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IMPACT OF FLUNIXIN MEGLUMINE, PHENYLBUTAZONE AND ELECTROACUPUNCTURE ON OCULAR PAIN AND CORNEAL WOUND HEALING IN THE DROMEDARY CAMEL (*Camelus dromedarius*)

Al Shehri A[1], Al Ghythan A[1], Hamoud B[2], Al Aiyan A[3] and Shawaf T[1*]

[1]Department of Clinical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa, Saudi Arabia
[2]SAAR Company for Environmental Reserves, Riyad, Saudi Arabia
[3]Department of Veterinary Medicine, College of Food and Agriculture, United Arab Emirates University, Al Ain, United Arab Emirates

ABSTRACT

This study aimed to determine the effects of flunixin meglumine, phenylbutazone, and electroacupuncture on corneal wound healing and pain relief in dromedary camels (*Camelus dromedarius*). The present study was conducted on sixteen dromedary camels (seven males and nine females). The camels were diagnosed with new corneal injury after undergoing general and ophthalmic examinations. An ophthalmological examination was performed to determine the dimensions of the corneal wound using an ophthalmoscope and florescence test to determine the measurement of the corneal wound. The study involved categorising camels into four groups and administering local ointment (gentamicin) to all camels. Furthermore, individualised treatment protocols were implemented for each group. The first group served as the control and received no treatment. The second group was treated with the flunixin meglumine, while the third group was injected with the phenylbutazone. The fourth group received electroacupuncture treatment once daily for a duration of five days. A comprehensive ocular pain scoring system was used, which involved the assessment of eight different ocular parameters to evaluate the effectiveness of the treatments. The mean maximum ocular pain level score at 12 hours after a corneal wound in the control group represented a mild-moderate level of pain greater than the mean maximum ocular pain level score in the phenylbutazone group. The flunixin meglumine and electroacupuncture treatment groups showed the lowest cumulative pain scores of all treatments. Electroacupuncture has been found to be an effective treatment for ocular pain relief and expediting corneal wound healing in camels. Flunixin meglumine was found to be the most reliable option in relieving ocular pain comparing to phenylbutazone or Electroacupuncture.

Key words: Camel, corneal, electroacupuncture, eye, flunixin, phenylbutazone, pain, wound

Acupuncture therapy, which originated from traditional Chinese medicine (Dewey and Xie, 2021; Harrison and Churgin, 2022; Hu and Liu, 2020), involves the insertion of fine needles to specific points on the body (Wei *et al,* 2020) to re-establish the homeostasis of the main organs by modulating the flow of blood and energy through the meridians (Matos *et al,* 2021). In humans, acupuncture can be useful in the treatment of many ailments, including ophthalmic conditions such as dry eye, myopia, paralytic strabismus, retinitis pigmentosa, optic atrophy, iritis, conjunctivitis, cataracts (Na *et al,* 2021; Nepp *et al,* 2002; Roy, 1980; Xu and Jin, 2021).

Many studies have also demonstrated the role of acupuncture in relieving pain. It has been proposed that acupuncture causes the release of endogenous opioid-like substances and activation of the diffuse noxious inhibitory control system mainly via neurotransmission modulation on the adrenergic, serotonin, and glutamate receptors in the central nervous system (Li *et al,* 2023; Makra *et al,* 2021).

Although acupuncture is used widely in many species, little scientific research has thus far documented the use of acupuncture techniques in camels, either for ophthalmic conditions or pain relief. Ocular trauma and corneal ulcers are more common in camels than other species and result in varying degrees of ocular pain as their eyes are in the lateral position and permanently prominent, optimizing vision (Gebreyohanes and Assen, 2017;

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Kumar *et al,* 2016). Camels are susceptible to eye injuries because they obtain food from trees and thorny weeds, which can cause corneal wounds and injuries to the ocular surface (Farouk *et al,* 2022; Gahlot, 2000). Moreover, camels suffer from a wide range of ophthalmic affections, including corneal lacerations, corneal opacity, and descemetocele (Bishnoi and Gahlot, 2004; Shawaf and Hussen, 2023). Free sensory nerve endings are found at the wing cell level of the epithelium, which makes the cornea one of the most sensitive of all body tissues. Corneal damage results primarily in inflammatory pain, requiring the routine use of nonsteroidal anti-inflammatory drugs (NSAIDs) in addition to specific etiological treatment.

