day 0 postoperatively, but there were no differences between groups at any time point. There was no difference in HR between groups at any time point.

Figure 2—Glasgow Composite Measure Pain Scale scores at each time point. Day –1 represents the preoperative time point and days 0, 1, 2, and 3 are 2 to 10 hours, 14 to 24 hours, 36 to 48 hours, and 60 to 72 hours postoperatively, respectively. Each box is drawn from the 25th percentile to the 75th percentile. The horizontal line inside the box shows the location of the median, and the symbol shows the location of the mean. Whiskers extend from the upper edge of the box to the largest observed value \( \leq 1.5 \times \text{IQR} \) above the 75th percentile, and from the lower edge of the box to the smallest observed value \( \geq 1.5 \times \text{IQR} \) below the 25th percentile. Observations outside the whiskers are identified with data markers. Significance is notated by an asterisk (*).

Figure 3—Sensory threshold testing (STT) via algometer (A), indirect systolic blood pressure (B), serum cortisol (C), and heart rate (D) values at each time point. All graphs represent mean ± SE. Day –1 represents the preoperative time point and days 0, 1, 2, and 3 are 2 to 10 hours, 14 to 24 hours, 36 to 48 hours, and 60 to 72 hours postoperatively, respectively. Significance is notated by an asterisk (*).
Discussion

In the present study, dogs undergoing an exploratory laparotomy that received SII with BLIS showed minimal to no difference in direct and indirect assessments of pain when compared to the saline group. Although we hypothesized that all variables would have a difference between test groups, only the BP on day 0 and GCMPS on day 3 were different between groups, leading to a partial rejection of our hypothesis. Additionally, 4 BLIS dogs received rescue analgesia as compared to 2 saline dogs, which was not a significant difference, leading to rejection of that portion of the hypothesis as well.

A limitation to this study, and any study evaluating pain in veterinary medicine, was the ability to accurately evaluate pain in dogs. A validated pain scale along with multiple objective assessments were implemented to decrease this limitation. Dogs were discharged when deemed medically appropriate by the attending clinician, and only 10 of 40 patients (4 within the saline group and 6 within the BLIS group) remained hospitalized and had assessments performed on day 3 postoperatively. Therefore, a small sample size may explain differences in GCMPS scores on day 3. Additionally, 65% of patients underwent >1 surgical procedure during the initial anesthetic episode, leading to possible variation in visceral pain and abdominal wall retraction. Due to small sample sizes of individual procedures, evaluation of pain associated with a specific surgery was unable to be performed. In validation of the short form of the GCMPS, the decision point for rescue analgesia was a score of 6. In the current study, although GCMPS scores were higher in the control group at day 3, the highest score in both groups was 3; thus, none of these patients would have received rescue analgesia. In fact, the median GCMPS for both groups at each time point remained <6, which could indicate that opioids administered for 18 hours postoperatively are sufficient for pain control for most patients undergoing abdominal surgeries. The short form of the GCMPS has been validated for clinical use, though contradictory information exists regarding whether anxiety in dogs can lead to higher scores. To control for false elevations in score due to anxiety, preoperative GCMPS and all other parameters were controlled to the preoperative baseline at each time point. Pain scores were performed by 1 investigator (LPH) and 1 of 5 other trained independent observers, both of whom were blinded to the assigned group. These independent observers were third- and fourth-year veterinary students and small animal rotating interns that had been trained in the use of the GCMPS by a board-certified surgeon, while the main observer was a small animal surgery resident. While 1 previous study indicated that student’s use of the GCMPS may vary from that of experienced clinicians, we had good interobserver agreement, making it less likely that experience level of the observer affected our results.

Rescue analgesia in the form of early or additional doses of methadone was at attending clinician discretion and based on patient examination in the current study. In the BLIS group, 4 of 20 dogs received rescue analgesia as compared to 2 of 20 control dogs; however, this difference was not significant. While ideally all rescue analgesia administration in this study would be based solely on pain scores, standard use and uniform training of hospital care personnel on use of the GCMPS were not in place in our hospital at the time this study was performed. We were concerned that having many different observers who were not trained in the use of this pain scoring system and using that system to determine when to provide analgesia could be detrimental for patient care, potentially allowing animals to remain painful without appropriate analgesia for longer time periods. For this reason, we elected to administer methadone on a set schedule for the first 18 hours postoperatively and administer rescue analgesia doses at the discretion of the attending clinician, as this was the standard of care in our hospital at that time. As rescue analgesia was administered at clinician discretion, it is possible that standardized use of GCMPS to determine rescue analgesia administration would have led to different results.

