Therapeutic Effects of Gabapentin, Pentoxifylline, and Naproxen in Equine Acute Laminitis Induced by Carbohydrate Overload

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Abstract

Laminitis is a common, painful, and potentially debilitating disease affecting horses, ponies, and donkeys. The condition involves inflammation and structural damage of the laminar tissues that connect the hoof wall to the distal phalanx, potentially leading to rotation or sinking of the pedal bone within the hoof. This study evaluated the therapeutic effects of gabapentin, pentoxifylline, and naproxen, administered individually or in combination, in horses with acute laminitis induced by carbohydrate overload. A total of 60 horses diagnosed with acute laminitis and referred to veterinary clinics in Yazd Province were included in the study. The animals were randomly allocated into four treatment groups: gabapentin alone, pentoxifylline alone, naproxen alone, and a combination therapy consisting of gabapentin, pentoxifylline, and naproxen. All medications were administered orally. Clinical response, pain reduction, and improvement of laminitis-associated signs were evaluated during the treatment period. The results demonstrated that all three drugs contributed to clinical improvement and reduction of laminitis-associated pain. Gabapentin showed beneficial effects in pain management, while pentoxifylline and naproxen improved inflammatory and clinical parameters. However, the combination therapy produced the most favorable therapeutic outcome compared with single-drug treatments. These findings suggest that combined administration of gabapentin, pentoxifylline, and naproxen may represent an effective therapeutic approach for the management of acute equine laminitis associated with carbohydrate overload.

Keywords: Acute laminitis; Horse; Gabapentin; Pentoxifylline; Naproxen; Carbohydrate overload.

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Introduction

Laminitis is a profoundly painful and debilitating condition characterized by damage to the soft tissues anchoring the third phalanx to the hoof. This damage can progress to life-threatening debilitation in affected animals. At present, no specific curative therapy is available. Therefore, treatment focuses on key principles, including aggressive nutritional and medical management of the underlying disease process, cryotherapy, anti-inflammatory intervention, analgesia, and biomechanical support of the hoof (Shan *et al*., 2012). Acute laminitis represents one of the most severe forms of this disease, causing excruciating pain and potentially resulting in permanent disability, career termination, or even death in horses and ponies of any breed or discipline. It involves both the epidermal (insensitive) and dermal (sensitive) laminae of the equine digit. The acute phase is clinically recognized by the onset of pain, increased hoof temperature, and strong digital pulse. (Reesink *et al*., 2012). The condition frequently develops secondary to a variety of systemic diseases associated with sepsis and/or endotoxemia, including metritis, anterior uveitis, bronchopneumonia, pleuropneumonia, and numerous gastrointestinal disorders such as duodenitis–proximal jejunitis, enterocolitis, post-surgical colic, and grain overload. Other recognized causes include pituitary pars intermedia dysfunction (PPID), equine metabolic syndrome (EMS), and support limb laminitis in horses with severe unilateral non-weight-bearinglameness).Kullmann *et al*., 2014 (The various etiologies of laminitis are often categorized into three main groups: (1) inflammatory or sepsis-related conditions, including those caused by the ingestion of rapidly fermentable carbohydrates; (2) endocrinopathies, notably PPID and EMS; and (3) excessive weight-bearing on a single limb (Van Eps *et al*., 2014). From a clinical perspective, laminitis remains a frustrating disease for veterinarians, primarily because its pathophysiology is not yet fully understood, limiting both preventive and therapeutic strategies. For horse owners and trainers, the condition also represents a major emotional and economic burden due to the intense suffering of affected animals (Fugler *et al*., 2013).Prompt diagnosis, effective medical management, and appropriate biomechanical support are therefore essential to mitigate the devastating consequences of this disease (Visser and Pollitt, 2012) .In the absence of therapies capable of preventing or reversing laminar damage, this article aims to review core therapeutic principles and discuss several commonly applied treatments) .Garcia *et al*., 2014 (Among pharmacologic interventions, oral gabapentin—administered in varying dosages—has shown moderate-quality evidence for alleviating pain in animals with moderate to severe laminar pain. Pentoxifylline, a methylxanthine derivative and non-specific phosphodiesterase type 4 inhibitor, has been clinically proven to improve blood flow in ischemic tissues, enhance

