

## Effect of Topical Administration of 0.8% Nalbuphine on the Cornea in Dogs after Phacoemulsification

Chen-Han LEE<sup>1)</sup>, Shiun-Long LIN<sup>1,2)</sup>, Ting-Ting CHI<sup>2)</sup>, Shu-Hao CHANG<sup>2)</sup> and Hsien-Chi WANG<sup>1,2)\*</sup>

<sup>1)</sup>Department of Veterinary Medicine, College of Veterinary Medicine, National Chung-Hsing University, 250-1 Kuo Kuang Road, Taichung 402, Taiwan

<sup>2)</sup>Veterinary Medicine Teaching Hospital, College of Veterinary Medicine, National Chung-Hsing University, 250-1 Kuo Kuang Road, Taichung 402, Taiwan

(Received 21 March 2012/Accepted 20 March 2013/Published online in J-STAGE 3 April 2013)

**ABSTRACT.** It is suggested that topical application of opioids may provide localized analgesia without delay in corneal wound healing. This study was designed to evaluate the effect of topical application of 0.8% nalbuphine on post-operative ocular pain in dogs. Twelve eyes from 11 dogs undergoing phacoemulsification cataract surgery were divided into a nalbuphine group (n=6) and saline group (n=6). Postoperatively, the nalbuphine group received 0.1 ml of topical 0.8% alkalized nalbuphine (pH 5.6) every 8 hr, and the saline group received 0.1 ml of topical saline (pH 5.9) as a placebo. All dogs received systemic postoperative pain managements with oral tramadol (4 mg/kg) and prednisolone (0.5 mg/kg) every 8 hr. All dogs received pre- and post-ophthalmic examinations. Pain was scored in the dogs using a pain scoring system modified from the University of Melbourne pain scale at 15, 30 and 60 min following the topical treatment on days 1 and 2 (24 and 48 hr after surgery). Eye blink frequency and corneal touch threshold (CTT) were recorded at the same time. There was no statistical difference in the pain score between groups. Significant decreases in CTT, blepharospasm and eye blink frequency were observed after the topical nalbuphine treatment. This indicated that topical application of 0.8% nalbuphine solution can produce a rapid reduction of corneal discomfort in dogs.

**KEY WORDS:** canine, corneal sensitivity, nalbuphine, phacoemulsification, topical.

doi: 10.1292/jvms.12-0125; *J. Vet. Med. Sci.* 75(8): 1041–1047, 2013

In the last decade, phacoemulsification has been becoming a common surgical procedure for restoring vision in veterinary patients with cataract [9, 12, 19]. Postoperative pain can be caused by intraocular manipulations that irritate intraocular tissue and induce the subsequent inflammatory response in the veterinary patient undergoing ocular surgery including phacoemulsification [13].

Limited options have been available for treatment of pain associated with ocular surgery, especially in the cases associated with corneal wounds. Treatment has included the use of topical anesthetics, topical or systemic nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics. Topical anesthetics, such as proparacaine, provide good short-acting corneal anesthesia by blocking action potentials in the sensory nerve membrane in dogs [7]. However, chronic use of proparacaine has been shown to cause delayed corneal healing and ulceration due to its epitheliotoxic effects; therefore, it should be used infrequently for short duration examination and diagnostic procedures [7]. Although NSAIDs have been used to treat ocular pain and inflammation in dogs, topical NSAIDs have toxic effects on corneal epithelial cells [6], and systemic NSAIDs can produce side effects, such as gastric ulceration and renal toxicity that could limit their use in certain patients [5].

Use of opioids is an option for treatment of pain due to ocular pain. One of them, morphine sulfate, is often used systemically to control pain, but has the potential for undesirable side effects. On the other hand, it is demonstrated that topical use of morphine relieves pain associated with corneal wounds in dogs [21] and rats [22]. Additionally, morphine did not cause a delay in corneal wound healing when it was used topically [21]. However, morphine usage is legally restricted, because of its abuse potential. Therefore, topical administration of morphine is troublesome in veterinary practice in many countries including Taiwan.

Nalbuphine belongs to the mixed agonist-antagonist opioids and exerts its analgesic action by antagonistic activity at  $\kappa$ -opioid receptors [17]. Nalbuphine is not a controlled drug, because it possesses  $\mu$ -opioid receptor antagonistic activity leading to less abuse potential [17]. Recently, this drug has offered an interesting alternative to morphine due to its analgesic effects and ease of use as a non-scheduled drug. It is expected that topical nalbuphine can be an alternative to topical morphine in veterinary practice. However, Clark *et al.* [3] failed to demonstrate an analgesic effect of topical nalbuphine on ocular pain experimentally induced by corneal ulcer in dogs. To date, the effectiveness of topical nalbuphine is still controversial.

