Bupivacaine liposomal injectable suspension (Nocita®) provides postoperative analgesia following eyelid injection in dogs undergoing enucleation.

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Abstract

OBJECTIVE: To evaluate the effectiveness of bupivacaine liposomal injectable suspension (BLIS) in reducing post-operative pain in dogs undergoing enucleation.

ANIMALS: 30 dogs

PROCEDURES: Client-owned dogs were randomly assigned to receive BLIS or saline. Dogs were premedicated with hydromorphone 0.1 mg/kg and acepromazine 0.01-0.04 mg/kg, induced with propofol to effect, and maintained with isoflurane. Dogs received a subconjunctival enucleation. Immediately prior to incision closure, the subcutaneous eyelid tissues were injected with BLIS or saline in a ring-block manner. All dogs received an oral 0.1 mg/kg dose of meloxicam at 8 hours postoperatively. Pain scoring and algometry of the incision was performed preoperatively and at 0, 1, 2, 4, 8, 24, 36, 48, and 72 hours postoperatively. Dogs received meloxicam following the 8-hour measurements. Rescue analgesia occurred with a pain score ≥ 3 in any category or ≥ 10 total.

RESULTS: Fewer dogs in the BLIS group ($p=0.010$) required rescue analgesia (20% versus 66% of saline controls). Dogs receiving BLIS had higher algometry values at T0 ($p=0.045$) and lower algometry values at T24 ($p=0.02$) and T48 ($p=0.014$). Pain scores at T1 ($p=0.042$) were higher in dogs that received saline. In all dogs that did not require rescue analgesia (both BLIS and saline), there was a significant increase in algometry values between T8 and T24 ($p=0.0056$).

CLINICAL RELEVANCE: Fewer dogs receiving BLIS required rescue analgesia, supporting its use as part of a multimodal pain management plan.

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Acknowledgements

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Background

Enucleation is a common procedure to treat painful, blinding ocular conditions in dogs, and clinicians frequently use systemic NSAIDs and opioids for postoperative analgesia. While effective, these medications may have side effects which limit their use. NSAIDs can lead to gastrointestinal ulceration and renal injury, while opioids may cause vomiting, ileus, and constipation.[1] Additionally, oral opioids have poor bioavailability and questionable efficacy in dogs,[1, 2] and additional concerns arise for prescribing due to the risk of diversion of Schedule II substances.[3]

Local anesthetics provide intraoperative and postoperative analgesia by blocking transmission of nociceptive nerves to the central nervous system, and side effects are rare at appropriate doses. Unlike other analgesics, these drugs have the potential to eliminate pain sensation, but most local anesthetics have a duration no longer than six hours after tissue diffusion.[4] A long-acting local anesthetic, bupivacaine liposomal injectable suspension (BLIS), was introduced into the veterinary market under the trade name Nocita®. Bupivacaine is encapsulated in a multivesicular liposome with a honeycomb structure which breaks down over time, slowly releasing bupivacaine from individual vesicles into the surrounding tissues and providing up to 72 hours of pain relief.[5] This drug has been approved in dogs for peri-incisional injection following surgery for cranial cruciate ligament instability and in cats undergoing onychectomy.[6] Since its release, it has also been assessed in dogs and cats undergoing ovariohysterectomy, in cattle for analgesia after castration, and in horses for orthopedic disease.[7-12] However, no studies assessing its use for ocular surgery have been performed.

A long-acting local anesthetic has the potential to greatly improve postoperative analgesia during the painful inflammatory phase and may be especially valuable for animals that are unable to tolerate postoperative NSAIDs or opioids. The purpose of this study was to assess the efficacy of bupivacaine liposomal injectable suspension (BLIS) to reduce pain after injection into the eyelids in dogs undergoing enucleation. We hypothesized that dogs receiving BLIS would have lower median pain scores and higher mean algometry values following surgery when compared to dogs that receive a saline placebo injection, and that significantly more animals receiving saline would require rescue analgesia relative to those receiving BLIS.

Methodology

Case selection

Dogs were selected from the general patient population presenting to the Ophthalmology Service at Kansas State University Veterinary Health Center from April 2021 until January 2023. Dogs were excluded if they were less than 6 months of age, weighed less than 3.4 kg, had orbital disease, injury to the face, or globe proptosis, had systemic disease that precluded the use of oral NSAIDs following surgery, or had previously received a systemic steroid or a NSAID within the previous three days. This study was approved by the Kansas State University Institutional Animal Care and Use Committee (protocol number 4492). All owners signed a consent form prior to enrolling their dogs in the study.

