Dose effect and duration of action of liposomal bupivacaine administered as a perineural analgesic in a reversible and adjustable frog-pressure model of equine lameness

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OBJECTIVE
To determine the dose effect of peri-neural liposomal bupivacaine (LB) in an induced forelimb lameness model.

ANIMALS
12 clinically normal adult horses.

METHODS
A randomized cross-over design was performed with 1 limb receiving saline and the other LB: low dose (6), high dose (6). Lameness was induced in 1 forelimb using a frog-pressure model. In the lame limb, peri-neural injection of the palmar nerves at the proximal sesamoid bones was performed using saline, low dose LB (0.25 mg/kg) (LDLB), or high dose LB (0.5mg/kg) (HDLB) in random order with a 1-week washout period between treatments. Distal limb swelling, mechanical nociceptive thresholds (MNT), and objective lameness data were collected before and up to 72 hours after peri-neural anesthesia. Data analysis was performed with mixed model ANOVA, equality of medians test, and Kaplan Meier survival analysis.

RESULTS
Compared with baseline, horses treated with LDLB and HDLB had improvements in MNT and lameness ($P < .001$). In the LDLB group, the median duration of analgesia was 4.5 hours (range = 3–6 hours) and the median return to lameness was 7 hours (range = 4–24 hours). In the HDLB group, the median duration of analgesia was 12 hours (range = 4–48 hours) and the median return to lameness was 9 hours (range = 3–48 hours). Mild to moderate swelling was identified in 11/12 (92%) LB limbs.

CLINICAL RELEVANCE
Both LDLB and HDLB resulted in loss of skin sensation and improvement of lameness. There was high variability among horses in duration of action for both doses.

Keywords: equine, perineural, liposomal, bupivacaine, lameness

Severe distal limb pain in the horse can be debilitating and costly to treat, often resulting in increased hospitalization and euthanasia.\(^1\) While these horses may benefit from intensive pain management protocols, management of acute and chronic conditions can be limited by side effects, administration limitations, drug costs, and most importantly limited demonstrated efficacy of medications.\(^2\) This unfortunately leads to inadequate pain control resulting in activation of the sympathetic nervous system with negative systemic effects.\(^3\) Current methods of analgesia typically include the administration of NSAIDs with the addition of α-2-adrenergic agonists or opioids for adjunctive pain control. With a more recent understanding of the benefits of a multimodal analgesic approach, drugs targeting neuropathic pain (eg, gabapentin) and constant-rate infusions of lidocaine, ketamine, and/or butorphanol have been investigated and utilized as either adjunctive or alternative medications.\(^2\) While a combination of therapies is available to mitigate severe pain in horses, concerns regarding
adverse effects, predominately on gastrointestinal motility, expense, and difficulty obtaining, or administering, many of these drugs make locoregional analgesia in multimodal protocols highly desirable.

Regional techniques may provide analgesia for both diagnostic and therapeutic procedures while minimizing side effects associated with systemic medications. Currently utilized local anesthetics, while safe, only provide a short duration of analgesia limiting their usefulness regarding long-term pain management due to required dosing frequency. Longer pain relief can be obtained either from a continuous application such as in the form of a long-term delivery system (peri-neural catheter) or a longer-acting local anesthetic.

Intermittent or continuous peri-neural nerve anesthesia provided by delivery systems is not only difficult to maintain but associated with several potential complications, including improper catheter placement, local edema formation, infection, pain, and lameness. Investigation of novel pharmacologic agents such as extended-release (liposomal encapsulated) bupivacaine offers hope for improved analgesia. Liposomal bupivacaine (LB), due to the slow degradation of liposomes, can sustain the release of bupivacaine resulting in a clinical analgesic effect of 72 hours in both dogs and humans.

