Efficacy and duration of effect for liposomal bupivacaine when administered perineurally to the palmar digital nerves of horses

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OBJECTIVE
To determine the efficacy and duration of effect for liposomal bupivacaine following perineural administration to the medial and lateral palmar digital nerves of horses.

ANIMALS
9 nonlame mares.

PROCEDURES
For each horse, 2 mL of liposomal bupivacaine (13.3 mg/mL; total dose, 53.2 mg or approx 0.11 mg/kg) or sterile saline (0.9% NaCl) solution was injected adjacent to the medial and lateral palmar digital nerves at the level of the distal aspect of the proximal sesamoid bones of a randomly selected forelimb. Twenty-one days later, the opposite treatment was administered in the contralateral forelimb. A digital algometer was used to measure the mechanical nociceptive threshold (MNT) immediately before and at predetermined times for 48 hours after injection of each treatment. The mean MNT was compared between the 2 treatments at each measurement time.

RESULTS
The mean MNT for the liposomal bupivacaine–treated limbs was significantly greater (ie, the limb was less sensitive) than that for the saline-treated limbs between 30 minutes and 4 hours after treatment injection. Following liposomal bupivacaine administration, 1 horse developed mild swelling at the injection sites that resolved without treatment within 24 hours. No other adverse effects were observed.

CONCLUSIONS AND CLINICAL RELEVANCE
Results suggested that liposomal bupivacaine is another option for perineural anesthesia in horses. Further research is necessary to determine the optimal dose and better elucidate the duration of effect for the drug when used for palmar digital nerve blocks in horses. (*Am J Vet Res* 2020;81:400–405)

Regional anesthesia is an important method for the elimination of sensation in a particular area of the body, often a limb, which for horses allows surgery to be performed with the animal in a standing position or decreases the requirements for other anesthetics when general anesthesia is necessary.[1–3] Local anesthetics can be infiltrated into a surgical site or injected adjacent to a nerve to desensitize the region innervated by that nerve. Unlike anesthetics that are systemically administered to provide analgesia, local anesthetics block the sensory transmission of noxious stimuli and can provide perioperative pain control.[4] Bupivacaine hydrochloride is the longest-acting local anesthetic commonly used in horses. When bupivacaine hydrochloride is administered perineurally to the palmar digital nerves of horses, it provides analgesia for approximately 90 minutes in animals with experimentally induced foot pain[5] and 180 minutes in animals exposed to a thermal nociceptive stimulus.[6] The duration of analgesia induced by bupivacaine hydrochloride can be extended by repeated perineural injections or administration of a constant rate infusion of the drug through an indwelling catheter placed perineurally.[7] Both of those methods require hospitalization of the patient and can result in complications, such as infection at the injection or catheter site.[8,9]

Liposomal bupivacaine is a recently developed local anesthetic that consists of many multivesicular liposomes.[10] Bupivacaine is released slowly from the honeycomb-like matrix of liposomes, thereby prolonging its efficacy. Liposomal bupivacaine relieves signs of pain in dogs for up to 72 hours after it is injected into a surgical wound[11] and is routinely used to provide analgesia for human patients who have undergone soft-tissue or orthopedic surgery.[12,13]

To our knowledge, studies to assess the efficacy and duration of effect of liposomal bupivacaine following perineural administration to horses are lack-

ABBREVIATIONS
MNT Mechanical nociceptive threshold

ing. The aim of the study reported here was to determine the efficacy and duration of effect of liposomal bupivacaine following perineural administration to the medial and lateral palmar digital nerves of horses. Given data regarding sensory blockade after perineural injection of liposomal bupivacaine in other species, we hypothesized that perineural injection of liposomal bupivacaine to the medial and lateral palmar digital nerves at the level of the distal aspect of the proximal sesamoid bones of horses would eliminate sensation to the digit for at least 8 hours as determined by measurement of the MNT.[14]