Randomization

Dogs were randomly assigned to receive BLIS (Nocita®, Elanco Animal Health) or sterile saline placebo injection via a random number generator (Random Number Generator Plus; RandomAppsInc) with all even-numbered dogs receiving BLIS and all odd-numbered dogs receiving an equal volume of sterile saline. The clinician performing pain scoring, algometry, and surgery (MAC) remained masked as to the group of each dog for the duration of the study.

Pain scoring, algometry, and rescue analgesia

Pain scoring and algometry were performed on all dogs to establish a baseline prior to premedication administration, and then repeated at extubation (T0) and 1, 2, 4, 8, 24, 36, 48, and 72 hours postoperatively. Pain-scoring was based on a modified form of a previously published subjective scoring system used to assess ocular pain in dogs **(Appendix A)**.[13] Dogs were

considered painful if they received a score of ≥3 in any single category or a total score of ≥10. Dogs that reached this threshold were administered additional analgesia and removed from the study. Algometry was performed using a device (Wagner Pain Test FPX 10, Wagner Instruments) modified with 3 mm diameter plastic tip to allow for focal peri-incisional pressure **(Figure 1)**. The algometer was new and certified as calibrated prior to the start of the study and was submitted for confirmation of calibration at the end of the study. Measurements were performed at two locations around the affected eye—dorsally just below the dorsal orbital rim and ventrally just above the ventral orbital rim—and these measurements were averaged. Pressure was released immediately when the dog displayed any form of discomfort. No more than 10 newtons of pressure were applied to avoid damage to the incision. All pain scoring and algometry measurements were performed by the same examiner (MAC).

Anesthesia and surgical procedure

All dogs were administered hydromorphone 0.1 mg/kg IM and acepromazine 0.01-0.04 mg/kg IM prior to surgery, and an IV catheter was placed into the cephalic or lateral saphenous vein. Anesthesia was induced with propofol IV to effect, up to 4-5 mg/kg, and maintained with 0.5-3% isoflurane. All dogs were placed on IV fluids and administered additional medications as needed to help maintain normal cardiovascular function, but no additional systemic analgesics or anxiolytics were given during surgery or recovery. Temperature, SpO_2, blood pressure, heart rate, and ECG waveform were monitored throughout anesthesia for all dogs.

A standard subconjunctival enucleation was performed in all animals by the same surgeon (MAC). Following removal of the globe, the deep orbital layer was closed with 4-0 Monocryl in

a simple continuous pattern. The surgeon then left the room, and the eyelids were injected with either BLIS diluted 1:1 with 0.9% sodium chloride or with 0.9% sodium chloride placebo. Dogs less than 20 kg received a total volume of 2 mL and dogs greater than 20 kg received a total volume of 3 mL. Diluted 1:1, these volumes ensured that dogs at the minimum weight to qualify for the study would not receive more than the labeled 5.3 mg/kg dose. Injections were performed prior to closure of the eyelids to allow the individual injecting to visualize the posterior surface of the cut eyelids, preventing full-thickness penetration of the needle into the orbit. Injections were performed by either the ophthalmology nurse or one of the coauthors (AJR) using a 22-gauge, 1 inch needle, placing the needle approximately 3-5 mm from the cut edge of the eyelids, within the center of the tissue **(Figure 2)**. A ring block was performed to include both upper and lower eyelids and the medial and lateral canthal regions. The surface of the tissue was rinsed with sterile saline to remove any residual BLIS. The surgeon returned and closed the eyelid subcutaneous tissue with 4-0 Monocryl in a simple continuous pattern and the skin with 4-0 Monocryl in an intradermal pattern.