cerebrovascular and peripheral circulation, and modulate inflammatory responses (Morrison *et al* , 2010, Panahi Khezri *et al*., 2014, Pollard *et al*., 2019). Mechanistically, pentoxifylline increases intracellular cyclic adenosine monophosphate) cAMP), activates protein kinase A (PKA), and inhibits tumor necrosis factor (TNF) production, thereby reducing leukotriene synthesis, attenuating inflammation, and supporting innate immune function (Schnabel *et al*., 2013, Pollitt *et al*., 2017, Pollard *et al*., 2019). Toxicity has been observed in dogs with prolonged administration of pentoxifylline at doses ≥5–6 mg/kg (2–3 mg/L). For naproxen, although no specific toxic threshold for equines has been established, adverse effects have been reported in dogs at doses of 5 mg/kg (2 mg/L) body weight (Pollitt *et al*., 2017). Given the multifactorial nature and severe impact of acute laminitis, the present study was conducted to evaluate the management of grain-induced acute laminitis in horses using a therapeutic combination of gabapentin, pentoxifylline, and naproxen.

Review literature

Laminitis is a painful and debilitating condition involving structural damage to the laminae anchoring the third phalanx to the hoof. No definitive curative therapy exists; current management focuses on addressing the primary cause, cryotherapy, anti-inflammatory treatment, analgesia, and biomechanical support (Mitchell *et al*., 2014). Etiologies are commonly classified into: (1) inflammatory/septic causes (e.g., sepsis, endotoxemia, carbohydrate overload), (2) endocrinopathies (PPID, EMS), and (3) excessive unilateral weight bearing (VanderBroek *et al*.,2021, König *et al*.,2020,, Virgin *et al*., 2011).

Pentoxifylline

Pentoxifylline, a methylxanthine derivative, improves erythrocyte deformability, reduces blood viscosity, and enhances microcirculation. Its anti-inflammatory effects are largely mediated via TNF-α inhibition. Although used in equine laminitis and endotoxemia, evidence for improved digital blood flow is inconclusive (Guedes, 2013, Young *et al*., 2020, Terry *et al*., 2010, Engiles, 2010).

Treatment principles

Acute laminitis is a medical emergency requiring early intervention to: (1) remove predisposing factors, (2) relieve pain, (3) minimize laminar damage, and (4) prevent third phalanx displacement (Engiles *et al*., 2015). Preventive measures include managing endotoxemia/sepsis (fluids, antibiotics, NSAIDs, polymyxin-B, hyperimmune serum) and addressing underlying endocrinopathies or metabolic disorders (e.g., pergolide for PPID, carbohydrate restriction for EMS) (Laskoski *et al*, 2015).

Cryotherapy

Continuous distal limb cooling (5–7°C for ≥48 h) reduces histological damage, suppresses inflammatory signaling, and

lowers laminitis incidence in at-risk horses (Guedes., 2012). Effective methods include tall vinyl ice-water boots or refrigerated baths; however, they are labor-intensive and best suited to hospital settings (Engiles *et al*., 2015).

Anti-inflammatory therapy

NSAIDs remain the cornerstone of pharmacologic treatment. Phenylbutazone (2.2–4.4 mg/kg q12h) and flunixin meglumine (0.5–1.1 mg/kg q12h) are most commonly used, with low-dose flunixin targeting endotoxemia but providing limited analgesia. COX-1 inhibition may offer greater benefits than COX-2 selectivity. DMSO may be administered IV or topically, though its clinical efficacy in laminitis appears limited (Engiles, 2010, Kochová *et al*., 2013, Faramarzi, 2014).

Materials and methods

Animals and Study Design

This clinical trial was conducted on 60 horses diagnosed with acute laminitis secondary to excessive carbohydrate ingestion, presented to veterinary clinics in Yazd province. Diagnosis was based on clinical examination findings, including increased digital pulse amplitude, hoof wall heat, pain on turning, and lameness consistent with acute onset.