Materials and Methods

Animals

All study protocols were reviewed and approved by the University of Tennessee Institutional Animal Care and Use Committee (protocol No. 2638 A2). Nine mares (6 American Quarter Horses and 3 Tennessee Walking Horses) from the University of Tennessee's teaching herd were used for the study. The horses ranged in age from 7 to 28 years (median age, 19 years) and in weight from 455 to 515 kg (median weight, 502 kg). For each horse, no evidence of lameness was observed when it was walked in a straight line and in a tight circle (ie, horses were sound), and the digit of both forelimbs had normal sensation as determined by withdrawal of the forelimb when pressure was applied to the digit with a pressure algometer.[a]

Study design

The study had a randomized crossover design. Each horse received a perineural injection of liposomal bupivacaine[b] (bupivacaine concentration, 13.3 mg/mL) or sterile saline (0.9% NaCl) solution (control) in a forelimb with a washout period of 21 days between treatments. Prior to injection of the first treatment, the order in which the liposomal bupivacaine and sterile saline solution were administered was determined randomly by the flip of a coin as was the forelimb in which the first treatment was to be administered. The second treatment was administered in the contralateral forelimb.

Treatment administration

Prior to treatment administration, each horse was sedated with xylazine hydrochloride (0.4 mg/kg, IV), and the area at the proposed injection sites was prepared with chlorhexidine scrub and 70% isopropyl alcohol in a routine manner. A 22-gauge, 2.54-cm-long needle was used to inject 2 mL of the assigned treatment, SC, adjacent to each (lateral and medial) palmar digital nerve at the level of the distal aspect of the proximal sesamoid bones of the selected forelimb. Thus, for the liposomal bupivacaine treatment, each horse received a total of 53.2 mg of the drug (calculated dose, 0.10 to 0.11 mg/kg).

MNT

The MNT of the digit of the treated forelimb was determined as described[15] by use of a pressure algometer[a] with a circular tip (diameter, 6 mm) before (baseline) and at 30 minutes and 1, 2, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours after injection of each treatment or until the criterion for discontinuation of testing was met. All MNT measurements were obtained by 1 investigator (MJM) who was unaware of (blinded to) the treatment administered. Briefly, the algometer was used to apply pressure (5 to 10 N/s) over a period of 5 to 10 seconds to the lateral heel bulb until the horse withdrew the limb or a maximum pressure of 50 N was achieved. The maximum applied pressure did not exceed 50 N because cutaneous lesions have been induced by the application of higher pressures.[16] The pressure applied at the time of the avoidance behavior (limb withdrawal) was recorded. For each designated measurement time, the MNT was recorded at 1- to 2-minute intervals until 3 consecutive measurements were obtained that were within 3 N of each other; the mean of the 3 measurements was calculated and used for analysis purposes. To prevent the horse from anticipating the application of pressure, its line of sight to the person applying the pressure was blocked by the handler's hand. Testing was discontinued when the MNT was less than the mean baseline MNT (ie, the horse withdrew the forelimb at a lower pressure than that applied before treatment) for 4 consecutive measurement times to prevent skin irritation and unnecessary discomfort to the horse. The procedure was repeated for the medial heel bulb of the treated forelimb.

The investigator responsible for obtaining the MNT measurements monitored the injection sites daily for evidence of inflammation, such as swelling, heat, and signs of pain when the sites were palpated. Each horse was also observed for lameness when walked in a straight line and in a tight circle on a daily basis for 5 days after treatment injection.

Statistical analysis

For each treatment at each MNT measurement time, the mean MNT for the lateral and medial heel bulbs was calculated for each horse. A linear mixed model for a crossover study design was used to assess the effects of treatment and time on the mean MNT. Diagnostic analysis was conducted on residuals to verify the model assumptions, with the Shapiro-Wilk and Levene tests used to evaluate residuals for normality and equal variance. A ranked transformation was applied prior to the final analysis because diagnostic analysis revealed violation of the assumptions of normality and equal variance. The Tukey adjustment was used when post hoc comparisons were necessary. All analyses were performed with a commercial statistical software program,[c] and values of $P < 0.05$ were considered significant.

Results

All 9 horses completed both treatment phases of the study. One horse developed mild swelling

Table 1—Mean ± SD MNT (N) for 9 nonlame horses immediately before (baseline) and at various times after injection of 2 mL of liposomal bupivacaine (13.3 mg/mL; 26.6 mg/nerve or approx 0.11 mg/kg) or sterile saline (0.9% NaCl) solution adjacent to both the medial and lateral palmar digital nerves at the level of the distal aspect of the proximal sesamoid bones of a forelimb.