In horses, administration of LB has been investigated as both peri-neural and local infiltration and has been demonstrated to cause minimal local or systemic effects. Additionally, a dose-dependent analgesic effect of LB was identified in mares undergoing laparoscopic ovariectomy. To date, there has been no investigation of a dose effect of LB when administered by peri-neural injection in horses.

The objectives of this study were to assess the efficacy and duration of analgesia using 2 LB doses in a frog-pressure model of lameness, as well as to report any adverse effects. The primary hypothesis was that liposomal bupivacaine would have a dose-dependent duration of analgesic effect when 2 doses were compared after peri-neural injection of the palmar nerves at the level of the proximal sesamoid bones (abaxial sesamoid nerve block). The second hypothesis was that there would be a low incidence of systemic or local side effects after either LB treatment.

**Methods**

**Horses**

Twelve clinically normal horses (2 Thoroughbreds, 1 Warmblood, 1 Paint Horse, and 8 Quarter Horses) from the university teaching herd with no evidence of forelimb lameness at the trot (grade 0/5, American Association of Equine Practitioners AAEP lameness scale) were used. The group consisted of 10 mares and 2 geldings, aged 6–22 years (median = 12.5 years), weighing 440–609 kg (median = 524.5 kg). IACUC approval (A2020 02-033-Y1-A4) was obtained before study initiation and ARRIVE guidelines were followed.

**Study design**

A sample size calculation was performed using data from a previous study with the expectation that the higher dose liposomal bupivacaine (HDLB; 0.5 mg/kg) group would be effective for analgesia and improvement in lameness for 24 hours duration longer than the lower dose liposomal bupivacaine (LDLB; 0.25 mg/kg) group with an expected standard deviation of 12 hours. To reach 80% power with a of 0.05, 6 horses were needed per group.

This study was performed as an incomplete, randomized, blocked, cross-over design; there were 4 blocks of 3 horses each over 4 weeks. Each group of horses was treated with saline (0.9%) (n = 12) and either low-dose liposomal bupivacaine (LDLB; 0.25 mg/kg) (n = 6); Nocita™, Elanco) or high-dose liposomal bupivacaine (HDLB; 0.5 mg/kg) (n = 6). After a 7-day wash-out period, the opposite treatment was performed on the contralateral forelimb. Horses were randomized to both initial treatment (LDLB/HDLB or saline) and initial forelimb (right or left) resulting in a total of 6 horses in each LB treatment group.

**Frog-pressure lameness model**

Horses’ feet were trimmed and shod by a certified journeyman farrier before initiating the study. Steel keg shoes with a bar welded across the branches at the level of the apex of the frog were placed on both forelimb hooves. A hole was drilled and tapped into the welded bar for placement of a headless screw in the bar before placement on the horse (Figure 1). Lameness was induced by the insertion of a headless 6 mm diameter threaded screw with a 2 mm diameter tapered end in the shoe of a single forelimb to induce grade 3 of 5 lameness on the AAEP scale, and screw length was recorded. Screws remained in the shoes during the data collection period (72 hours). Upon completion of the study, screws and shoes were removed the screw tract was gently debrided and treated with an iodine-based solution, a minimum of twice over 24 hours, before return to turnout.

**Horse clinical assessments and mechanical nociceptive threshold (MNT) testing**

An approximately 1 cm circular dot of acrylic paint was placed over the dorsolateral aspect of the...
distal pastern region (~1.5 cm proximal to the coronary band and 1.5 cm lateral to midline) of the treated limb. A digital pressure algometer (FPX 100, Wagner Instruments) with a 1 cm² rubber tip was used to apply pressure on the marked area at 5–10 kg/cm²/s until the horse demonstrated avoidance behavior (started to move the limb). The average of 3 MNT measurements at each timepoint was recorded. Temperature, pulse, and respiratory rate were also recorded at each timepoint for each horse.