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently employed to manage ocular pain and facilitate corneal ulcer healing in camels. However, their clinical efficacy in treating these conditions has not been evaluated yet (Makra *et al,* 2021). However, adverse events related to the administration of ophthalmic NSAIDs, including burning and stinging, hyperemia of the conjunctiva, and contact dermatitis, have been reported (Calder *et al,* 2005; Gaynes and Fiscella, 2002).

This study is aimed to evaluate the effects of electroacupuncture (EA) as compared to systemic NSAID treatment, relatively new in veterinary practice (Dewey and Xie, 2021; Jiang *et al,* 2022; Leite Ferreira *et al,* 2022), on corneal wound healing and ocular pain in dromedary camels.

Materials and Methods

2.1 Ethical approval

The study was approved for research purposes by the Ethics Committee at King Faisal University in Saudi Arabia (Approval number: KFU-REC-2024-OCT-EA00010)

2.2 Animals and clinical examination

The present study was conducted between May 2022 and October, 2024 on 16 dromedary camels (seven males and nine females). Camels had a median age ±SEM of 7 ±4.5 years and a median weight ±SEM of 365 ±115 kg. All camels afflicted with ophthalmological ailments were chosen at random from those brought to the Veterinary Teaching Hospital, College of Veterinary Medicine, King Faisal University. General and ophthalmic examinations confirmed that the camels were affected with new corneal injury. After general examination to exclude camels with other health disorders except corneal injury, ophthalmological examination was performed to determine the dimensions of the corneal wound using ophthalmoscope and florescence test to determine the measurement of corneal wound. Camels with a corneal wound between 5 and 10 mm were enrolled in the present study. Corneal wounds in the camels were controlled using fluorescein dye stain (fluorescein sodium ophthalmic strips, Eickemeyer) during the treatment period (Fig 1A, B). Eight ocular parameters were used in the ocular pain scoring system. The corneal wound was defined as cured when fluorescein dye was no longer retained; treatments and pain scoring were discontinued for that camel. The corneal wound healing was determined by measuring the wound length (mm) using Image J software.

2.4 Treatment groups

Camels were divided into 4 groups (each group had 4 camels), and all camels were treated with local ointment (Gentamicin), in addition to special treatment for each group according to the study.

The first group was not treated (control) after creating the corneal wound, while the second group was treated with the NSAID flunixin meglumine (Finadyne®, MSD Animal Health) once a day for five days at a dose of 1.1 mg/kg, intravenously. The third group was injected with the NSAID phenylbutazone (phenylbutazone 20% ®, SPI, Saudi Arabia) at a dose of 2.2 mg/kg intravenously once a day for five days. EA treatment was applied to the fourth group once daily for 5 days.

In the current study, four local acupoints were used according to a previous study in equines (Makra *et al,* 2021). EA treatment was applied for 20 minutes to the GB1 (gall bladder meridian), BL1 (bladder meridian), ST1 (stomach meridian), and TH23 (triple heater meridian) points every 24 h until the lesion healed (Fig 2A, B). For EA, we used 0.25 mm x 30 mm long Chinese steel needles (TEWA, Acupuncture needle) connected to an EA device (SDZ-II, Suzhou Medical Appliance Factory, China) at 4 acupuncture points around the eye (ST1, GB1, BL1, and TH23). A human "sensitive high frequency" protocol (recommended by the manufacturer for pain treatment in the human face) was used (80 Hz, 60 ms). The intensity gradually increased at the beginning until fine muscle fasciculation was noticed on the eyelid (20-30 mA), and this intensity was maintained for 20 minutes (Makra *et al,* 2021).