Time relative to treatment injection (h)	Treatment		*P* value
	Liposomal bupivacaine	Saline solution	
Baseline	17.41 ± 2.77	18.11 ± 3.46	1.00
0.5	48.94 ± 1.05*	20.61 ± 3.74	< 0.001
1	48.67 ± 1.33*	19.99 ± 4.26	< 0.001
2	48.61 ± 1.39*	19.04 ± 4.10	< 0.001
4	43.25 ± 3.27*	16.92 ± 3.80	< 0.001
6	34.34 ± 5.41	23.87 ± 4.76	0.12
8	25.41 ± 4.62	24.41 ± 4.35	0.93
12	19.83 ± 3.57	24.12 ± 4.06	1.00
18	19.85 ± 3.50	20.69 ± 3.83	0.98
24	17.50 ± 3.09	22.85 ± 2.19	1.00
30	17.26 ± 3.21	23.21 ± 1.79	1.00
36	17.32 ± 2.71	17.50 ± 1.02	0.99
48	16.49 ± 2.54	16.61 ± 3.56	1.00

Each horse received each treatment with a 21-day washout period between treatments. The order in which the treatments were administered and the forelimb in which the first treatment was administered were randomized.

*Within a row, value differs significantly ($P < 0.05$) from that for the saline solution treatment.

(0.5-cm-diameter raised area) at both injection sites 48 hours after administration of liposomal bupivacaine. That horse did not exhibit any signs of pain when the swollen areas were palpated. The swelling resolved without treatment within 24 hours. None of the horses developed lameness when walked in a straight line or in a tight circle following administration of either treatment.

Mechanical nociceptive thresholds were recorded for 195 of 216 (90%) possible measurement times (9 horses × 2 treatments × 12 measurement times/treatment). The criterion to discontinue MNT testing (ie, 4 consecutive MNT measurements < the baseline MNT) was met for 21 of the final 6 designated measurement times in 7 horses. The baseline MNT did not differ significantly between limbs injected with liposomal bupivacaine and those injected with sterile saline solution. The mean MNT for liposomal bupivacaine–treated limbs was significantly greater than the mean MNT for control limbs at 30 minutes and 1, 2, and 4 hours after injection of the assigned treatment. The mean MNT did not differ significantly between liposomal bupivacaine–treated limbs and control limbs at any time beyond 4 hours after injection **(Table 1)**.

Discussion

Results of the present study suggested that liposomal bupivacaine was an effective perineural anesthetic for horses. For the horses of the present study, the mean MNT following perineural administration of liposomal bupivacaine to the palmar digital nerves of a randomly selected forelimb was significantly increased (the area was less sensitive to applied pressure), compared with the mean MNT following perineural administration of sterile saline solution (control) at all measurement times between 30 minutes and 4 hours after injection of the respective treatments. The mean MNT did not differ significantly between the liposomal bupivacaine–treated and control limbs at 6 hours after injection of the assigned treatment. The MNT was not measured between 4 and 6 hours after injection of the assigned treatment; therefore, it was not possible to determine the exact time at which the MNT no longer differed significantly between the 2 treatments (ie, we could not determine the exact duration of efficacy for liposomal bupivacaine).

All horses of the present study received xylazine prior to administration of each treatment to facilitate accurate perineural needle placement. Results of a previous study[17] indicate that xylazine affects the MNT of horses for 15 minutes after injection, but that effect is no longer apparent at 30 minutes after injection. Thus, in the present study, the initial post-treatment MNT measurement was not obtained until 30 minutes after injection of xylazine and the assigned treatment. For the control limbs of the present study, the mean MNT at 30 minutes after treatment administration did not differ significantly from that at baseline (immediately before treatment administration), which suggested that xylazine did not affect MNT measurements.

Findings of the present study failed to support our hypothesis that perineural administration of liposomal bupivacaine would significantly increase the MNT of treated limbs for at least 8 hours after injection. However, the mean MNT for the liposomal bupivacaine–treated limbs between 30 minutes and 4 hours after injection was close to the maximum possible MNT (50 N), which suggested that anesthesia of the foot was almost complete during that period.