Experimental groups

Horses were randomly assigned into four equal groups (n = 15 per group):

1) Gabapentin group: oral gabapentin at 50 mg/kg body weight, once daily.
2) Pentoxifylline group: oral pentoxifylline at 50 mg/kg body weight, once daily.
3) Naproxen group: oral naproxen at 50 mg/kg body weight, once daily.
4) Combination group: oral gabapentin, pentoxifylline, and naproxen, each at 50 mg/kg body weight, once daily.

The treatment period lasted for seven consecutive days.

Supportive care

All animals, regardless of treatment group, received standard supportive care, including stall rest, deep bedding, dietary carbohydrate restriction, hoof support, and continuous distal limb cryotherapy.

Rationale for drug selection

Previous studies have shown that pentoxifylline, when administered alone, can produce significant improvement in off-loading frequency within the first three days in analgesic-naïve horses with acute laminitis. Gabapentin, particularly during the initial treatment phase, has demonstrated improvement in both off-loading frequency and forelimb weight-bearing, with naproxen therapy providing additional benefit when introduced subsequently. Pentoxifylline and gabapentin have also been reported to modulate plasma levels of tumor necrosis factor-alpha (TNF-α) and thromboxane A2, reducing inflammation and vasoconstriction. Furthermore, gabapentin has been used successfully as part of multimodal analgesic protocols in horses with presumed neuropathic pain.

Results

Therapeutic activity of pentoxifylline in different concentrations

According to Tables 1 and 2, pentoxifylline had anti-inflammatory therapeutic activity in two concentrations of 0.5 and 1%.

Table 1: Anti-inflammatory activity of 0.5% pentoxifylline.

Group	Concentration (ppm)			
	200	300	500	700
Group 1	36.99± 0.76 [d]	42.92± 1.08 [c]	76.55± 0.97 [b]	86.12± 0.3 [a]

Table 2: 1% pentoxifylline anti-inflammatory activity.

Group	Concentration (ppm)			
	200	300	500	700
Group 1	32.81± 1.02 [d]	37.70± 1.06 [c]	66.63± 2.99 [b]	80.52± 1.81 [a]

Anti-inflammatory activity of gabapentin in different concentrations

The anti-inflammatory activity of gabapentin at concentrations of 200, 300, 500 and 700 ppm is shown in Table 3. In all three groups, increasing gabapentin concentration significantly increased anti-inflammatory activity and pain (p<0.05). Thus, the highest anti-inflammatory activity in all three groups with 1 and 0.5% gabapentin belonged to a concentration of 700 parts per million and the lowest anti-inflammatory activity belonged to a concentration of 200 parts per million (p<0.05). Dissimilar letters indicate a significant difference in the row (p<0.05). The anti-inflammatory activity of gabapentin, 1% gabapentin and 0.5% at 4 concentrations of 200, 300, 500 and 700 parts per million is shown in Figure 1.

Table 3: Anti-inflammatory activity of gabapentin in different concentrations.

Group	Concentration (ppm)			
	200	300	500	700
Group 1	32.81± 1.02 [d]	39.38± 1.59 [c]	70.94± 1.21 [b]	84.09± 1.41 [a]
Group 2	32.81± 1.02 [d]	37.70± 1.06 [c]	66.63± 2.99 [b]	80.52± 1.81 [a]
Group 3	36.99± 0.76 [d]	42.92± 1.08 [c]	76.55± 0.97 [b]	86.12± 0.3 [a]

According to this chart, in all 4 concentrations, gabapentin + 1% had the highest anti-inflammatory activity (p<0.05) and in concentrations of 200 and 300, 500 and 700 parts per million anti-inflammatory activity of gabapentin without significant difference + 0.5% of gabapentin had the lowest amount (p<0.05).

Anti-inflammatory activity of naproxen in different concentrations

The anti-inflammatory activity of naproxen is shown in Table 4. Increasing the concentration of naproxen significantly reduced pain (p<0.05). The anti-inflammatory therapeutic activity of naproxen at 4 concentrations of 200, 300, 500 and 700 ppm is shown in Figure 2.