The purpose of this study was to evaluate the efficacy of topical nalbuphine for the treatment of postoperative ocular pain in dogs undergoing phacoemulsification. This is, to our knowledge, the first clinical study to evaluate the effects of topical nalbuphine on ocular pain in dogs undergoing phacoemulsification.

\*CORRESPONDENCE TO: WANG, H.-C., Department of Veterinary Medicine, College of Veterinary Medicine, National Chung-Hsing University, 250-1 Kuo Kuang Road, Taichung 402, Taiwan.  
e-mail: hcwang@dragon.nchu.edu.tw

## MATERIALS AND METHODS

**Animals:** This study included 12 eyes from 11 owner-owned dogs that received phacoemulsification cataract surgery at the Veterinary Medical Teaching Hospital, National Chung Hsing University. One of these dogs received the surgery on both eyes with an interval of 30 days. The dogs were 3 to 13 years of age ( $7.8 \pm 2.4$  years) and weighed from 3 to 32.3 kg ( $11.7 \pm 8.8$  kg), and their physical statuses before surgery were judged to be Class II or III of the American Society of Anesthesiologists (ASA) classification [1] based on a physical examination, complete blood count and serum biochemical analysis. All eyes were evaluated by a complete ophthalmic examination including the Schirmer tear test (STT), slit lamp biomicroscopy, applanation tonometry, fluorescein staining test, ocular ultrasonography and indirect ophthalmoscopy before surgery.

**Preparation of topical nalbuphine solution:** The commercially available products of 1% nalbuphine injection (Bain<sup>®</sup>, Genovate, Hsinchu, Taiwan) and 7% sodium bicarbonate (sodium bicarbonate, Astar, Hsinchu, Taiwan) were used for preparing topical alkalinized nalbuphine solution. Topical 0.8% nalbuphine solution with a pH of 5.6 was prepared by adding 0.25 ml of 7% sodium bicarbonate to 1 ml of 1% nalbuphine injection. The prepared topical nalbuphine solution was used within 1 day.

**Presurgical treatments and anesthesia protocol:** For 3 days before surgery, all dogs were medicated with topical prednisolone acetate (PRED FORTE<sup>®</sup>, Allergan, Irvine, CA, U.S.A.) and systemic amoxicillin (15 mg/kg PO; Amoxicillin, Yung Shin, Taichung, Taiwan) three times daily. During 90 min prior to surgery, topical administrations of prednisolone acetate and mydriatic drugs (tropicamide 0.5%/phenylephrine HCl 0.5%; Mydrin-P<sup>®</sup>, Tah Min, Santen, Taiwan) into the surgical eye were repeated every 30 min. Each drop was applied at intervals of 15 min. The dogs were premedicated with morphine (0.5 mg/kg IM; Morphine, Food and Drug administration, Taipei, Taiwan) and midazolam (0.2 mg/kg IV; Midazo<sup>®</sup>, Genovate). At least 10 min after premedication, the dogs were anesthetized with propofol (2–4 mg/kg IV; Propofol-Lipuro<sup>®</sup>, B. Braun, Melsungen, Germany) and intubated with an endotracheal tube. Anesthesia was maintained with isoflurane (FORANE<sup>®</sup>, Baxter, Deerfield, IL, U.S.A.) vaporized in oxygen. The dogs were ventilated mechanically to maintain the partial pressure of end-tidal CO<sub>2</sub> between 35 and 45 mmHg. Ringer's solution (Ringer's<sup>®</sup>, TA YU, Hsinchu, Taiwan) was administered at a minimum rate of 10 ml/kg/hr. Atracurium besylate (0.25 mg/kg IV; GENSO<sup>®</sup>, Genovate) was used for eyeball centralization. Atropine or dobutamine was applied as appropriate when patients appeared to have bradycardia and/or hypotension. The dogs were placed on a circulating water blanket (JorVet, Loveland, CO, U.S.A.) during anesthesia.

**Surgical procedures:** The phacoemulsification cataract surgeries were performed with the coaxial (one-handed) or bimanual technique. The anterior chamber was entered at the 12 o'clock position with a 2.75 mm keratome. In the bimanual procedure, a side hole was created at the 3 o'clock