Time points for analysis included 2 to 10 hours, 14 to 24 hours, 36 to 48 hours, and 60 to 72 hours to represent days 0 to 3, respectively. These time points were chosen to ensure the 6 trained independent observers would be available to assess all patients, ensuring good interobserver agreement. By choosing these times, any patient included in the study would therefore be able to be examined upon arrival to the hospital in the morning on the days following surgery, to represent days 1, 2, and 3, as would be typical in a clinical setting. This ensured that all patients included had all parameters performed by 2 of 6 people, rather than relying on the dog’s busy and variable care team to evaluate all parameters at specific times, which would likely have led to a substantial variation in interobserver agreement. However, the wide time range for each day could have led to variation in results for assessed variables, as pain levels at 14 and 24 hours after surgery may be different.

Blood pressure at day 0 was higher in the saline group than in the BLIS group, although this value was still within the normotensive range (149.6 mm Hg). No additional significant differences were seen in BP at any time point. Bupivacaine alone has a duration of action of 6 to 7 hours; therefore, it is possible that bupivacaine, which is more cost-effective, would have been as effective as BLIS at day 0 testing. The pilot study evaluating BLIS for stifle surgery found that though BLIS was effective for 72 hours, the number of dogs that received BLIS and remained comfortable based on GCMPS decreased from 19 of 24 (79.2%) to 10 of 24 (42%) at 24 and 48 hours, respectively. Previous studies have compared BLIS to bupivacaine, which is more cost-effective, would have been as effective as BLIS at day 0 testing. The pilot study evaluating BLIS for stifle surgery found that though BLIS was effective for 72 hours, the number of dogs that received BLIS and remained comfortable based on GCMPS decreased from 19 of 24 (79.2%) to 10 of 24 (42%) at 24 and 48 hours, respectively. Previous studies have compared BLIS to bupivacaine for management of pain after different surgical procedures. One study found that a TAP block performed with 0.5% bupivacaine hydrochloride (0.5BH) potentiated with dexmedetomidine or BLIS alone yielded lower pain scores and less requirement for rescue analgesia in dogs undergoing elective ovariohysterectomy than dogs with no block; however, no additional benefit was noted with BLIS as compared to 0.5BH and dexmedetomidine. Another study compared BLIS to 0.5BH for postoperative...
pain control in dogs undergoing a tibial plateau leveling osteotomy. Dogs that received 0.5BH were more likely to require rescue analgesia compared to dogs that received BLIS; however, there was no difference in pain scores between test groups. A more recent clinical study found substantially longer sciatic nerve block duration with BLIS (96 hours) compared to 0.5BH potentiated with dexmedetomidine (24 hours) in healthy Beagles. However, BLIS provided inconsistent fluctuations of sensory, motor, and proprioceptive block over time, potentially indicating a nonlinear release of bupivacaine from liposomal vesicles, which was not observed in the limbs treated with 0.5BH with dexmedetomidine. An additional study evaluating administration of BLIS compared to saline control in dogs undergoing a tibial plateau leveling osteotomy and receiving carprofen postoperatively found that BLIS did not provide an analgesic effect discernable by GCMPs or percent body weight distribution on the surgical limb using a weight distribution platform. The results of these studies indicate that for certain procedures BLIS may not provide much additional benefit over bupivacaine alone or bupivacaine potentiated with dexmedetomidine.

The manufacturer-recommended dose for dogs undergoing cranial cruciate ligament surgery was used in the current study, despite a full laparotomy incision being 2 to 3 times the length of a typical cranial cruciate ligament surgery incision. The lack of efficacy noted in the current study may be due to dilution of the product over a much larger area. All dogs in the current study had BLIS diluted 1:1 with sterile saline, as per manufacturer guidelines and as performed by some surgeons in the original pilot study testing BLIS in veterinary patients. In studies that found more consistent evidence of effectiveness, no dilution was used. This may indicate that dilution of BLIS could lead to decreased effectiveness in providing pain relief, though dilution does not appear to impact efficacy in people. Up to 30 mg of BLIS/kg has been injected subcutaneously twice weekly for 4 weeks in dogs and rabbits, and no clinical signs consistent with CNS toxicity or ECG abnormalities were noted. Future studies could evaluate whether higher dosages of BLIS that would eliminate or decrease the need for dilution would be effective in longer incisions. Additionally, differences in soft tissue pain compared to orthopedic pain may have affected the efficacy of BLIS in the present study.

Clinical efficacy of BLIS has been extensively evaluated in people. Compared to placebo or active agents, BLIS did not demonstrate significant pain relief in 74.6% (47/63) of randomized clinical trials in a systematic review. Additionally, BLIS did not reduce opioid consumption in 85.71% (48/56) of randomized clinical trials, regardless of the comparative agent (placebo, bupivacaine, or other analgesia). Pain scores were not lower in people receiving BLIS in 69.0% (20/29) of studies evaluating BLIS compared to bupivacaine or other active agent administration. Moreover, clinical trials with a financial conflict of interest related to the BLIS manufacturer were 14 times more likely to report pain relief and 12 times more likely to report decreased opioid consumption in patients receiving BLIS compared to patients receiving a control. In dogs, there are 4 veterinary clinical trials evaluating the efficacy of BLIS. In 1 study funded by the drug manufacturer, pain scores were lower and fewer dogs required rescue analgesia in the BLIS group compared to the control animals undergoing lateral retinacular suture placement with arthrotomy. In contrast, in 3 veterinary clinical trials without manufacturer funding support, benefit of BLIS administration was found in 1 study in which BLIS dogs were less likely to require rescue analgesia but no benefit of BLIS was found in the other 2 studies.