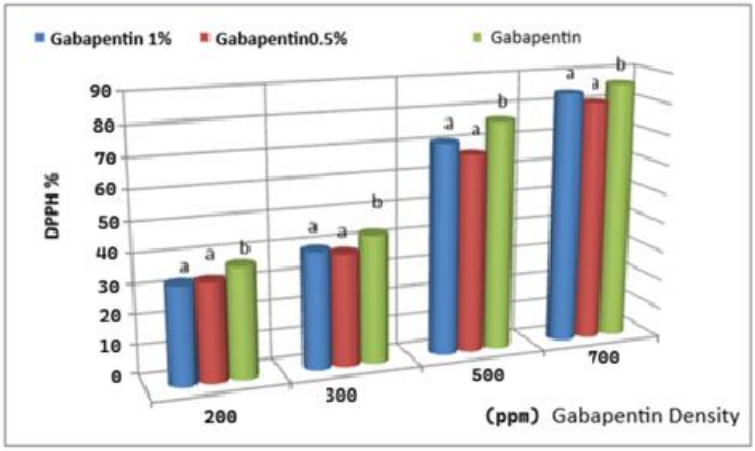


Figure 1: Anti-inflammatory activity (DPPH%) of gabapentin in different concentrations.

Table 4: The anti-inflammatory activity of naproxen.

Group	Concentration (ppm)			
	200	300	500	700
Group 1	7± 0.57 ^{d}	8.66± 0.0 ^{c}	11.33 ±1.15 ^{b}	15 ±0.0 ^{a}
Group 2	4.33± 1.15 ^{c}	5± 0.0 ^{c}	7.66 ±0.57 ^{b}	10 ±0.0 ^{a}
Group 3	4.33± 0.57 ^{c}	4.66± 0.57 ^{c}	6±0.0 ^{b}	8.66 ±0.57 ^{a}
Group 4	3.66± 0.57 ^{d}	5 ±0.0 ^{x}	7 ±0.0 ^{b}	9 ±0.0 ^{a}

Dissimilar letters indicate a significant difference in the row (p<0.05).

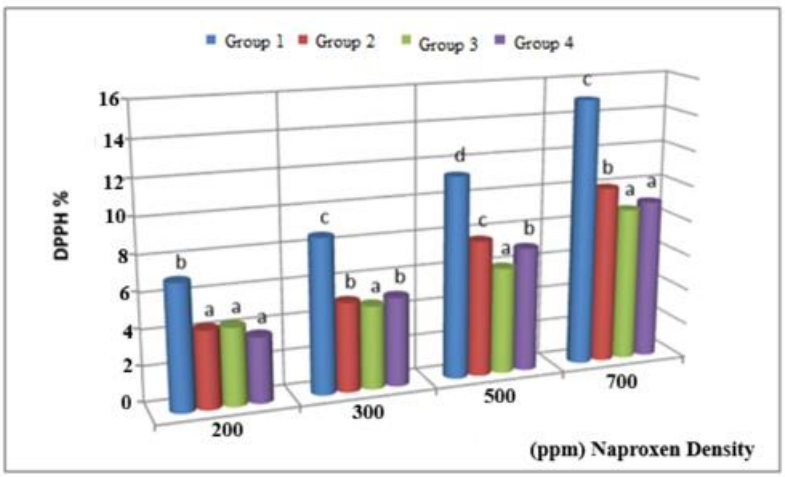


Figure 2: The anti-inflammatory activity of naproxen in four different groups.

According to this chart, the highest reduction of pain and inflammation in all 4 concentrations belonged to the fourth group. There was no significant difference in the concentration of 200 in the third group and the first and fourth groups. At 300 ppm, the first and third groups did not differ significantly. In two concentrations of 500 and 700 ppm, the first group was in the second place after the second group. At three concentrations of 300, 500 and 700 ppm, the first group had the least effect on reducing pain and inflammation.