position with a 19-gauge needle. Following sodium chondroitin sulfate-sodium hyaluronate (DisCoVisc<sup>®</sup>, Alcon, Puurs, Belgium) injection into the anterior chamber, a continuous curvilinear capsulorhexis was performed with Utrata forceps. A central groove was sculpted by phacoemulsification to break the lens into halves, each half was broken into quarters, and then each quarter was emulsified and aspirated. Residual lens cortex was removed by irrigation-aspiration, and then 0.2 ml Heparin (5,000 U/ml; Hepac<sup>®</sup>, Nang Kuang, Tainan, Taiwan) and 0.4 ml epinephrine (1 mg/ml; Adrenalin<sup>®</sup>, China Chemical & Pharmaceutical Co., Ltd., Hsinchu, Taiwan) were added to the intraocular irrigating fluid (BSS; Balanced Salt Solution<sup>®</sup> 500 ml/bot; Alcon). The intraocular lenses (IOL) (three-piece acrylic foldable IOL, 30 D; AcrySof<sup>®</sup>, Alcon, Fort Worth, TX, U.S.A.) were inserted through the capsulotomy incision into the capsular bag with an IOL inserter without enlarging the corneal incision and centered in the visual axis. Intraocular lenses were not placed in all cases; the decision to place a lens or not was based on the condition of the patient's lens capsule, zonular fibers and the volition of the owners. The corneal incision was partially closed with 10-0 nylon sutures using a spatula needle in a simple interrupted pattern. A corneal edema was created at the incision site by injection of BSS into the stoma to keep the aqueous fluid in the anterior chamber. Subconjunctival injection of amikacin (diluted to 25 mg/ml; Acemycin<sup>®</sup>, Yung Shin) and prednisolone sodium succinate (25 mg/ml; Lyo-Donison<sup>®</sup>, China Chemical & Pharmaceutical Co., Ltd.) was performed immediately after surgery.

**Postoperative treatments and treatment groups:** The dogs and their surgical eyes were allocated randomly to the nalbuphine group (6 eyes from 6 separate dogs) and saline group (another 6 eyes from 6 separate dogs) (Table 1). The dogs in the nalbuphine group received topical application of the topical nalbuphine solution (0.1 ml) on their surgical eyes every 8 hr for 2 days after surgery. The dogs in the saline group received topical applications of saline (0.1 ml, pH 5.9) on their surgical eyes every 8 hr for 2 days after surgery. In addition, all dogs received postoperative topical treatments with corticosteroid (prednisolone acetate ophthalmic suspension 1%, every 2 hr; PRED FORTE<sup>®</sup>, Allergan), antibiotics (tobramycin 0.3%, every 6 hr; Tobrex<sup>®</sup>, Alcon) and corticosteroid/antibiotics (dexamethasone/ neomycin/polymyxin B, every 24 hr; Maxitrol<sup>®</sup>, Alcon) on their surgical eyes. In addition to these topical treatments, all dogs received systemic treatments with corticosteroids (prednisolone 0.5 mg/kg orally, every 8 hr for the first 4 to 7 days and then tapered; Prednisolone<sup>®</sup>, YUNG SHIN, Taichung, Taiwan), antibiotics (amoxicillin 15 mg/kg orally, every 8 hr for the first 7 days) and analgesics (tramadol 4 mg/kg orally, every 8 hr for 3 days; Tramed<sup>®</sup>, Swiss Pharmaceutical Co., Ltd., Tainan, Taiwan).

**Scoring of pain and examinations:** The ocular pain of all dogs was assessed using a subjective pain scoring system (a modified University of Melbourne Pain Scale) according to a previous study [3] (Table 2). Categories for scoring of pain included comfort, blepharospasm, unprovoked behavior and interactive behaviors. Pain scores were recorded prior to

Table 1. Distribution of baseline characteristics

Variables	Nalbuphine group (n=6)	Saline group (n=6)
Surgical eye	Right eye (2) Left eye (4)	Right eye (2) Left eye (4)
Lens luxation	(1)	(1)
Surgical type	Coaxial (1) Bimanual (5)	Coaxial (2) Bimanual (4)
IOL implantation	(3)	(3)

The numbers of dogs are shown in parentheses.

surgery and at 24 hr (day 1) and 48 hr (day 2) after surgery. At days 1 and 2, pain scores were recorded before (baseline) and 15, 30 and 60 min after topical nalbuphine application. Eye blink frequency, blepharospasm, corneal edema and corneal touch threshold (CTT) were recorded at the same time. Eye blink frequency was measured for 1 min while dogs were in their resting position. The measurement of the degree of blepharospasm was compared with that of the other eye in the same dog. The scales used for assessing eye blink frequency and the extent of blepharospasm were based on the scale of eyelid opening and modified from previous studies [3, 15, 20]. The signs of ocular pain were identified by the degree of blepharospasm (the number of incomplete blinks per min) and the frequency of eyelid blinking (the number of complete blinks per min). To prevent disturbing the dogs, the investigator was distant from the dogs during the measurement of pain score and eye blink frequency. CTT was measured by use of a Cochet-Bonnet aesthesiometer (Luneau Ophtalmologie, Chartres Cedex, France) [11, 21, 23] following the evaluation of pain score and eye blink frequency. CTT measurements were conducted in the dogs sitting or in sternal recumbency with minimum head restraint or eyelid manipulation. The nylon monofilament of