In the present study, only 1 horse developed mild self-limiting swelling at the injection sites following liposomal bupivacaine administration. No other adverse effects were observed. Those findings were

consistent with results of another study[18] in which no adverse effects were observed in horses following intra-articular administration of liposomal bupivacaine. For 7 of the 9 horses of the present study, the MNT was not recorded for a total of 21 measurement times owing to apparent increasing sensitivity of the foot to the pressure applied by the algometer, which indicated that the foot was no longer desensitized.

The duration of effect for bupivacaine hydrochloride but not liposomal bupivacaine has been evaluated in horses. In 1 study,[5] perineural administration of 7.5 mg of bupivacaine hydrochloride adjacent to the palmar digital nerves of horses decreased the severity of lameness induced by the placement of a steel clamp around the hoof for a mean of 90 minutes; however, the duration of skin desensitization was not evaluated in that study. In another study,[6] perineural administration of bupivacaine hydrochloride adjacent to the lateral palmar digital nerve of horses decreased the response to a heat lamp–induced thermal nociceptive stimulus in a dose-dependent manner; the duration of effect ranged from 30 to 180 minutes following administration of bupivacaine hydrochloride at doses of 0.5 and 10 mg, respectively. The formulations of bupivacaine hydrochloride and liposomal bupivacaine differ substantially; therefore, the duration of effect for specific doses cannot be directly compared between the 2 formulations.[19]

The apparent duration of regional anesthesia (< 6 hours) following perineural administration of liposomal bupivacaine to the horses of the present study was shorter than that following perineural administration of the drug to pigs[14] and rabbits.[20] In anesthetized pigs, perineural administration of liposomal bupivacaine adjacent to the sciatic nerve decreased motor function for a mean of 10 hours and blocked sensation for a mean of 9.2 hours.[14] In anesthetized rabbits, motor blockade of the forelimb was observed for 10 hours after perineural injection of liposomal bupivacaine adjacent to the brachial plexus.[20] Differences in the duration of effect for liposomal bupivacaine among the horses of the present study and the pigs[14] and rabbits[20] of those other studies likely reflect differences in dose of the drug administered, nerve size, or species. Those differences might also be associated with the greater precision achieved when liposomal bupivacaine was injected while the animal was anesthetized and the nerve exposed.

In human medicine, perineural administration of liposomal bupivacaine is commonly performed intraoperatively and significantly decreases postoperative pain in patients following shoulder surgery and decreases the need for opioid rescue analgesia within 48 hours after surgery.[21] Human patients who receive liposomal bupivacaine following surgery have better pain scores (ie, less pain) and postoperative mobility and are hospitalized for a shorter time, compared with patients who receive bupivacaine hydrochloride.[21–24] Conversely, in other studies,[25,26] the postoperative pain score did not differ significantly between human patients who received liposomal bupivacaine and those who received bupivacaine hydrochloride. We are not aware of any clinical studies that evaluated the duration of skin sensation loss in human patients following regional anesthesia with liposomal bupivacaine. Therefore, comparisons between human studies and the present study are difficult.

Liposomal bupivacaine has been used as a perineural anesthetic and has been administered periarticularly to dogs[11] and human patients.[8,9] Dogs that underwent stifle joint surgery and received liposomal bupivacaine periarticularly at the time of surgery had fewer signs of pain 72 hours after surgery than did similar dogs that received isotonic saline solution periarticularly.[11] The investigators of that study[11] concluded that periarticular administration of liposomal bupivacaine had the potential to provide analgesia for 72 hours after injection in dogs. In human patients, a similar degree of analgesia was achieved for patients who received local infiltration of liposomal bupivacaine at a surgical site and those who received other local anesthetics by constant rate infusion through an indwelling perineural catheter; however, infusion of liposomal bupivacaine was less expensive and associated with fewer complications than constant rate infusion of local anesthetics.[8,9]