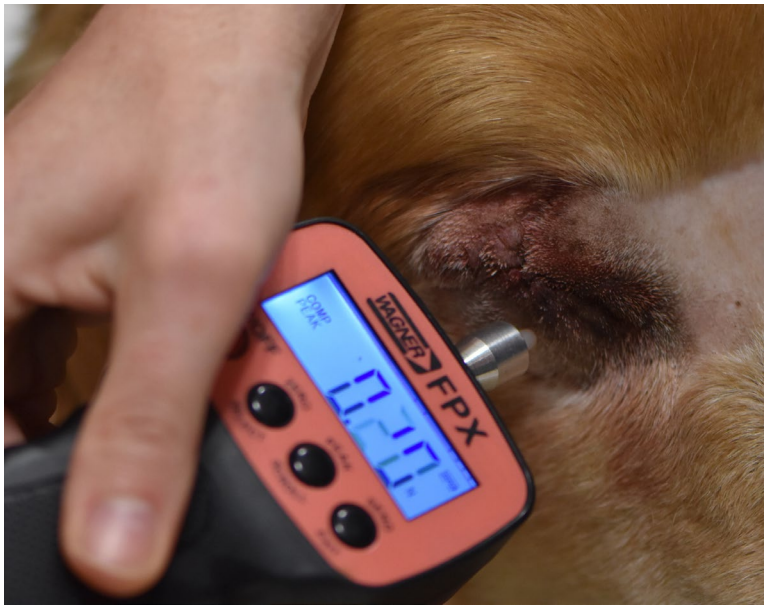
Postoperative medications

Dogs received oral meloxicam at 0.1 mg/kg, based on lean body weight, after the 8-hour postoperative pain scoring was performed and then every 24 hours thereafter for a total of three to five days. Antibiotics were not routinely given. No other medications were administered unless the dog became painful and exceeded the established set pain score limits.

Statistical analysis

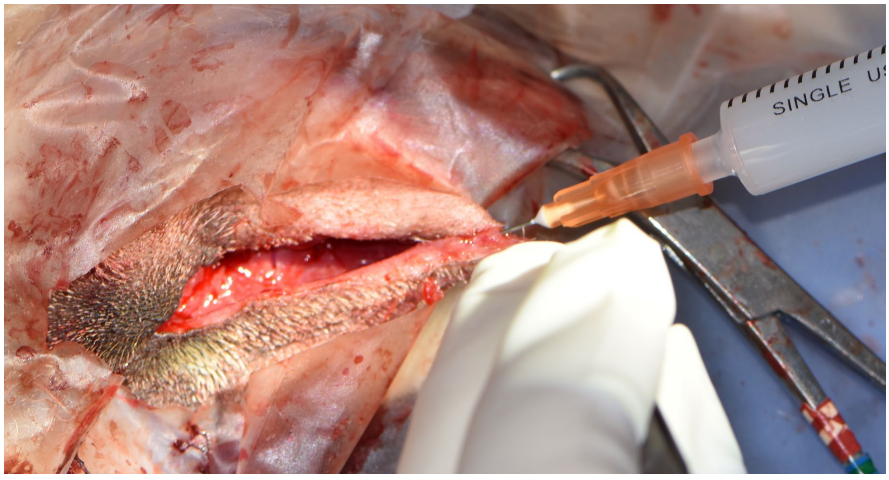
Statistical analysis was performed using commercially available software (WINKS SDA Version 7.0.9 Professional, TexaSoft) and in all cases $p \leq 0.05$ was considered significant. Treatment groups and rescued vs non-rescued dogs were compared for differences in algometry values at each timepoint, weight, or age using an Independent Group T-test. When comparing pain scores at each timepoint between treatment groups and between rescued and non-rescued animals, a Mann-Whitney U test was performed. A Chi-Square test was used to assess the need for rescue between treatment groups. When comparing the differences in pain score between two timepoints, a Wilcoxon's Signed Rank test was used. When comparing the differences in algometry values at two timepoints, a Paired T-test was used. Results for parametric data were presented as mean +/- standard deviation. Results for nonparametric data were presented as median and range.

Figure 1 : Algometry testing in a postoperative dog.



A handheld algometer was used to apply pressure adjacent to the incision site at two locations. Both locations were approximately half-way along the length of the incision, located ventral to the dorsal orbital rim and dorsal to the ventral orbital rim. A modified, 3 mm plastic tip was used to help insure localized pressure to the site. Pressure was immediately removed with any display of discomfort from the dog or if 10 newtons of pressure was achieved.

Figure 2 : Injection of BLIS following closure of the deep periorbital tissue and prior to closure of the eyelids.



The eyelid margins of dogs were injected with BLIS or saline using a 22-guage, 1" needle approximately 3-5 mm from the cut margin, distributing the entire volume of the syringe around the incision in a ring-block fashion.

Results

Thirty-seven dogs were enrolled into the study. Three dogs were excluded due to anesthetic complications requiring deviation from the anesthetic protocol and four additional dogs were excluded due to protocol deviations not related to anesthesia. Ultimately, 30 dogs completed the study and data collected from these dogs were used for statistical analysis.