The forelimbs of each horse were subjectively evaluated and palpated for any indication of swelling, heat, pain, or other adverse reactions, and any findings were recorded as normal (0), mild (1), moderate (2), or severe (3) for each category. All assessments were performed before peri-neural injection (baseline) and at 15 minutes, 1, 2, 6, 12, 24, 36, 48, 60, and 72 hours postinjection. After the first day of data collection for the first block (3 horses, 1 limb in each group; saline, LDLB, HDLB), horses in the LB groups were found to have returned to sensation and lameness at the 6-hour timepoint. For all subsequent blocks of horses (blocks 2 through 4) and the second limb of the first block of horses, additional hourly assessments were added between 2 and 8 hours postinjection to identify any early changes. In the last 6 horses (blocks 3 and 4), if lameness and MNTs were noted to return to baseline values for 2 consecutive timepoints, then further data collection was truncated. Return to sensation for MNT was defined as an average MNT less than twice the baseline MNT value.

Perineural anesthesia

After induction of lameness and after collection of baseline data, either (1) LDLB (0.25 mg/kg) (n = 6), (2) HDLB (0.5 mg/kg) (n = 6), or (3) 0.9% saline (n = 12) of comparable LB volume was injected subcutaneously around both medial and lateral palmar nerves at the level of the proximal sesamoid bones (abaxial sesamoid block). The total volume was divided evenly between the medial and lateral aspects of the limb. The skin was aseptically prepared with betadine and alcohol before injection. A 22 gauge, 1 inch hypodermic needle was used to perform the peri-neural injection over the palpable neurovascular bundle. Loss of skin sensation was evaluated subjectively at 15 minutes postinjection using increasing pressure with a needle cap.

Lameness trials and inertial sensor instrumentation and analysis

Lameness was evaluated at the trot in a straight line over a level, firm-packed dirt surface. Lameness was subjectively graded according to the AAEP scale for each horse by 3 boarded diplomats (Diplomate of the American College of Veterinary Surgeons-Large Animal; 2), Diplomate of the American College of Veterinary Sports Medicine and Rehabilitation; 1) and recorded lameness consensus was reached. Objective lameness evaluation was additionally performed using an inertial sensor system (Lameness Locator, Equinosis LLC) of each horse at each timepoint, which has been previously described. Subjective and objective lameness data were used to categorize a return to lameness in the limb that had received the peri-neural injection. Lameness was induced at time 0 (baseline) and evaluated at 1, 2, 6, 12, 24, 36, 48, 60, and 72 hours postinjection.

Statistical analysis

Data was analyzed using commercial software (STATA 13, StataCorp LLC). Data was assessed for normality using Shapiro-Wilk tests and visual evaluation of histograms and QQ plots. Data did not meet the criteria for normality, so all variables were ranked before analysis, and medians and ranges were calculated. Mixed model linear regression with the horse as a random effect and treatment, time, and their interaction as a fixed effect was used to analyze MNTs. When necessary, multiple comparisons were made with Scheffe's post hoc test. Equality of medians and Kaplan Meier Survival Analysis was used to assess the return to sensation and return to lameness. Significance was set at P < .05.

Results

Animals and clinical assessments

All horses had a subjective loss of skin sensation at 15 minutes post-LB injection in both the low and high-dose groups; horses in the saline group did not have a loss of skin sensation. All horses in all 3 groups had normal physical examinations (temperature, pulse, and respiratory rates) at all timepoints evaluated (Table 1). All horses also subjectively displayed normal stall behavior, feed and water consumption, and fecal and urinary output. Limb swelling of the LDLB and HDLB groups were significantly increased compared to before peri-neural anesthesia (P < .0001); however, no difference was noted between the 2 treatment groups (P = .5). No control horses had swelling after injection of saline. For the LB groups, 5 of the low-dose horses had swelling (4 mild, 1 moderate) and all 6 of the high-dose horses had swelling (4 mild, 2 moderate). All swelling either resolved by 72 hours (3 horses by 48 hours) or was minimal at 72 hours (1 horse). No horses had clinically significant inflammation (eg, severe swelling, signs of pain on palpation) requiring treatment.