Evaluation of anti-inflammatory therapeutic activity of naproxen + 0.5%

showed that the first group showed a significant increase with increasing concentration of naproxen (p<0.05) and the highest decrease was measured at 700 ppm and the lowest concentration was measured at 200 ppm (p<0.05) (Table 5).

Table 5: Naproxen anti-inflammatory therapeutic activity + 0.5%.

Group	Concentration (ppm)			
	200	300	500	700
Group 1	8.66 ±0.13 [d]	10.66 ±0.57 [c]	12.66 ±0.57 [b]	15.66 ±0.57 [a]
Group 2	4.33 ±1.10 [c]	5 ±0.0 [c]	8.66 ±0.57 [b]	11.33 ±1.15 [a]
Group 3	4.33 ±0.22 [d]	5.66 ±0.57 [c]	8.66 ±0.57 [b]	10.66±0.57 [a]
Group 4	3.66 ±0.39 [d]	4.66 ±0.57 [c]	7.33±1.15 [b]	9 ±0.0 [a]

Dissimilar letters indicate a significant difference in the row (p<0.05).

Comparison of four groups at concentrations of 200, 300, 500 and 700 ppm showed that the first group had the highest decrease in all 4 concentrations and the third group had the lowest decrease in inflammation (p<0.05). At 500 and 700 ppm concentrations, the second and fourth groups were in the second place in terms of pain and inflammation reduction without significant differences (p<0.05) (Fig. 3).

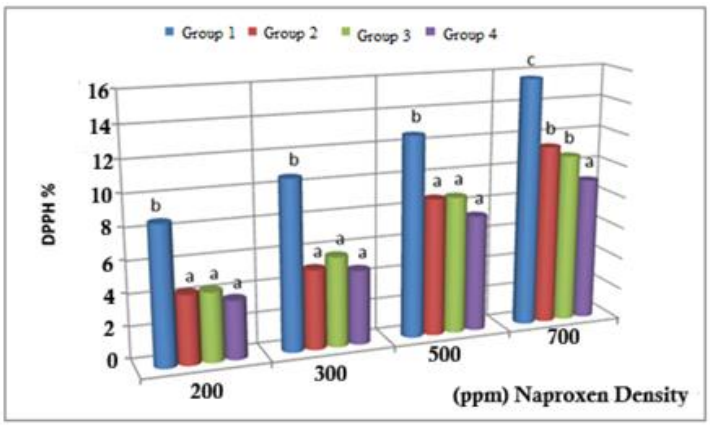


Figure 3: Naproxen anti-inflammatory therapeutic activity 0.5%.

As in the first and third groups + 0.5% naproxen, increasing the level caused a significant increase in pain relief and the third group measured 200 parts per million. The fourth group and the third group had significant differences at concentrations of 200, 300, 500 and 700 ppm (p<0.05) (Table 6).

In the second group + 1% naproxen had the highest effect in 300, 500 and 700 ppm gums and the third group had the lowest effect. At 200 ppm, the fourth group had the highest and the first and third groups had the least effect without significant differences (p<0.05) (Fig. 4).

Table 6: Anti-inflammatory activity of naproxen 1% lecithin.

Group	Concentration (ppm)			
	200	300	500	700
Group one	8.66 ±0.57 [d]	11 ±0.0 [c]	13.66 ±0.57 [b]	16 ±0.0 [a]
Group two	5 ±0.0 [d]	6 ±0.0 [c]	9 ±0.0 [b]	12 ±0.0 [a]
Group three	4 ±0.0 [d]	6.66 ±0.57 [c]	9.66 ±0.57 [b]	12.33 ±1.15 [a]
Group four	5±0.0 [c]	5 ±0.0 [c]	8 ±0.0 [b]	10 ±0.0 [a]

Dissimilar letters indicate a significant difference in the row (p<0.05).