the aesthesiometer was advanced slowly toward the globe and applied perpendicular to the cornea, and the pressure was increased until a slight deflection of the filament was evident (Fig. 2). CTT was determined by use of an initial length of 2 cm for the aesthesiometer filament. When a blink reflex was not detected, the filament length was decreased in 0.125-cm increments, and testing was repeated until a blink reflex was evident. Corneal sensitivity, defined as the CTT, was recorded as the length of the aesthesiometer filament that induced a blink reflex. Pain score, eye blink frequency and CTT were evaluated by the same investigator (C.-H. L.), who was unaware of the grouping.

Additionally, each dog underwent a daily ophthalmic examination including slit lamp biomicroscopy, indirect ophthalmoscopy, applanation tonometry, STT and corneal fluorescein staining. Ocular findings including corneal edema, conjunctival hyperemia and aqueous flare were scored using a modified Hackett-McDonald scoring system [15] (Table 3).

**Statistical analysis:** Data were expressed as means  $\pm$  SD. Variables in the nalbuphine group were compared with those in the saline group with the Mann-Whitney U test. Within each group, comparisons of variables before versus after treatment and the differences between baseline values and the values measured at each subsequent time point were performed by the Wilcoxon signed-rank test. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 17.0. Differences were considered significant at a value of  $P < 0.05$ .

## RESULTS

Surgical times were  $35.7 \pm 11.1$  min in the nalbuphine group and  $43.0 \pm 8.6$  min in the saline group. Cornea wounds of all surgical eyes healed without severe complications by 5 days after surgery. Positive results of fluorescein staining were found in 4 eyes (2 eyes in the nalbuphine group and 2

Table 2. The modified University of Melbourne Pain Scale [3] used for assessing the extent of comfort, blepharospasm, behavior and interactive behaviors

Observation	Score	Criteria
Comfort	0	Patient asleep, calm or awake, interested in surroundings
	1	Mild agitation or depressed, uninterested in surroundings
	2	Moderate agitation, restless and uncomfortable
	3	Extremely agitated, thrashing
Blepharospasm	0	Eyelid is completely open, in normal position
	1	Eyelid is partially closed so that the palpebral opening is decreased by 1/3
	2	Eyelid is partially closed so that the palpebral opening is decreased by 2/3
	3	Eyelid is completely closed
Behavior (unprovoked)	0	Normal
	1	Minor changes
	2	Moderately abnormal (less mobile or alert than normal, unaware of surroundings or very restless)
	3	Markedly abnormal (very restless, vocalizing, self-mutilation, grunting, facing back of cage)
Interactive behaviors	0	Normal
	1	Pulls away when eye touched
	2	Vocalizes when eye touched, reluctant to move but will if coaxed
	3	Violent reaction to touching of eye, snapping, growling when approached, will not move when coaxed

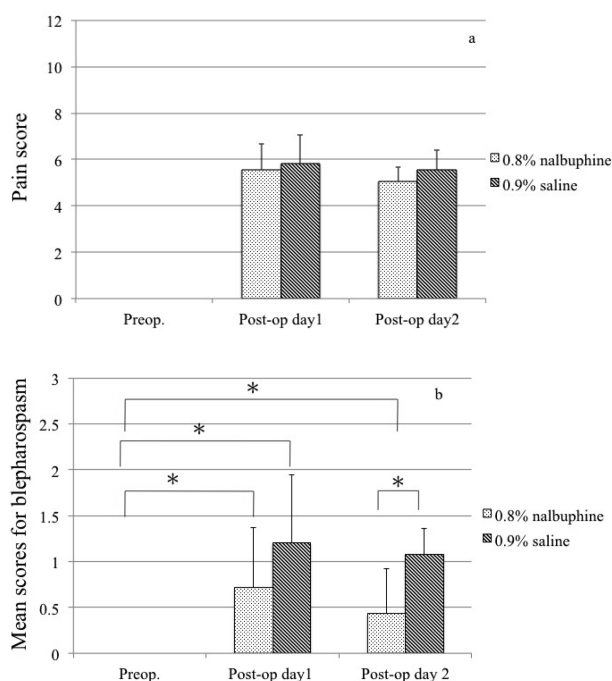


Fig. 1. Total pain scores (a) and scores for blepharospasm (b) measured before and after surgery. The postoperative pain was evaluated as mild to moderate in both groups just before postoperative treatment (baseline) on days 1 and 2. On day 1, the nalbuphine group and saline group both had a significant increase in baseline mean scores for blepharospasm ( $P < 0.05$ ). On day 2, no significant difference was noted in the nalbuphine group, and the difference was still significant in the saline group ( $P < 0.05$ ).