Mechanical nociceptive threshold (MNT) testing

Controlling for time, there was a significant difference in MNTs among the 3 treatments with both LDLB and HDLB significantly different from the saline group (P < .0001); there was no significant difference between the LDLB and HDLB groups (P = .20). In the saline group, there was no significant difference in MNT over time (P = .13). At 15 minutes postinjection, MNTs of the LDLB and HDLB groups were significantly increased compared to before peri-neural anesthesia (P < .0001). For the LDLB group, there was a significant effect of time on MNT.
AJVR (P < .0001), with significant differences in MNTs at 15 minutes through 4 hours postinjection compared to baseline. For the HDLB group, there was a significant effect of time on MNT (P < .0001), with significant differences in MNTs at 15 minutes through 8 hours postinjection compared to baseline. Median and interquartile ranges of MNT values are presented (Table 2), with a return to sensation being defined as a return to individual horses’ baseline. For the LDLB group, 1 horse had a return to sensation at 3 hours, 2 horses had a return of sensation at 4 hours, 2 horses had a return to sensation at 5 hours, and 1 horse had a return to sensation at 6 hours. For the HDLB group, 2 horses had a return to sensation at 4 hours, 3 horses had a return to sensation at 12 hours, and 1 horse had a return to sensation at 48 hours. There was not a significant difference between LDLB and HDLB for return to sensation (P = .096) (Figure 2).

**Lameness**

All horses had grade 3 out of 5 lameness induced with the screw model, and a similar level of lameness was maintained with the same screw length for the duration of the study. After perineural anesthesia, lameness was significantly improved, or decreased when treated with LB compared to control (P > .001). There was no significant difference in the time to return to lameness between LDLB and HDLB (P = .72). When horses were treated with LDLB, the return to lameness was 4–24 hours, with a median return to the lameness of 7 hours; return to lameness

Table 1—Physical examination parameters of horses before and up to 72 hours after peri-neural injection of the palmar digital nerves at the proximal sesamoid bones with saline (n = 12), low dose liposomal bupivacaine (LDLB) (0.25 mg/kg, n = 6), and high dose liposomal bupivacaine (HDLB) (0.5 mg/kg, n = 6). Median and Interquartile ranges (in parentheses) are included.

<table>
<thead>
<tr>
<th>Group</th>
<th>Temperature ref. range</th>
<th>Heart rate ref. range</th>
<th>Respiratory rate ref. range</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>99 to 101.5 °F</td>
<td>24 to 50 beats/min</td>
<td>12 to 32 breaths/min</td>
</tr>
<tr>
<td>Saline</td>
<td>99.8 °F (97.3 to 101.0 °F)</td>
<td>40 beats/min (24 to 60 beats/min)</td>
<td>20 breaths/min (12 to 36 breaths/min)</td>
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<tr>
<td>LDLB</td>
<td>99.5 °F (97.1 to 101.3 °F)</td>
<td>36 beats/min (28 to 48 beats/min)</td>
<td>20 breaths/min (12 to 28 breaths/min)</td>
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<tr>
<td>HDLB</td>
<td>99.9 °F (97.8 to 100.7 °F)</td>
<td>40 beats/min (24 to 60 beats/min)</td>
<td>20 breaths/min (12 to 32 breaths/min)</td>
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</tbody>
</table>

Table 2—Mechanical nociceptive thresholds (MNTs) of the dorsal pastern region of front limbs before and up to 72 hours after peri-neural injection of the palmar digital nerves at the proximal sesamoid bones with saline, LDLB (0.25 mg/kg), and HDLB (0.5 mg/kg).