2.5 Pain scoring

For the ocular pain scores in camels, a scoring system designed for horses (Makra *et al,* 2021) was

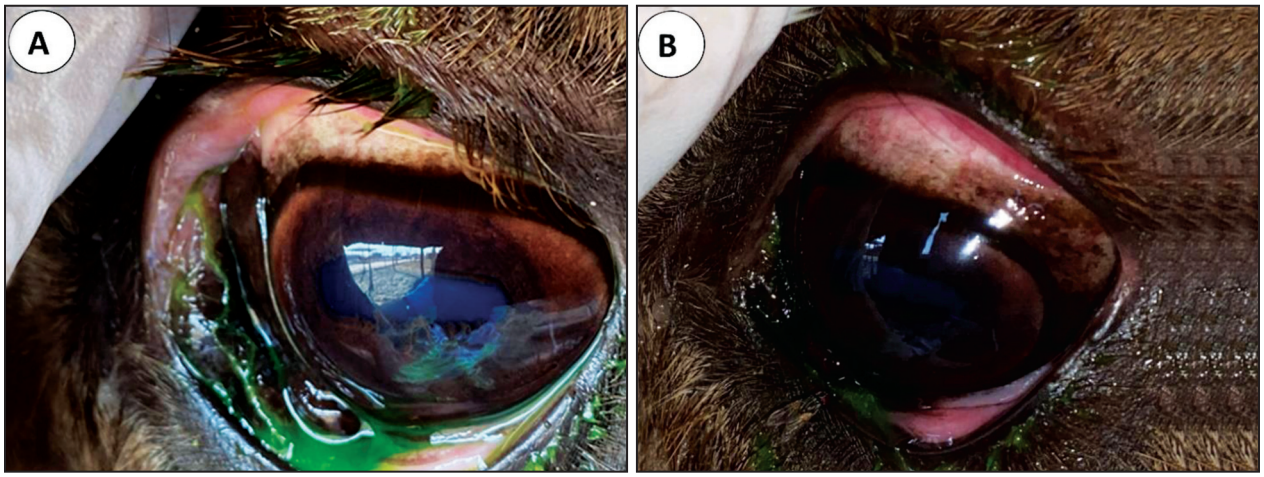

Fig 1. **A:** Corneal wound in camel were controlled using stained with fluorescein dye during the treatment period; **B:** Corneal wound in the same camel after treatment showed negative result for staining using fluorescein dye.

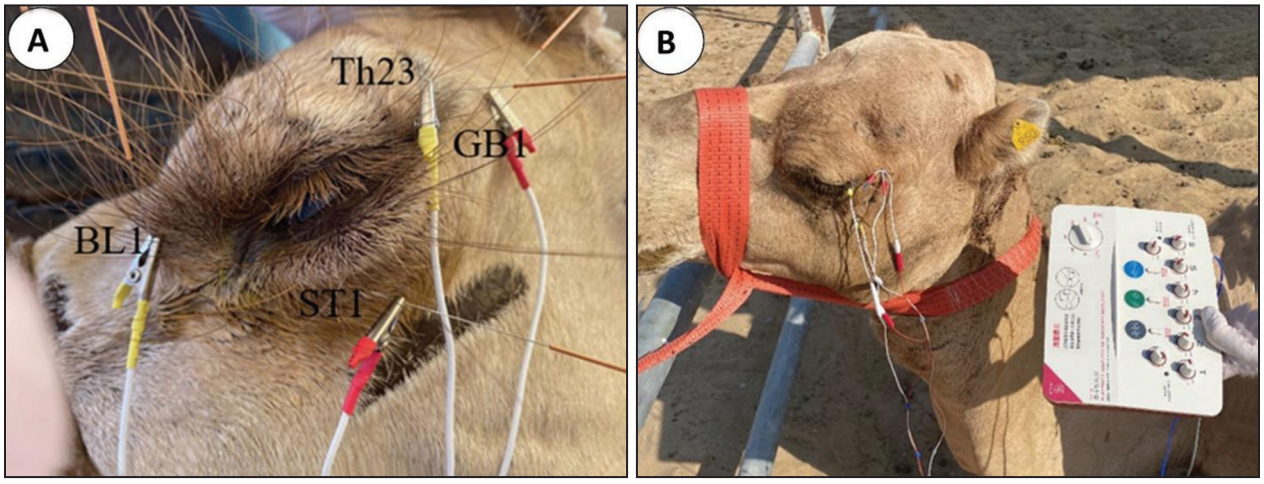

Fig 2. **A:** Electroacupuncture (EA) treatment in camel affected with corneal wound showed the acupuncture points: GB1 (gall bladder meridian), BL1 (bladder meridian), ST1 (stomach meridian), and TH23 (triple heater meridian) points; **B:** shows the treatment procedure using an electroacupuncture device and connecting wires to acupuncture points around the eye.