eyes in the saline group) at the surgical incision after surgery. No correlation between use of an aesthesiometer and corneal lesions was found according to the size and location of the lesions. In the study, there was no difference in the corneal wound healing time between the nalbuphine ( $3.33 \pm 0.51$  days) and saline groups ( $3.50 \pm 0.55$  days). The preoperative STT values were  $20.2 \pm 2.9$  mm in the nalbuphine group and  $18.2 \pm 4.6$  mm in the saline group. Compared with the preoperative values, the postoperative STT values were decreased to  $15.7 \pm 3.5$  mm on the day 1 and  $16.8 \pm 2.9$  mm on the day 2 in the nalbuphine group and  $14.5 \pm 5.1$  mm on the day 1 and  $15.6 \pm 6.1$  mm on the day 2 in the saline group. Compared with the values of STT before surgery, a decrease in values after surgery was noted in both groups. No significant difference was noted within each group on the days 1 and 2. In both groups, mild to moderate (scores 1–2) conjunctival hyperemia and mild to severe (scores 1–3) corneal edema appeared on the days 1 and 2, but aqueous flare was not observed after surgery. There was no significant difference in changes in ocular findings after surgery between the nalbuphine and saline groups.

Changes in the pain score and eye blink frequency are shown in Figs. 1 and 2. The eye blink frequency was 2–11 times/min before surgery in both groups. The postoperative pain was evaluated as mild to moderate (total pain scores

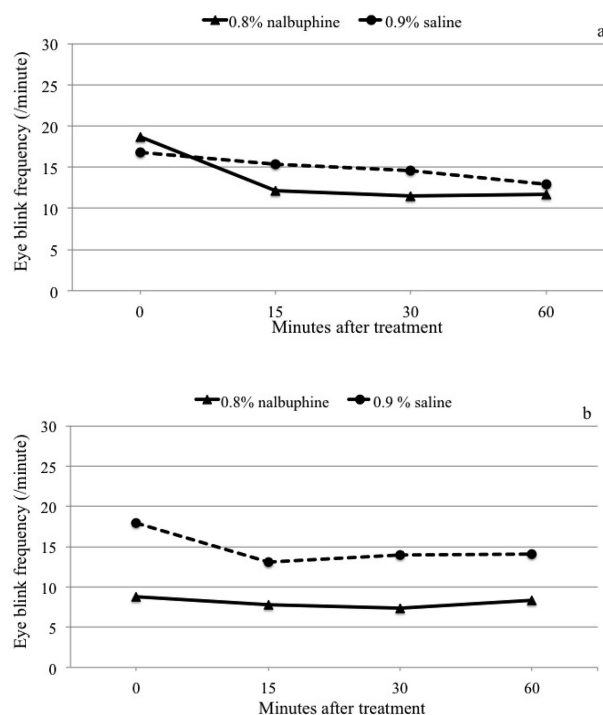


Fig. 2. Values of eye blink frequency measured before and after treatment in the nalbuphine and saline group. a: postoperative day 1. b: postoperative day 2. No significant difference was observed between the two groups on day 1, whereas a significant difference was noted at 15, 30 and 60 min after treatment on day 2. The significant differences were noted before treatment ( $P = 0.005$ ) and at 15 ( $P = 0.05$ ), 30 ( $P = 0.018$ ) and 60 ( $P = 0.005$ ) min after treatment on day 2 postoperatively.

4–7) in both groups (Fig. 1a). Positive changes in scores were only detected in the category of blepharospasm. The nalbuphine and saline groups had a significant increase in baseline mean scores for blepharospasm ( $P = 0.023$  and  $0.038$ , respectively) on the day 1, whereas the scores were significantly decreased in the nalbuphine group on the day 2, compared with the saline group ( $P = 0.034$ ) (Fig. 1b). The baseline value of eye blink frequency was significantly increased in both groups after surgery. On day 1, eye blink frequency was not significantly different between the two groups before treatment, and no significant difference was observed between the two groups at any time point after treatment (Fig. 2a). On day 2, significant decreases in the eye blink frequency were observed in the nalbuphine group before treatment ( $P = 0.005$ ) and at 15 ( $P = 0.05$ ), 30 ( $P = 0.018$ ) and 60 ( $P = 0.005$ ) min after treatment on day 2 compared with the saline group (Fig. 2b).

Changes in CTT are shown in Fig. 3. Topical nalbuphine produced decreases of  $2.84 \pm 0.13$  and  $2.98 \pm 0.36$  mm in the CTT value at 30 and 60 min and after administration on day 1, respectively. It produced decreases of  $2.98 \pm 0.58$  and  $2.62 \pm 0.43$  mm in the CTT value at 30 and 60 min after administration on day 2, respectively. There was no significant difference in the CTT between groups.