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Median (kg/cm²)</th>
<th>LDLB</th>
<th>HDLB</th>
<th>P-value</th>
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<tr>
<td>0</td>
<td>4.6</td>
<td>4.6</td>
<td>4.9</td>
<td>.68</td>
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<tr>
<td></td>
<td>IQR 3.4–5.6</td>
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<td>3.3–5.8</td>
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<tr>
<td>0.25</td>
<td>3.9</td>
<td>17.6*</td>
<td>18.7*</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>IQR 2.6–5.3</td>
<td>15.1–19.3</td>
<td>15.7–20.8</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.8</td>
<td>18.9*</td>
<td>18.1*</td>
<td>&lt; .001</td>
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<tr>
<td></td>
<td>IQR 3.7–6.0</td>
<td>17.1–20.1</td>
<td>17.3–18.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.3</td>
<td>19.3*</td>
<td>20.5*</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>IQR 3.2–5.4</td>
<td>19.1–20.8</td>
<td>17.7–20.7</td>
<td></td>
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<tr>
<td>3</td>
<td>4.6</td>
<td>11.8*</td>
<td>19.2*</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>IQR 3.4–5.2</td>
<td>11.7–15.8</td>
<td>18.2–20.0</td>
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<tr>
<td>4</td>
<td>4.0</td>
<td>5.8</td>
<td>10.8*</td>
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<tr>
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<td>3.6–13.3</td>
<td>7.6–18.5</td>
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<tr>
<td>5</td>
<td>4.2</td>
<td>5.1</td>
<td>16.7*</td>
<td>&lt; .001</td>
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<tr>
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<td>IQR 4.0–5.0</td>
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<td>7.4–19.0</td>
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<td>6</td>
<td>3.9</td>
<td>4.5</td>
<td>16.3*</td>
<td>&lt; .001</td>
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<tr>
<td></td>
<td>IQR 3.2–5.8</td>
<td>3.6–5.8</td>
<td>7.1–19.4</td>
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<td>.12</td>
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<td>48</td>
<td>6.3</td>
<td>3.9</td>
<td>4.4*</td>
<td>.02</td>
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<tr>
<td></td>
<td>IQR 3.8–8.7</td>
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<td>60</td>
<td>5.5</td>
<td>6.5</td>
<td>4.9</td>
<td>.72</td>
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<tr>
<td>72</td>
<td>6.3</td>
<td>4.8</td>
<td>4.5</td>
<td>.61</td>
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<td>IQR 4.1–6.5</td>
<td>2.2–7.4</td>
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<td></td>
</tr>
</tbody>
</table>

IQR = Interquartile range. LDLB = Low dose liposomal bupivacaine. HDLB = High dose liposomal bupivacaine.

*indicates a significant difference in MNT between the treated group (LDLB and HDLB) and saline within a row.
occurred at 4 hours in 1 horse, 6 hours in 2 horses, 8 hours in 1 horse, 12 hours in 1 horse, and 24 hours in 1 horse. When treated with HDLB, the return to lameness was 3–48 hours with a median of 9 hours; return to lameness occurred at 3 hours in 1 horse, 5 hours in 1 horse, 6 hours in 1 horse, 12 hours in 2 horses, and 48 hours in 1 horse. There was not a significant difference between LDLB and HDLB for return to lameness ($P = 1.0$) (Figure 2).

**Discussion**

In the present study, a dose-dependent effect on skin sensation and lameness of the 2 examined doses of LB as administered by peri-neural injection could not be identified and no horse had loss of skin sensation or loss of lameness at 72 hours. For the horses of the present study, a response to pressure was found, as determined by an increase in MNTs, was significantly higher after peri-neural administration of LB to the palmar digital nerves compared to the administration of saline solution. This effect lasted at least 3 hours, however, was not statistically different between LDLB and HDLB.