The primary reason for enucleation included glaucoma (n=17 dogs), corneal ulceration (n=6 dogs), uveal neoplasia (n=3 dogs), chronic uveitis (n=2 dogs), and penetrating trauma to the globe (n=2 dogs). The following breeds of dogs completed the study: mixed breed (n=9), Shih Tzu (n=3), Labrador (n=3), Golden Retriever (n=2), and one each of the following: American Cocker Spaniel, Bichon, Boxer, Cairn terrier, Chihuahua, Goldendoodle, German Shepherd, German Shorthair Pointer, Lhasa Apso, Miniature Australian Shepherd, Pug, Shiba Inu, and Whippet. There were 18 spayed females (8 assigned to BLIS, 10 assigned to saline), 10 castrated males (6 assigned to BLIS, 4 assigned to saline), and 2 intact males (1 assigned to BLIS, 1 assigned to saline).

The average age of all dogs was 9.22 years (range 0.75-14.50 years) and average weight was 20.13 kg (range 5.7-48.20 kg). Of those dogs that received BLIS, the average age was 8.91 +/- 3.53 years and average weight was 17.69 +/- 13.11 kg. Of those dogs that received saline, the average age was 9.54 +/- 3.21 years and average weight was 22.57 +/- 13.53 kg. Age and weight were not significantly different between the two groups.

Four dogs were administered analgesia or anxiolytic medications within 24 hours prior to anesthesia. Systemic medications included codeine (n=2 dogs), gabapentin (n=1 dog), and trazodone (n=1 dog); these drugs were all administered at least 18 hours prior to premedication. All four dogs were randomized to the saline group. One dog receiving codeine and one dog receiving trazodone remained comfortable throughout the study. The other two dogs became painful prior to completion of the study.

Concurrent surgical procedures

Concurrent surgical procedures were performed in four dogs. One dog received a chemical ciliary body ablation in the contralateral eye. This dog was randomized to the BLIS group and did not require rescue analgesia. In one dog, phacoemulsification was performed in the contralateral eye. This dog was randomized to receive saline and became painful four hours following surgery. The remaining two dogs received bilateral enucleations. In both cases, one eye had glaucoma refractory to medical management and the other eye was permanently blind from glaucoma, but the intraocular pressure was controlled at the time of surgery. The second eye was enucleated due to the concern for uncontrolled glaucoma in the future. The eye with uncontrolled glaucoma was considered the primary concern and therefore was enucleated first and was used for all pain measurements. Both dogs that received bilateral enucleations were randomized to receive BLIS and both surgical sites of each dog received an injection with BLIS. Neither dog required rescue analgesia.

Rescue analgesia

Age and weight were not significantly different between dogs requiring rescue analgesia and those that did not. Of the dogs that received BLIS, 3/15 (20%) required rescue analgesia. Of the dogs that received saline, 10/15 (66%) required rescue analgesia. The need for rescue analgesia was significantly more likely (p=0.010) to occur in the saline group when compared to dogs receiving BLIS. Rescue analgesia was administered at T1 (6 dogs), T2 (1 dog), T4 (2 dogs), and T8 (4 dogs) **(Figure 3)**. All dogs that were comfortable at T8 remained comfortable until the final 72-hour pain measurement.

Pain scoring and algometry

At most timepoints, there was no significant difference in algometry and pain score between dogs receiving BLIS vs saline. The exceptions to this were at T0, when dogs that received BLIS had a significantly higher algometry value than those that received saline (p=0.045), and at T24 and T48, when dogs that received BLIS had a significantly lower mean algometry score (p=0.02 and p=0.014, respectively) **(Figure 4)**. There was a difference in median pain score between the two groups at T1, when dogs that received saline had a significantly higher pain score than those that received BLIS (p=0.042), but not at any other time **(Figure 5)**.

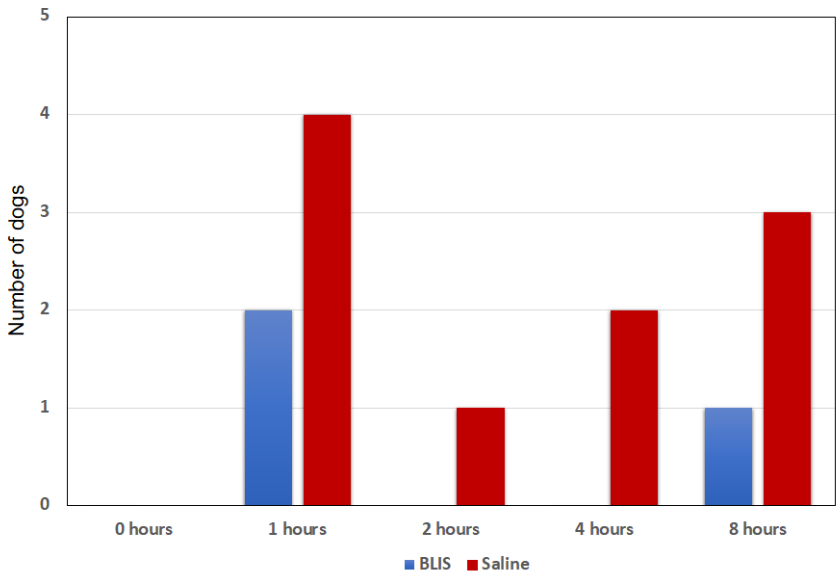
Dogs were also analyzed by need for rescue analgesia, regardless of treatment group. There was no significant difference in algometry values between dogs that received rescue and those that did not, up to the T8 time point. Pain scores were significantly higher in dogs requiring rescue relative to those that did not at T8 (p=0.009), but not at any other times **(Figure 6)**.