Table 3. The modified Hackett-McDonald Ocular Scoring System [15] used for assessing the extent of corneal edema, conjunctival hyperemia and aqueous flare (the ocular scoring system)

Observation	Score	Criteria
Corneal edema	0	Normal cornea
	1	Mild loss of transparency. Only the epithelium and/or the anterior half of the stroma is involved as observed with an optical section of the slit lamp. With diffuse illumination, the underlying structures are clearly visible, although some cloudiness may be readily apparent.
	2	Moderate loss of transparency. Involvement of the entire thickness of the stroma. With an optical section, the endothelial surface is still visible. However, with diffuse illumination, the underlying structures are just barely visible.
	3	Severe loss of transparency. Involvement of the entire thickness of the stroma. With an optical section, the endothelium is not clearly visualized. With diffuse illumination, the underlying structure cannot be seen.
Conjunctival hyperemia	0	Normal conjunctiva
	1	Mild hyperemia. A flushed, reddish color predominantly confined to the palpebral conjunctiva with some perilimbal injection.
	2	Moderate hyperemia. The palpebral conjunctiva appears bright red with accompanying perilimbal injection covering at least 75% of the circumference of the perilimbal region.
	3	Severe hyperemia. Both the bulbar and palpebral conjunctiva exhibit a dark, beefy red color with pronounced perilimbal injection. Petechiae on the conjunctiva may be present. The petechiae generally predominate along the nictitating membrane and/or the upper palpebral conjunctiva.
Aqueous flare	0	Normal anterior chamber
	1	Mild flare. The intensity of the light beam in the anterior chamber is less than the intensity of the slit beam as it passes through the lens.
	2	Moderate flare. The slit lamp beam in the anterior chamber is equally opaque compared with the beam passing through the normal lens.
	3	Severe flare. The slit beam in the anterior chamber is more opaque than that passing through the lens.

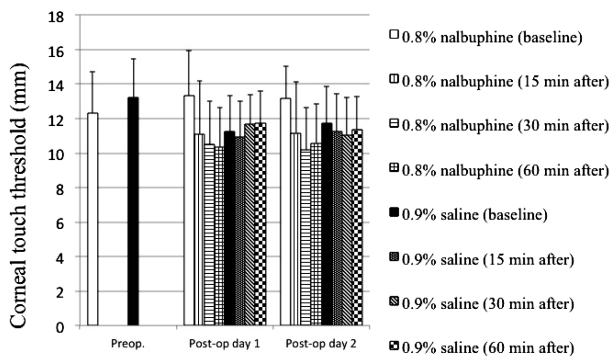


Fig. 3. Mean CTT values measured before and after surgery in each group. Lower baseline corneal sensitivity was observed in the nalbuphine group than in the saline group before surgery, whereas higher baseline corneal sensitivity was noted in the nalbuphine group after surgery. A significant decrease in mean CTT values was noted at 15, 30 and 60 min after treatment with topical nalbuphine.

## DISCUSSION

In this study, we failed to demonstrate the analgesic impact of topical application of nalbuphine on postoperative ocular pain in dogs undergoing phacoemulsification. On the other hand, topical nalbuphine rapidly decreased blepharospasm and eye blink frequency without interference with cornea healing. Therefore, it is expected that topical nalbuphine may have a clinically relevant effect on ocular pain relief

in dogs.

Nalbuphine is a kappa opioid receptor agonist that has been used topically for evaluating anesthetic and analgesic effects in clinically normal dogs and horses and in dogs with experimentally created corneal ulcers [2, 3, 23]. In a previous study, topical administration of 1% nalbuphine solution decreased corneal sensitivity in dogs with healthy corneas, but failed to relieve ocular pain caused by corneal ulcer. Similar results were observed in this study. All our dogs received oral tramadol (4 mg/kg, every 8 hr) and prednisolone (0.5 mg/kg, every 8 hr) as a systemic postoperative treatment. In our clinical experience, the degree of postoperative pain is mild in almost all dogs undergoing phacoemulsification. Tramadol is a centrally acting "atypical" opioid analgesic [16]. Tramadol can be used safely in dogs to control early pain after ovariohysterectomy without significant adverse effects [14]. Prednisolone is a glucocorticoid and produces a potent anti-inflammatory effect by the inhibition of phospholipase A<sub>2</sub>, the precursor of arachidonic acid [8]. It was supposed that the combination of tramadol and prednisolone might provide a multimodal analgesic effect and effectively reduce postoperative pain in our dogs. Consequently, we failed to demonstrate the analgesic impact of the topical nalbuphine on postoperative pain, because the multimodal analgesic effects might decrease the pain level and mask the actual analgesic effect of the topical nalbuphine.