The analgesic effect of LB has been reported to have variable duration in horses. In 2 studies of peri-neural injection, LB resulted in analgesia for 4 to 6 hours. Another study, found improvement in MNTs and lameness for up to 24 hours. A dose effect was proposed, as a larger dose of LB was used compared to the other 2 studies (39.9 mg/nerve vs 26.6 mg/nerve). In the current study, despite the significant improvement in MNTs and lameness, there appeared to be variability in the return to sensation and return to lameness with both variables being independent of one another. Loss of skin (superficial) mechanoreception has been demonstrated to not directly equate to loss of sensation of deeper structures. Silva et al demonstrated that in horses blocked with lidocaine, over half of the horses had no loss of skin sensation; however, bupivacaine resulted in all but 1 horse losing skin sensation in which blockade did not occur even 30 minutes after administration. In another study comparing lidocaine and mepivacaine peri-neural blocks, skin sensation returned sooner than lameness. Loss of sensation took place in all horses that were administered LB in this study by 15 minutes. Horses administered LDLB were noted to have a median return of skin sensation before a median return to lameness; the opposite was found in the HDLB, with a return to lameness occurring sooner than a return to sensation.

Liposomal bupivacaine has been noted to induce mild granulomatous inflammation of adipose tissue. In this study, we identified mild to moderate swelling around the LB injection sites, which did not appear to be dose-dependent. Despite the swelling noted, none of the horses demonstrated marked heat or pain on palpation of the injection sites and clinical signs were self-resolving making the clinical significance unknown. Other studies have variable results, with 2 equine studies with a substantially lower volume (< 2 mL/site) resulting in mild inflammation in 10% to 30% of horses. Another study of slightly higher volumes (3 mL/site) showed no signs of inflammation. Opinions regarding skin preparation before regional anesthesia vary but typically consist of a light preparation of the site with gauze sponges soaked in 70% isopropyl alcohol or antiseptic followed by alcohol until the area visually is viewed as clean. In this study, the skin was lightly prepared with betadine and alcohol for all treatment groups including saline as is done commonly for peri-neural injections. Previously, this same protocol followed by local injection of LB was performed and showed no swelling. In this study, in addition to the larger volume, a larger needle size was used for the administration of the LB, and this may have allowed for possible interactions of the skin preparation and medication to occur and be responsible for the increased swelling as well as caused increased focal trauma.
Interactions with skin preparation may also be responsible for possible variability in the range of both duration of action and return to lameness. The manufacturer recommends avoiding premature destruction of liposomes and release of drugs that have been documented to occur with co-administration of other drugs such as local anesthetics or contact with antimicrobials. Inadvertent uncontrolled drug release may have occurred in this study due to inadequate drying time or the presence of antiseptic or alcohol on the skin. Alternate causes of variability of analgesia may be a direct result of using a larger and longer needle size used to inject the large volume. When evaluating the administration technique regarding total knee arthroplasty, it has been noted that the limited diffusion compared to other local anesthetics has made postoperative outcomes markedly affected by deposition and administration. Possible deposition of LB farther away from the nerve, which may have occurred by placement of the needle farther than anticipated may have resulted in a weaker effect than hypothesized from the higher concentration. Intraneural injections similarly have demonstrated longer sensory blockade than perineural without persistent motor or sensory deficit and no evidence of nerve injury when evaluating liposomal bupivacaine directly. Thus, the injection technique may be very important for a longer duration of action.

There are several limitations of the study. The main limitation of the study was the small sample size. Based on previous work, it was anticipated that 6 horses in each of the LB groups would be sufficient. However, based on the return of skin sensation data from the study, 19 horses per group would be necessary. Additionally, only 2 doses of LB were investigated, and while both were higher than previously investigated studies, they are below the recommended dose (5.3 mg/kg) that would be volume and cost-prohibitive.

Overall, the current study demonstrated LB effectively reduced pain and lameness with the examined doses. However, there was a high variability of LB on the duration of action at both examined doses. Regardless of dose, there may be local swelling postinjection that is likely to resolve without additional treatment. Additional investigation of these or other doses of LB would be necessary to determine if 72 hours of analgesia can be achieved by this route of administration.

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Disclosures

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References


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