Of the dogs that received BLIS and did not require rescue, there were significantly higher algometry values at T24 relative to T8 (p=0.0056). Pain scores were not significantly different between those two timepoints. When comparing algometry and pain scores of these same dogs at T24 to those at T36, T48, and T72, there was no significant difference.

Postoperative complications

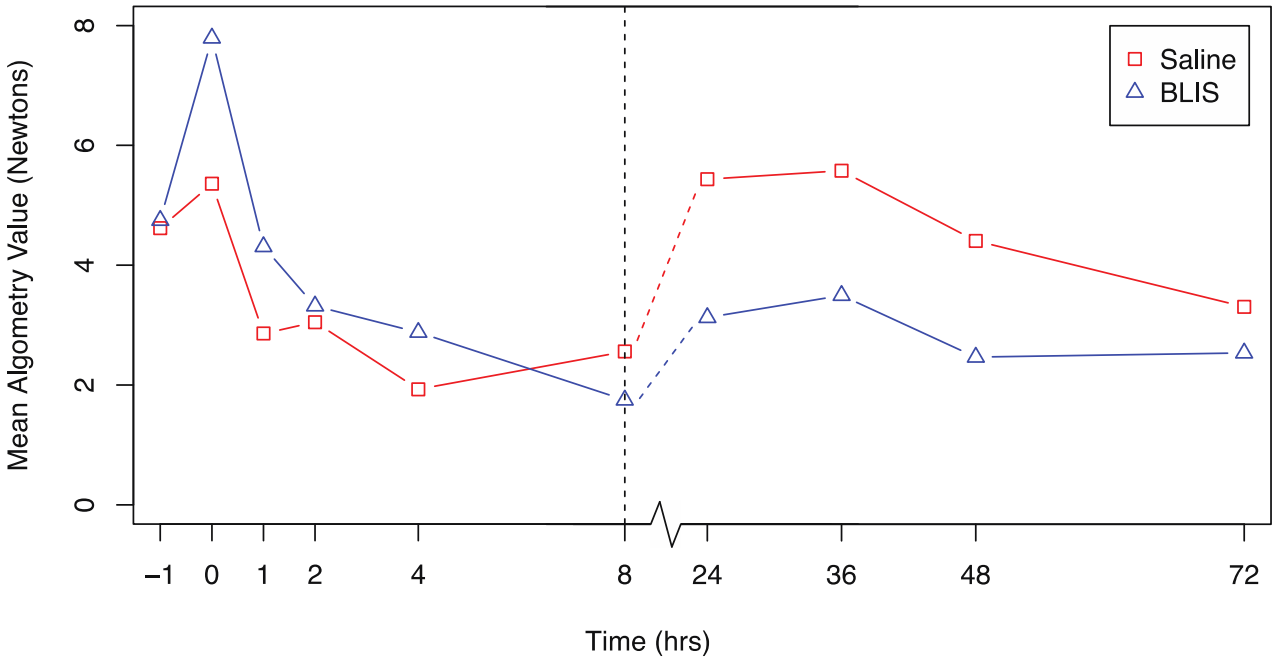
Only one dog developed a postoperative complication that could be attributed to surgery. This dog developed an incisional infection and had been randomized to the saline group.

Figure 3 : The number of dogs requiring rescue analgesia in the BLIS (blue) and saline (red) treatment groups at each timepoint.