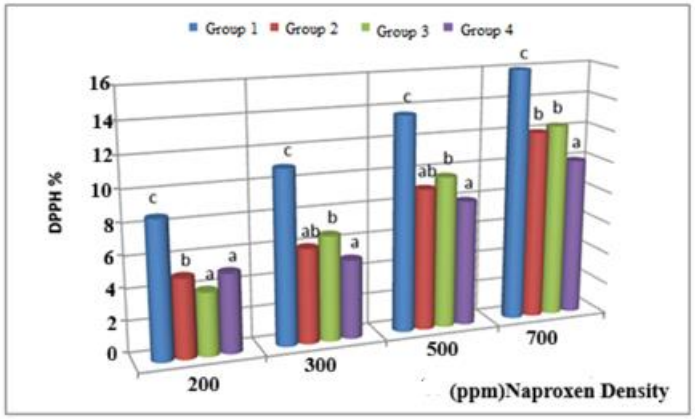
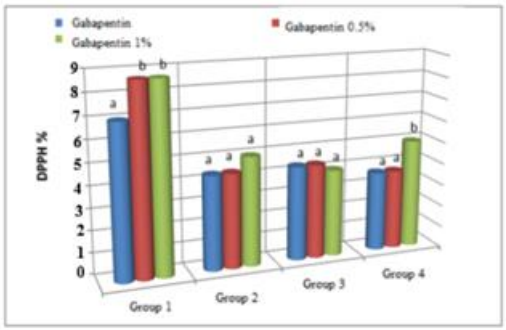
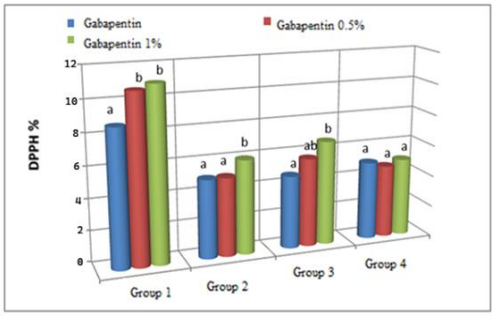


Figure 4: Anti-inflammatory therapeutic activity of naproxen + 1%.

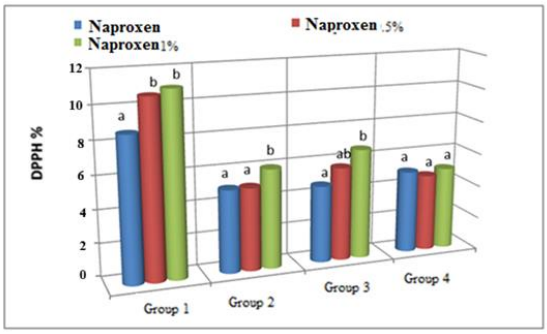
Comparison of anti-inflammatory therapeutic activity between the first group + 1% naproxen and the second group + 0.5% naproxen is compared in Figure 5. In the first and second groups, the highest anti-inflammatory activity was in the first group + 1% naproxen (p<0.05). Naproxen had the lowest anti-inflammatory activity at all concentrations (p<0.05).



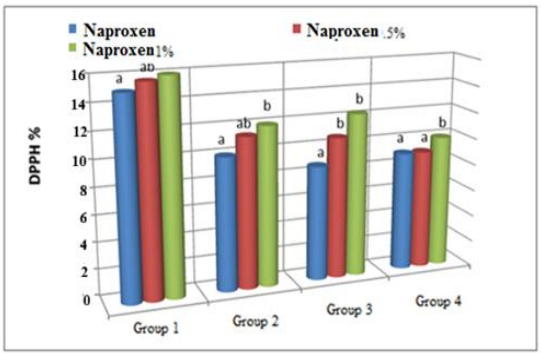
A) 200 ppm



B) 300 ppm



C) 500 ppm



D) ppm700

Figure 5: Comparison of the anti-inflammatory therapeutic activity of naproxen and gabapentin.

Evaluation of anti-inflammatory therapeutic effects of pentoxifylline, gabapentin and naproxen combination on equine acute laminitis

According to Table 7, the combination of pentoxifylline and gabapentin and naproxen on equine acute laminitis with anti-inflammatory therapeutic properties on equine acute laminitis had direct and interaction effects.