The pain scoring system used in this study was modified from the University of Melbourne Pain Score and has been validated in several studies [3, 20]. It has been pointed out that there are some limitations of subjective pain scoring

systems. Pain assessment in animals is highly subjective, and the response to pain is variable. Evaluation of ocular pain level is hard to perform equitably in dogs, especially in stressful and restless dogs. The degree of corneal pain sensation may be altered by mental status or changed circumstances. Since our dogs were hospitalized for at least 2 days following phacoemulsification, the dogs might have been under great stress because of the unfamiliar environment. Consequently, we failed to demonstrate the analgesic impact of the topical nalbuphine on the postoperative pain evaluated by the subjective pain score system.

Blepharospasm and eye blinking are clinical signs of discomfort in the cornea and are used as signs of cornea pain in experimental studies in dogs [3, 21]. In this study, blepharospasm and eye blink frequency were significantly reduced by the topical nalbuphine application. In addition, the CTT was also reduced by the topical nalbuphine application. It has been reported that tear production and corneal sensitivity were reduced immediately after phacoemulsification in human patients, although there is no involvement of lacrimal glands in the surgical procedures [10]. In this study, the STT values decreased after surgery in both groups. The corneal sensitivity would be reduced by the decreased tear production in our dogs. However, a significant decrease in blepharospasm and eye blink frequency in conjunction with decreases in CTT was observed after the topical application of nalbuphine. Therefore, it is considered that topical application of nalbuphine solution can produce a clinically relevant reduction in cornea discomfort in dogs.

Topical opiates and other types of analgesics targeting specific receptors on nerve cells were thought to have the potential to be ideal analgesics that may have no side effects on the cornea [4]. In a previous study [18], topical application of 1% morphine solution produced a 0.4- to 0.9-cm decrement in CTT value 30 min after administration in dogs. In this study, a 0.297- to 0.799-cm decrement in CTT value was observed 30 min after the topical nalbuphine application in the dogs that received topical dexamethasone at the same time. It is considered that topical application of 0.8% nalbuphine solution can produce a clinically relevant reduction in cornea discomfort within 30 min, but that the efficacy may be lower than that of topical 1% morphine.

The nalbuphine injection is easy to obtain commercially and is more convenient for veterinary clinicians when they prepare a topical nalbuphine solution compared with when they prepare the solution with non-pharmaceutical grade chemicals. In this study, the 1% nalbuphine injection was alkalized to a pH of 5.6. In previous studies, topical 1 to 1.2% nalbuphine solutions were prepared by adding powdered nalbuphine to aqueous solution with a pH of 6.0–6.2 [3, 23]. The commercial formulation of nalbuphine with a pH 3.6 may cause irritation of the cornea. Therefore, the 1% nalbuphine injection was alkalized to a pH of 5.6 to minimize the irritation. As expected, no irritative response was found in canine eyes that received topical nalbuphine.

In conclusion, our results suggested that the prepared 0.8% nalbuphine solution can decrease the corneal sensitivity at 15, 30 and 60 min after topical administration and may

have a clinically relevant effect on ocular pain relief after phacoemulsification.