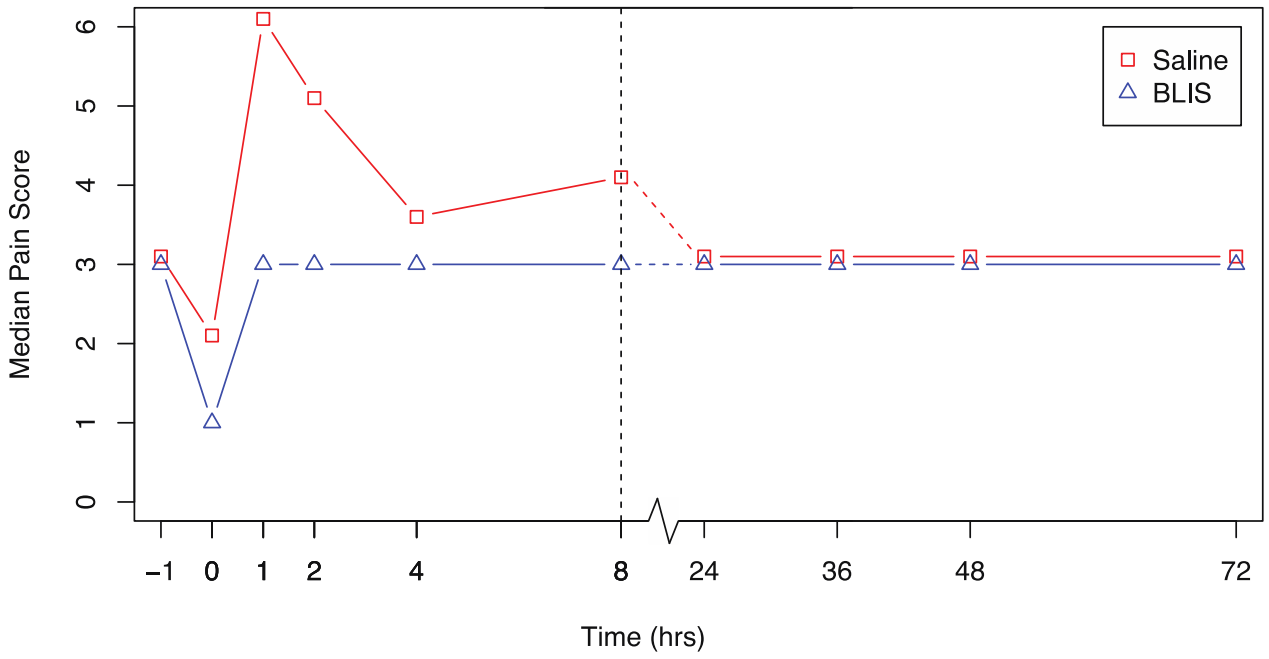
Significantly more dogs receiving saline (10/15) required rescue analgesia relative to dogs receiving BLIS (3/15). No dogs in the study required rescue after the 8-hour postoperative timepoint.

Figure 4 : Mean algometry values in newtons at each timepoint for dogs receiving BLIS (squares) vs saline (triangles).



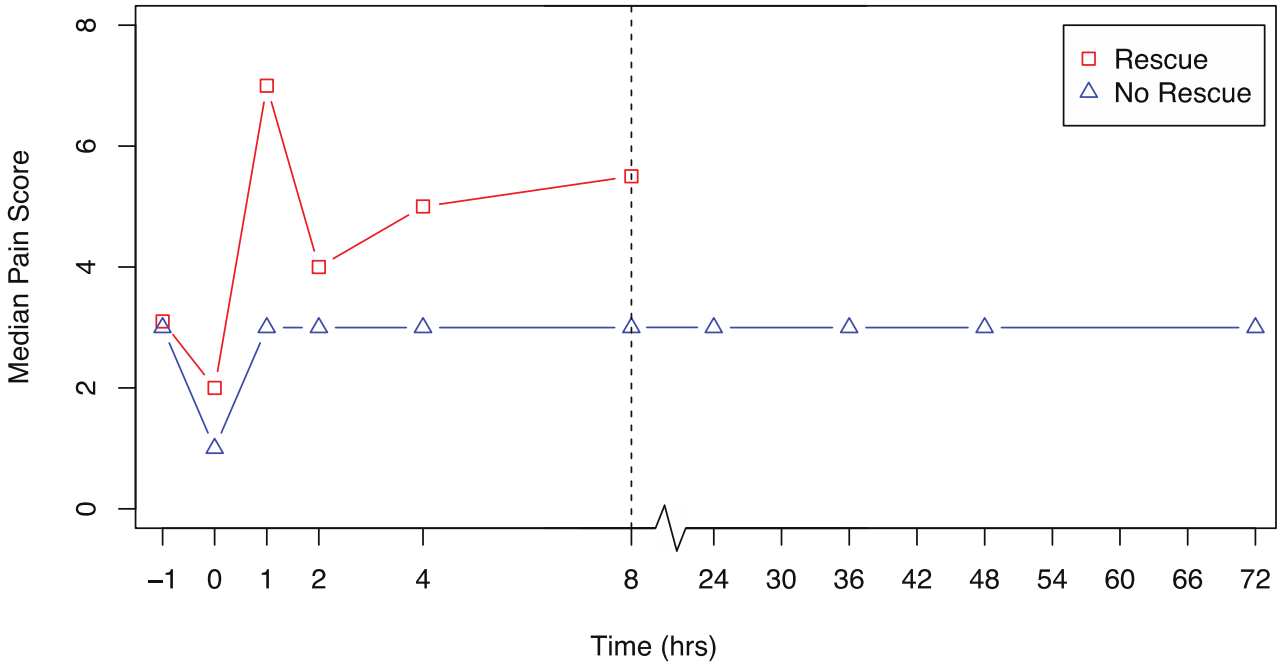
Although dogs receiving BLIS had a higher mean algometry value though 4 hours postoperatively, this was only significant at T0 (p=0.02). Dogs receiving saline had higher algometry values at T8 onward, which were significant at T24 (p=0.02) and T48 (p=0.014). The pre-operative values are labeled as time -1.