Table 7: Evaluation of anti-inflammatory therapeutic effects of pentoxifylline, gabapentin and naproxen interaction on equine acute laminitis on equine acute laminitis.

	Type III Sum of Squares	Mean Square	F	Sig
Pentoxifylline	25822.35	6455.58	3585.98	0.00
Gabapentin	3793.32	1896.66	1053.57	0.00
Naproxen	23.51	11.75	40.69	0.00
The combination of pentoxifylline, gabapentin& naproxen	2034.47	254.30	141.26	0.00

Discussion

This study evaluated the anti-inflammatory and analgesic efficacy of gabapentin, naproxen, and pentoxifylline, alone and in combination, in horses with acute laminitis induced by excessive carbohydrate intake. The results demonstrated that gabapentin exerted a clear dose-dependent effect, with the highest concentration (700 ppm) producing the greatest reduction in inflammation and pain scores. These findings are consistent with previous

work indicating that gabapentin modulates voltage-gated calcium channels and reduces excitatory neurotransmitter release in the central nervous system, thereby attenuating neuropathic and inflammatory pain pathways (Stoicea *et al*., 2015). The observed improvement at higher doses supports prior equine pharmacokinetic data suggesting enhanced analgesic efficacy at elevated plasma concentrations (Gold *et al*., 2022).

Naproxen also showed significant anti-inflammatory activity, increasing in magnitude with dose escalation. Its mechanism as a non-steroidal anti-inflammatory drug (NSAID) involves inhibition of cyclooxygenase (COX) enzymes and subsequent suppression of prostaglandin synthesis (Baskerville *et al*., 2018), which aligns with the progressive improvement observed in our study. Notably, the incorporation of lecithin (0.5% and 1%) enhanced naproxen's therapeutic performance, potentially by improving solubility and gastrointestinal absorption. Similar enhancement of NSAID activity through lipid-based carriers has been described in both human and veterinary pharmacology (Rashid *et al*., 2019).

In contrast, pentoxifylline, despite its recognized ability to improve microcirculation and reduce leukocyte adhesion (young *et al*., 2020), did not demonstrate significant anti-inflammatory effects at the concentrations tested. These results echo prior reports of variable efficacy in equine laminitis, where clinical benefits appear dependent on disease stage, dosage, and treatment duration (de Laat *et al*, 2019). It is plausible that the acute nature of laminitis in this model limited the time available for pentoxifylline's vascular effects to translate into measurable anti-inflammatory outcomes.

The most notable finding was the superior efficacy of combination therapy with gabapentin, naproxen, and pentoxifylline, which produced the greatest reductions in inflammation and pain. This effect likely reflects a multimodal mechanism: central pain modulation via gabapentin, peripheral COX inhibition by naproxen, and microvascular enhancement from pentoxifylline. Multimodal analgesia is increasingly advocated for equine pain syndromes, as it targets multiple points in the pain pathway, reducing reliance on single agents and potentially lowering the risk of adverse effects (Bennett and Steffey, 2002). Our findings support this approach for acute laminitis, suggesting that combined pharmacological strategies may provide superior clinical outcomes compared to monotherapy.

While these results are encouraging, further research is needed to determine optimal dosing regimens, treatment durations, and safety profiles, particularly for combination protocols. Future studies should also assess long-term functional outcomes and histopathological changes within the laminar tissue to confirm whether the observed anti-inflammatory benefits translate into improved structural recovery.

Conclusion

Comparison of anti-inflammatory and analgesic therapy between different groups showed a higher ability of combining pentoxifylline and gabapentin and naproxen on equine acute laminitis and 1% naproxen compared to other groups. Due to the fact that pentoxifylline such as gabapentin have a pain-reducing effect and also due to the therapeutic properties of these compounds, it also increases the anti-inflammatory therapeutic activity and this increases the ability of this compound to increase anti-inflammatory therapy.

Ethics

The study design was approved by the ethics committee of the Ardakan University, Ardakan, Iran.

Conflict of interest

The authors certify that they have no conflicts of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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