A limitation of the present study was that the effect of perineurally administered liposomal bupivacaine on cutaneous sensation was only evaluated in nonlame horses. The effect of liposomal bupivacaine on the alleviation of experimentally induced or naturally occurring lameness or surgical pain was not evaluated. The effectiveness of regional anesthesia is commonly assessed by loss of sensation in the dermatome innervated by the anesthetized nerve,[27] and loss of cutaneous sensation within the dermatome is assumed to be an indicator of the loss of pain in structures deep within the desensitized region. However, results of other studies[5,16] indicate that the presence or absence of sensation within the dermatome of an anesthetized nerve is not a good indicator of successful blockade of the target nerve. In a study[5] of 9 horses with experimentally induced foot pain, a significant decrease in lameness despite the presence of cutaneous sensation was observed in 1 and 5 horses following the use of bupivacaine hydrochloride and lidocaine, respectively, to perform a palmar digital nerve block; the remaining horses had a decrease in lameness and the loss of cutaneous sensation. In another study[16] of horses with experimentally induced foot pain, the use of lidocaine hydrochloride to perform a palmar digital nerve block did not consistently resolve lameness even though both heel bulbs had complete loss of skin sensation in all evaluated feet. Investigators of that study[16] also reported that sensation within the dermatome returned before lameness recurred. We could not find any studies in the veterinary literature that were conducted to determine whether the use of liposomal bupivacaine for regional anesthesia in horses is effective for alleviating pain associated with lameness.

Other limitations of the present study included the small sample size and the fact that only 1 dose of liposomal bupivacaine (26.6 mg) was injected adjacent to each palmar digital nerve. That dose was lower than the dose of liposomal bupivacaine (133 mg) recommended for regional anesthesia of the brachial plexus in human patients undergoing shoulder surgery.[21] Results of a study[6] in which bupivacaine hydrochloride was used to perform blocks of the palmar digital nerve and desensitize the forelimb digits of horses indicate that the onset of skin desensitization was quicker and the duration of effect was longer as the dose of bupivacaine administered increased. For human patients, 266 mg of liposomal bupivacaine is the maximum quantity recommended for local infiltration at a surgery site because that dose is associated with nontoxic plasma concentrations of the drug.[28] Had we chosen to administer 133 mg of liposomal bupivacaine adjacent to both the lateral and medial palmar digital nerves (ie, 266 mg of liposomal bupivacaine per forelimb; equivalent to the dose recommended for the interscalene block of the brachial plexus in human patients) of the horses in the present study, it would have required the injection of 10 mL of the commercially available formulation of the drug at each injection site, which is a large volume to inject in that region. We chose to inject 26.6 mg of liposomal bupivacaine adjacent to each palmar digital nerve because intra-articular administration of a similar dose (0.12 mg/kg; approx 60 mg) of the drug to horses did not cause any adverse effects and the injectate volume was 2 mL at each site, which is the volume of local anesthetic solution commonly administered when an abaxial sesamoid nerve block is performed in horses.[27] In the present study, the mean MNT for liposomal bupivacaine–treated limbs was significantly greater (the limb was less sensitive to pressure) than that for the control limbs between 30 minutes and 4 hours after injection of the assigned treatment. It is possible that injection of a higher dose of liposomal bupivacaine may have resulted in a longer duration of effect. Further research is warranted to determine the optimal dose of liposomal bupivacaine for palmar digital nerve blocks in horses. Finally, the present study did not compare the duration of effect between palmar digital nerve blocks performed with liposomal bupivacaine and those performed with bupivacaine hydrochloride. That information is necessary to help inform equine practitioners' decisions regarding which bupivacaine preparation is most appropriate for regional anesthesia in individual horses.

Findings of the present study suggested that perineural injection of liposomal bupivacaine (26.6 mg/palmar digital nerve or a total dose of approx 0.11 mg/kg) significantly increased the MNT of the digit between 30 minutes and 4 hours after injection of the drug without any apparent adverse effects. Liposomal bupivacaine can be considered another option for perineural anesthesia in horses.

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Footnotes

a. Digital Force Dial, Wagner Instruments, Greenwich, Conn.
b. Nocita, Aratana Therapeutics, Leawood, Kan.
c. SAS, version 9.4 TS1M4 for Windows 64X, SAS Institute Inc, Cary, NC.

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