Figure 5 : Median pain scores at each time point for dogs receiving BLIS (triangles) or saline (squares).



Pain scores were higher at all postoperative timepoints through T8, but this difference was only significant at T1 (p=0.042). Median pain scores were equal between the groups at T24 onward. The pre-operative scores are labeled as time -1.

Figure 6 : Median pain scores at each time point for dogs requiring rescue (squares) versus those that did not (triangles).



Pain scores were only significantly different between dogs requiring rescue and those that did not at T8 (p=0.009). The pre-operative scores are labeled as time -1

Discussion

This study showed that dogs treated with BLIS were significantly less likely to require analgesic rescue postoperatively, supporting its use as part of a multimodal analgesic approach in dogs undergoing enucleation. Of dogs that received BLIS, 20% required rescue analgesia; in contrast, 66% of dogs in the placebo group required rescue. Interestingly, algometry and pain scoring were not consistently different between the two groups, with algometry values significantly higher in the BLIS group immediately after surgery at T0, and then significantly reduced in the BLIS group relative to saline at T24 and T48. Additionally, dogs in the BLIS group that did not require rescue analgesia had a significantly higher algometry reading at T24 relative to T8, likely due to administration of meloxicam. However, there was no significant difference in algometry values at later timepoints (T36, T48, or T72) relative to T24. The overall lack of difference in algometry and pain scoring between the two groups maybe have been secondary to a type II error given the small number of animals in the study.

There are several possible explanations for BLIS-treated dogs becoming uncomfortable following surgery. Injection technique is an important consideration, in addition to the inherent limitations of pain scoring. First, the ring block was performed in a single plane within the eyelids. This technique was simple, helping to ensure reproducibility throughout the study. However, it is possible that nerves deeper or more superficial to the plane of injection could still provide pain sensation to the cut margins of the eyelids. It is also possible that the ring block was not completed 360 degrees around in some dogs. Additionally, this technique does not block any traumatized tissue within the orbit. Altering the injection technique to include a larger area within the eyelid as well as some of the damaged orbital tissue may reduce the number of dogs

that have uncontrolled pain following surgery. Lastly, pain scoring is subjective and the examiner may have misinterpreted certain behaviors, such as those attributable to anxiety or dysphoria, as consistent with pain. Given that 20% of dogs that received BLIS required rescue analgesia in this study, we would recommend its use as part of a multimodal analgesic approach rather than as a sole agent for pain control.

Interestingly, dogs that received BLIS had significantly lower algometry values than dogs in the saline group at T24 and T48, indicating greater incisional sensitivity. A possible explanation for this unexpected finding was a selection bias in the saline group. This subset of dogs, who had progressed to the T8 timepoint without the benefit of any analgesia beyond their premedication opioid, may have been especially stoic and less likely to show evidence of pain regardless of treatment received. Since it is possible that all dogs experienced some discomfort with increasing algometer pressure due to transfer of this pressure to the deeper tissues in the orbit, those dogs that were naturally more stoic may have skewed their algometry values upward. Another possibility for this finding is a post-block hypersensitivity of nociceptive receptors or afferent transmission and modulation of pain. Rebound pain occurs within the first 12-24 hours after resolution of the nerve block, and in one study was reported in just under half of people who received regional anesthesia.[14] Although not well-understood, proposed mechanisms for rebound pain include trauma from block placement, increased inflammation secondary to properties of the local anesthetic on the surrounding tissue, or nociceptive memory which may result in worsened pain after resolution of the block.[15] In these cases, pain is described as very severe and more intense than would be expected for the surgical stimulus.[15] It is possible that a proportion of dogs in the BLIS group had rebound pain, which may have been compounded by the repeated