## REFERENCES

1. Ament, R. 1979. Origin of the ASA classification. *Anesthesiology* **51**: 179. [Medline] [CrossRef]
2. Aquino, S. L., Van Der Woerd, A. and Eaton, J. S. 2005. The effect of topical nalbuphine on corneal sensitivity in normal canine eyes. p. 43. In: Proceedings of the 36th Annual Meeting of the American College of Veterinary Ophthalmology.
3. Clark, J. S., Bentley, E. and Smith, L. J. 2011. Evaluation of topical nalbuphine or oral tramadol as analgesics for corneal pain in dogs: a pilot study. *Vet. Ophthalmol.* **14**: 358–364. [Medline] [CrossRef]
4. Faktorovich, E. G. 2009. Ophthalmology management. New Approaches to Pain Management after PRK [cited 2009 September 1] Available from <http://www.ophtmanagement.com/article.aspx?article=103393>.
5. Giuliano, E. A. 2004. Nonsteroidal anti-inflammatory drugs in veterinary ophthalmology. *Vet. Clin. North. Am. Small Anim. Pract.* **34**: 707–723. [Medline] [CrossRef]
6. Hendrix, D. V., Ward, D. A. and Barnhill, M. A. 2002. Effects of anti-inflammatory drugs and preservatives on morphologic characteristics and migration of canine corneal epithelial cells in tissue culture. *Vet. Ophthalmol.* **5**: 127–135. [Medline] [CrossRef]
7. Herring, I. P., Bobofchak, M. A., Landry, M. P. and Ward, D. L. 2005. Duration of effect and effect of multiple doses of topical ophthalmic 0.5% proparacaine hydrochloride in clinically normal dogs. *Am. J. Vet. Res.* **66**: 77–80. [Medline] [CrossRef]
8. Johnston, S. A. and Fox, S. M. 1997. Mechanisms of action of anti-inflammatory drugs used for the treatment of osteoarthritis. *J. Am. Vet. Med. Assoc.* **210**: 1486–1492. [Medline]
9. Johnstone, N. and Ward, D. A. 2005. The incidence of posterior capsule disruption during phacoemulsification and associated postoperative complication rates in dogs: 244 eyes (1995–2002). *Vet. Ophthalmol.* **8**: 47–50. [Medline] [CrossRef]
10. Khanal, S., Tomlinson, A., Esakowitz, L., Bhatt, P., Jones, D., Nabili, S. and Mukerji, S. 2008. Changes in corneal sensitivity and tear physiology after phacoemulsification. *Ophthalmic. Physiol. Opt.* **28**: 127–134. [Medline] [CrossRef]
11. Kim, J., Kim, N. S., Lee, K. C., Lee, H. B., Kim, M. S. and Kim, H. S. 2013. Effect of topical anesthesia on evaluation of corneal sensitivity and intraocular pressure in rats and dogs. *Vet. Ophthalmol.* **16**: 43–46. [Medline] [CrossRef]
12. Klein, H. E., Krohne, S. G., Moore, G. E. and Stiles, J. 2011. Postoperative complications and visual outcomes of phacoemulsification in 103 dogs (179 eyes): 2006–2008. *Vet. Ophthalmol.* **14**: 114–120. [Medline] [CrossRef]
13. Maggs, D. J., Miller, P. E. and Ofri, R. 2008. Ocular pharmacology and therapeutics. pp. 33–61. In: Slatter's Fundamentals of Veterinary Ophthalmology, 4th ed. (Maggs, D. J. ed.), Saunders Elsevier, St. Louis.
14. Mastrocinque, S. and Fantoni, D. T. 2003. A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. *Vet. Anaesth. Analg.* **30**: 220–228. [Medline] [CrossRef]
15. Munger, R. J. 2002. Veterinary ophthalmology in laboratory animal studies. *Vet. Ophthalmol.* **5**: 167–175. [Medline] [CrossRef]
16. Raffa, R. B., Friderichs, E., Reimann, W., Shank, R. P., Codd, E. E. and Vaught, J. L. 1992. Opioid and nonopioid components independently contribute to the mechanism of action of trams-

- dol, an 'atypical' opioid analgesic. *J. Pharmacol. Exp. Ther.* **260**: 275–285. [[Medline](#)]
17. Schmidt, W. K., Tam, S. W., Sholtzberger, G. S., Smith, D. H. Jr., Clark, R. and Vernier, V. G. 1985. Nalbuphine. *Drug Alcohol Depend.* **14**: 339–362. [[Medline](#)] [[CrossRef](#)]
  18. Shen, Y., Tong, J. P. and Li, Y. M. 2004. Corneal relaxing incision combined with phacoemulsification and IOL implantation. *J. Zhejiang. Univ. Sci.* **5**: 985–988. [[Medline](#)] [[CrossRef](#)]
  19. Sigle, K. J. and Nasisse, N. P. 2006. Long-term complications after phacoemulsification for cataract removal in dogs: 172 cases (1995–2002). *J. Am. Vet. Med. Assoc.* **228**: 74–79. [[Medline](#)] [[CrossRef](#)]
  20. Smith, L. J., Bentley, E., Shih, A. and Miller, P. E. 2004. Systemic lidocaine infusion as an analgesic for intraocular surgery in dogs: a pilot study. *Vet. Anaesth. Analg.* **31**: 53–63. [[Medline](#)] [[CrossRef](#)]
  21. Stiles, J., Honda, C. N., Krohne, S. G. and Kazacos, E. A. 2003. Effect of topical administration of 1% morphine sulfate solution on signs of pain and corneal wound healing in dogs. *Am. J. Vet. Res.* **64**: 813–818. [[Medline](#)] [[CrossRef](#)]
  22. Wenk, H. N., Nannenga, M. N. and Honda, C. N. 2003. Effect of morphine sulphate eye drops on hyperalgesia in the rat cornea. *Pain* **105**: 455–465. [[Medline](#)] [[CrossRef](#)]
  23. Wotman, K. L. and Utter, M. E. 2010. Effect of treatment with a topical ophthalmic preparation of 1% nalbuphine solution on corneal sensitivity in clinically normal horses. *Am. J. Vet. Res.* **71**: 223–228. [[Medline](#)] [[CrossRef](#)]