modified to incorporate ocular pain points in cattle (Dewell *et al,* 2014). Eight parameters were used in the ocular pain scoring system: corneal touch threshold, response to palpation of the adnexa, blepharospasm, photophobia, tearing (epiphora), eyelid swelling, corneal opacity and conjunctival hyperemia (Table 1). The pain of all camels was scored after corneal healing to establish baseline parameters (T0). Pain scoring points were recorded by two independent observers every four hours in the first 24 hours (0, 4, 8, 12, 16, 20 and 24 hours) postoperatively (T0 to T6), then twice daily through the fifth day (T7 to T16). The intensity of ocular signs was graded on a scale (0: normal, 1: mild, 2: moderate, and 3: severe) (Table 1).

2.5 *Statistical analysis*

The average pain scores for blepharospasm, tearing, eyelid swelling, corneal opacity, conjunctival hyperemia, and chemosis were calculated for various time points and graphed as a function of time. Corneal wound length was analysed with a two-way repeated-measure ANOVA and Bonferroni's test for multiple comparisons with significance set at $p < 0.05$.

Results

The selection process for the camels with corneal wounds was challenging due to the limited availability of cases that matched in wound dimensions and quality. Nevertheless, we were able to select cases with similar wound dimensions and fresh injuries that were less than a day old. Average changes in ocular pain scores over time were calculated for all eight parameters at various time intervals for each group, and the results were combined according to treatment groups (Fig 3).

Fig 4A shows the mean corneal wound healing in each treatment group over time. Fig 4B shows the changes in mean pain scores over time are illustrated in. ocular pain scoring started at 0 hours (T1) and ended at 144 hours (T16). Generally, the mean total Ocular pain scores decreased appreciably by the end of the study (T16, 144 hours). The mean maximum ocular pain score, representing a mild-moderate level of pain, reached 21.75 points in the control group 12 hours after corneal injury, while the mean maximum ocular pain score reached 21 points in the phenylbutazone group, 20.75 in the EA group, and 20 in the flunixin meglumine group. The mean ocular pain score after 24 hours had decreased in the camels treated with flunixin meglumine and EA to 17.5 points, and the control group scores were nearly equal to the phenylbutazone group with 19.5 and 19 points, respectively. The study found that administration of flunixin meglumine resulted in the lowest mean ocular pain score (11.25 points) after 48 hours of treatment, followed by the EA group with 13.5 points. On the fourth day, it was noted that the mean ocular pain decreased in the EA group (score 9.5) more than all other groups, while the flunixin meglumine treatment group score was 11, the phenylbutazone group was 13.5 and the control group was 13.75.

Table 1. Detailed ocular scoring system points for studied camels.

Ocular Score Parameter	Criteria	Points
Central corneal touch threshold	Normal compared with the initial value (increase <10%)	0
	11%-30% increase	1
	30%-50% increase	2
	>50% increase	3
Response to palpation of adnexa	No reaction	0
	Mild reaction or reaction to subsequent palpation	1
	Pull the head immediately away	2
	Violent reaction, avoidance behavior	3
Blepharospasm	Lids are completely open, in normal position	0
	Lids are partially closed, <50%	1
	Lids are partially closed, >50%	2
	Lids are completely closed	3
Photophobia	No intolerance to a bright light	0
	Partial intolerance to a bright light, <50%	1
	Partial intolerance to a bright light, >50%	2
	Full intolerance to a bright light	3
Tearing (epiphora)	No tearing	0
	Mild tearing	1
	Moderate tearing	2
	Marked tearing	3
Eyelid swelling	No swelling	0
	Mild swelling	1
	Moderate swelling	2
	Marked swelling	3
Corneal opacity/edema	No opacity	0
	Lesional or perilesional mild opacity	1
	Moderate opacity	2
	Complete corneal opacity	3
Conjunctival hyperemia/chemosis	Normal pink	0
	Mild injection	1
	Moderate injection, chemosis	2
	Marked hyperemia, chemosis	3