peri-incisional trauma from prior algometry measurements. Rebound pain is often a transient phenomenon, lasting four to six hours in people.[14] We saw a consistent reduction in algometry values for dogs receiving BLIS starting at T8 and continuing through T72. This could be explained if the 12 dogs remaining in the BLIS group from T8 onward had resolution of their blocks spread out over the remaining time-period, which could have driven the mean algometry value for the group downward. Although suspected rebound pain has been documented in rats following injection with BLIS, to our knowledge it has not been studied in dogs receiving this drug.[16]

Given the pharmacokinetics of hydromorphone, it is unlikely that this premedication had a significant effect on reducing the number of animals that ultimately required rescue analgesia postoperatively. Hydromorphone has a duration of four to six hours after a single dose.[17,18] When accounting for time for induction of anesthesia and the surgical procedure, the T8 pain scoring was performed approximately 10 hours following premedication, which was immediately prior to the administration of meloxicam. We would therefore expect that dogs would no longer be experiencing a significant analgesic effect from preoperative hydromorphone. However, we cannot exclude a dog-related variability in the metabolism of hydromorphone, and some dogs may have had prolonged analgesia.

The main limitation of this study was the use of a postoperative NSAID the evening following surgery. Given the ethical implications of withholding analgesia following a surgical procedure, the authors felt that this intervention was necessary for the welfare of the dogs enrolled in the study. As demonstrated, a third of dogs that received a placebo injection did not show adequate

evidence of pain at the T8 timepoint to be removed from the study. Without postoperative meloxicam, these dogs may have completed without the benefit of any postoperative analgesia. This benefit is further supported when comparing algometry values prior to (T8) and after (T24) administration of meloxicam, which showed a significant increase in values, indicating that pain sensitivity was reduced after starting the NSAID.

Administration of meloxicam may have allowed dogs to remain comfortable enough complete the 72-hour study duration, so we are unable to confirm that BLIS alone would have been sufficient to keep dogs comfortable for the labeled timeframe. Dogs receiving BLIS had no significant difference in algometry or pain score values at T24 when compared to T36, T48, or T72. This would support that a continued benefit from BIS administration, but cannot be definitively proven given the confounding effect of meloxicam administration. Previous studies have confirmed that BLIS can provide up to 72 hours of postoperative analgesia when given alone, although this duration is not consistent for all animals, with 62.5% of animals requiring rescue by 72 hours in one study.[19,20] A future study without the benefit of a postoperative NSAID would be required to determine if BLIS could provide adequate analgesia for up to 72 hours when used in the manner described in this study.

Conclusion

In conclusion, there were significantly fewer dogs receiving BLIS that required rescue analgesia after enucleation, supporting its use as an analgesic if administered in the subcutaneous tissues of the eyelids prior to closure. It is possible that some animals became painful due to orbital tissue damage that was not blocked. Given that some dogs required rescue analgesia despite receiving BLIS, it may be considered as part of a multimodal pain management approach.

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Appendix A - Subjective pain scoring system

Appendix A Table A.1: Subjective pain scoring sys

Category	Score	Description
Comfort	0	Asleep or calm
	1	Awake, interested in surroundings
	2	Mild agitation or depressed, uninterested in surroundings
	3	Moderate agitation, restless, and uncomfortable
	4	Extremely agitated and thrashing
Movement	0	Quiet
	1	1-2 position changes per minute
	2	2-6 position changes per minute
	3	Continuous position changes
Palpation of incision	0	Too sedate to evaluate
	1	Normal/no pain on palpation
	2	Allows palpation, but moves away when operated eye is touched
	3	Will not allow the operated eye to be touched
	4	Will not allow the head to be touched
Behavior (unprovoked)	0	Too sedate to evaluate
	1	Normal
	2	Minor changes
	3	Moderately abnormal (less mobile or alert, unaware of surroundings, or very restless)
	4	Markedly abnormal (very restless, self-mutilation, grunting, or facing back of cage)
Vocalization	0	Quiet
	1	Crying (but responds/calms with quiet voice and stroking), or dysphoric
	2	Intermittent crying, no response to quiet voice and stroking
	3	Constant crying, no response to stroking or voice