In the current study, all dogs received 3 doses of methadone (0.2 mg/kg, IV, q 6 h) postoperatively to ensure comfort, as no dog received NSAIDs. Opioid administration was noted to be important to many owners who only agreed to enroll their dog into the study with the knowledge that opioids would be provided to all participants. The potential for masking of efficacy of BLIS with concurrent opioid administration should be considered. Terminal elimination half-life after IV administration of 0.4 mg of methadone/kg is approximately 3.9 ± 1.0 hours with a plasma clearance rate of 27.9 ± 7.6 mL/min/kg in dogs. At a dose of 0.2 mg/kg, all patients would likely have had clearance of clinically effective serum levels of methadone by 16 to 22 hours after surgery. Nevertheless, the only parameter past day 1 postoperatively that was different between groups was the day 3 GCMPs. Thus, even if day 1 postoperative pain was controlled by methadone in both groups, a benefit of BLIS on days 2 and 3 would be expected given the stated duration of effect of BLIS of 72 hours.

Serum cortisol is used as an objective measurement of pain in human and veterinary medicine. Though not pathognomonic for pain, several studies have documented decreased cortisol levels with increasing analgesic efficacy while other studies have not found a difference in cortisol levels despite other evaluated factors indicating differences in pain. Serum cortisol in dogs receiving BLIS as compared to saline, although both groups had an increase in serum cortisol at day 0 as compared to baseline and subsequent postoperative days. This is likely secondary to stress from recent surgical trauma and anesthesia; however, an increase in cortisol approximately 1 hour after receiving methadone has also been reported in dogs.

STT with an algometer was performed to evaluate pressure tolerance at the incision. STT on all days was lower for the BLIS group at all time points (Figure 2), including day −1 preoperatively. Once controlled to baseline, there was no significant difference between study groups. There is substantial variation in test-retest repeatability for mechanical threshold testing using a calibrated veterinary pressure algometer, and the algometer used in the present study has been validated for use in dogs. Because operator experience has been shown to affect results of mechanical threshold testing using a calibrated veterinary pressure algometer, the same investigator (LPH) performed STT throughout the entirety of the study.
Based on the results of the current study, BLIS does not increase the chance of surgical site infection when used as previously described for cranial cruciate ligament surgery in dogs. Only 1 of the 34 dogs with follow-up developed a surgical site infection, and although this dog received SII with BLIS, there was no difference in the occurrence of surgical site infections compared to the saline group. Previous veterinary studies have found similar results, with no increase in infection rate or adverse events with administration of BLIS for stifle surgery.\textsuperscript{12,13} Two animal model studies of the BLIS drug used in people noted a granulomatous inflammatory response on histology in some dogs receiving the product, but dosing was variable in this study, ranging from 9 to 25 mg/kg.\textsuperscript{45,46} In one of these studies,\textsuperscript{45} dogs in all groups (BLIS, control, and bupivacaine) had granulomatous reactions by day 15, leading the authors to conclude that the granulomatous inflammation was likely secondary to the suture material used for incisional closure. In the other study,\textsuperscript{46} minimal to mild granulomatous inflammation of adipose tissue around nerve roots in the brachial plexus was noted in 6 of 12 dogs on day 15. This was considered by the authors to be a normal response to the liposomes and not an adverse event. The granulomatous reactions were not considered to influence wound healing in either study. In the study reported here, histologic evaluation of the wound was not performed; however, no owners or veterinarians reported issues or concerns with the incision, other than 1 dog that developed a surgical site infection. No other adverse events were observed.

As with any clinical study, there were limitations in our study that prevented the standardization of all variables. Although all patients had a ventral midline abdominal incision, a variety of surgical procedures were performed, which may have resulted in variations in postoperative pain. Rescue analgesia doses were given at the discretion of the attending clinician rather than on the basis of objective pain parameters. Also, dogs were discharged from the hospital at the discretion of the attending clinician on the basis of clinical status, which could be affected by individual clinician preferences. Additionally, the number of cases that were able to be included due to available financial resources may have prevented us from finding any differences that may have been present if a larger number of cases had been included.

In conclusion, in this population of dogs undergoing exploratory laparotomy, minimal differences in pain measures were found with BLIS administration when compared to a saline control. Despite the lack of effectiveness of BLIS, there was no difference in complications or surgical site infection postoperatively between the BLIS and saline groups. Future studies should evaluate whether incision length and dilution impact the effectiveness of BLIS.

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