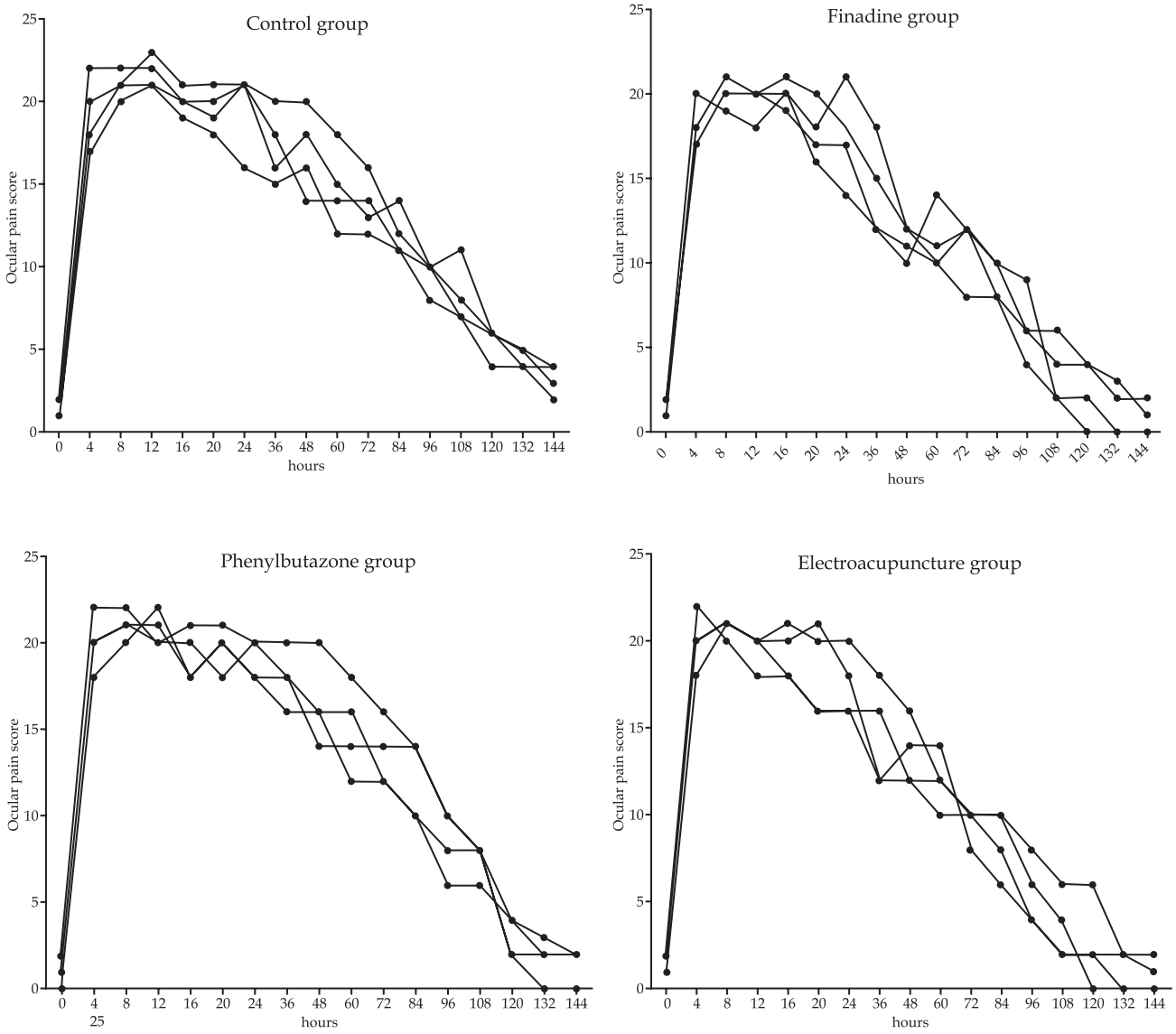

Fig 3. Mean ocular pain scores over time for all eight parameters at various time points for each group.

All corneal wounds were healed, as noted by negative fluorescein uptake, within an average of seven days. None of the eyes became infected or demonstrated any other severe complication. Despite a negative fluorescein test result for corneal wounds in most groups after the seventh day post-injury, some ocular signs such as opacity, corneal scars, and blepharospasms persisted in the treated eye for more than another seven days. It was also noted that the flunixin meglumine treatment group had faster corneal wound healing than the rest of the groups. The speed of corneal wound healing in the EA group was faster than in the phenylbutazone and control groups. There was a positive correlation between corneal wound healing and the ocular pain score in all groups.

Discussion

Acupuncture theory suggests that many acupuncture points are suitable to treat ocular pain and corneal wounds, including systemic and local points (Cariello *et al,* 2006). The main use of acupuncture in medical therapy is based on its analgesic and anti-inflammatory effects (Parmen *et al,* 2014). Due to the lack of information on the use of Chinese acupuncture in camels, the target points for electroacupuncture in the present study were selected based on previous studies conducted in cattle (Kim *et al,* 2004) and horses (Makra *et al,* 2021) with some modification in acupuncture needle placement due to the anatomical differences around the camel eye. Data in this study demonstrated that peak pain levels persisted for up to 24 hours in most treated groups.

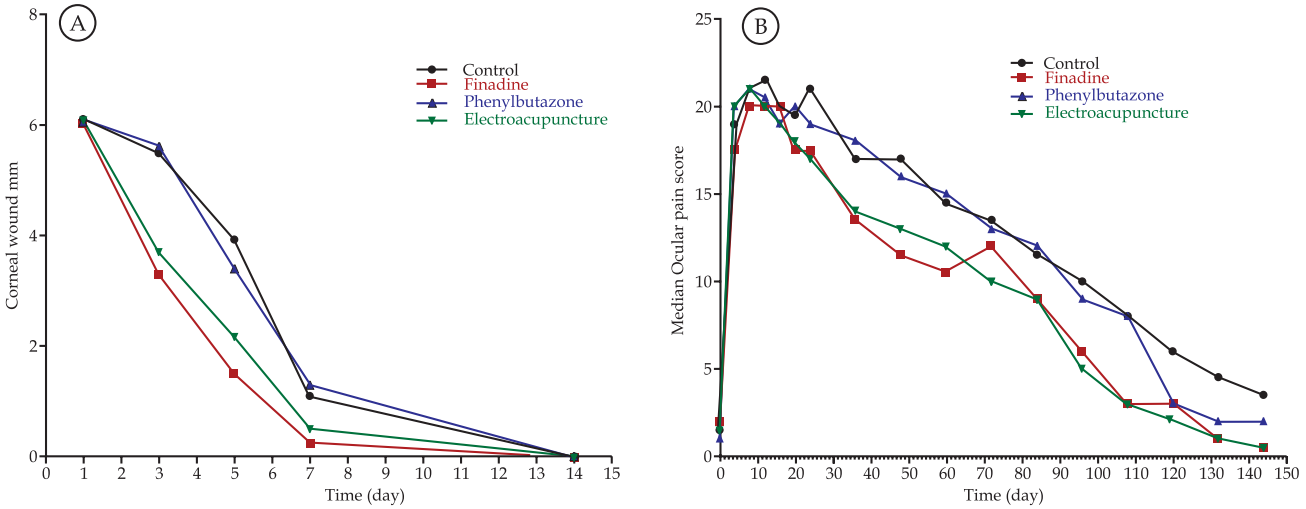

Fig 4. **A:** The Mean corneal wound healing (mm) of treatment groups over time; **B:** Mean total pain scores for all treatment groups over time.

These findings provided additional information about peak pain levels and pain persistence in ocular disorders in dromedary camels. The decreased peak pain after administration of the flunixin meglumine and phenylbutazone compared to the control group was consistent with previous studies in humans treated with oral NSAIDs after keratectomy (Ripa *et al,* 2020). Our observations indicate significant improvements in the condition of camels treated with NSAIDs, with reduced ocular pain evident after 72 hours of initiating the treatment. These findings are consistent with previous studies (Galera and Brooks, 2012; Hong *et al,* 2014; Singer *et al,* 2015). This pain persistence is longer than that observed by Sobas *et al* (2017), who reported a significant decrease in ocular pain score after 24 hours in humans. In dogs, a significant decrease in pain occurred after 48 hours (Clark *et al,* 2011; Dewey and Xie, 2021; Jiang *et al,* 2022).

The response to central corneal touch threshold palpation in the present study varied substantially over time, consistent with previous observations in bovine calves (Dewell *et al,* 2014). However, in the same calf study, no association between corneal wound healing and corneal touch threshold parameters was observed.

Blepharospasm in the present study varied the most of all pain and healing parameters in each camel and demonstrated a similar trend to pain severity over time. Similar results were reported in cattle and horses previously (Dewell *et al,* 2014; Makra *et al,* 2021). Blepharospasms were also previously observed as the most predominant sign of pain in dromedary camels with eyelid disorders and ocular discharge (Abdella *et al,* 2018). For many ocular pain parameter scores in horses, Makra *et al* (2021) reported that only blepharospasm was most consistently correlated with pain.

The tearing parameter in the current study may vary by climate, and camel eyes are generally very wet and full of tears (Am *et al,* 2018). The tearing score in the present study did not reflect the degree of pain in camels due to the absence of significant difference among treated groups. Tearing continued at a high level until 48 hours post-injury remained mild or moderate until the end of the experiment and has been observed to continue even when camel corneal wounds healed completely.

Corneal opacity was reported in dromedary camels and considered as an important sign of corneal ulceration (Abdella *et al,* 2018; Kumar *et al,* 2016). Nassaralla *et al* (1995) reported reduced corneal opacity after NSAID treatment in rabbits affected with corneal damage, which is in consistent with the present study results. The administration of EA in camels was more effective in reducing corneal opacity after injury compared to the no-treatment control and phenylbutazone groups, in which corneal opacity clearly persisted until the fourth day. Cariello *et al* (2006) also reported the positive effect of EA treatment on corneal opacity in rabbits.

In the present work, corneal wound healing was observed at the end of the first week post-injury in most groups, even in control camels which was consistent in equine observed by Makra *et al* (2021) and Raghunathan *et al* (2017), who evaluated the speed of corneal wound healing. The healing speed of corneal wounds in camels treated with flunixin

meglumine or phenylbutazone was faster than that of the untreated group; similar results for NSAIDs in ocular disorders were reported previously (Singer *et al,* 2015; Ting and Ghosh, 2019). Most previous studies highlighted the importance of using NSAIDs through systemic injection and avoiding using them through local use in the eye. Systemic administration prevents local side effects on the ocular surface that might delay the healing of corneal wounds and directly damage the anterior part of the eye (Hong *et al,* 2014; Ripa *et al,* 2020). Previous studies have also noted that long-term use of anti-inflammatories may cause serious gastrointestinal, hepatic and renal side effects (Fayez *et al,* 2023; Fernandez *et al,* 2019; Monteiro-Steagall *et al,* 2013). The speed of corneal wound healing in camels treated with EA in present study was faster than in the group of camels treated with phenylbutazone. Makra *et al* (2021) investigated the EA technique in ocular disorders in horses. EA also demonstrated a significant improvement in corneal injury in rats (Yang *et al,* 2022).

In conclusion, our data provide important information on ocular pain management in dromedary camels. Flunixin meglumine is more reliable in relieving ocular pain than phenylbutazone or EA. All treatments were more effective than the no-treatment control in relieving ocular pain and hastening the recovery from corneal wounds. The data we have collected will serve as a valuable resource for conducting further research on the efficacy of EA therapy for managing ocular pain and promoting corneal wound healing in dromedary camels and other animal species.

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Conflicts of interest

None

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