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# Evaluation of the Analgesic Efficacy and Safety of Preemptive Nefopam Compared with Tramadol in Feline Orthopedic Surgery

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***Abstract*—** Objective: To compare the clinical efficacy and safety of preemptive nefopam, a non-opioid analgesic, with tramadol, an opioid agonist, for managing post-operative pain in cats undergoing orthopedic surgery.

Animals and Procedures: Twenty-four adult male Himalayan cats were randomly assigned to three groups (n=8). A tibial defect was surgically induced to create a standardized pain model. The Control group received a xylazine-ketamine anesthetic protocol. The Tramadol group received preemptive tramadol (4 mg/kg, IM), and the Nefopam group received preemptive nefopam (2 mg/kg, IM), both administered 10 minutes before anesthesia. Post-operative analgesia was assessed via pain scores, and time to return to normal appetite and gait.

Results: Both preemptive groups demonstrated superior post-operative outcomes compared to the control group. Pain scores were significantly lower in the tramadol and nefopam groups, with complete resolution by day 5 versus day 6 in the control group. Time to return to appetite (171.87±2.97 min for tramadol, 175.62±5.03 min for nefopam) and gait (2.37±0.26 days for tramadol, 2.37±0.18 days for nefopam) was significantly faster than in the control group (247.37±5.62 min for appetite return and 4.62±0.18 days for normal gait return, respectively). No significant difference in analgesic efficacy was found between the nefopam and tramadol groups. Hemodynamically , tramadol induced significant bradycardia (117.75±0.75 beat per minutes at time 110min ), whereas nefopam caused a significant increase in systolic blood pressure(149.75±5.06 after 30 min of administration of anesthetic mixture ). Critically, serum creatinine levels remained within normal physiological limits in all groups.

Conclusions: Preemptive nefopam was associated with post-operative analgesia similar to tramadol in cats undergoing painful orthopedic surgery. Due to its efficacy and no nephrotoxicity at the dose administered, nefopam could serve as a novel non-opioid painkiller that supports multimodal analgesic protocols in feline clinical practice.

***Keywords*** **—** Nefopam, Tramadol, Feline, Preemptive Analgesia, Post-operative Pain.

## INTRODUCTION

Anesthesia for feline patients, although a routine approach, entails great challenges, including high mortality rates and complications involving hypothermia and hypotension (1,2). Optimal anesthetic agents and close perioperative monitoring should be targeted to prevent these risks and enhance patient outcomes (3). Preemptive analgesia is a therapeutic approach in which agents are administered before a painful event to prevent central sensitization and reduce postoperative discomfort and the necessity for multiple drugs (4). It is crucial in preemptive analgesia in veterinary medicine in order to prevent central sensitization and thus to decrease pain during the postoperative period, and to reduce the patient's dependence on supplementary analgesics and complications during an operation in a postoperative period (5).

Studies in veterinary patients have confirmed the benefits of this approach, leading to improved recovery trajectories (4).

While tramadol is widely used for moderate pain in cats, its potential side effects warrant investigation into alternatives (4). Its analgesic and potential local anesthetic profiles have been investigated across various species (6), establishing it as a standard agent for comparative studies. Nefopam, a non-opioid analgesic effective in dogs, has not been thoroughly documented in feline clinical literature (7), but its use in cats has not been previously recorded in scientific literature.

Therefore, this study prospectively evaluates the efficacy and safety of preemptive nefopam versus tramadol in a standardized feline orthopedic pain model.

## MATERIALS AND MTHODS

**Setting of the research and ethical comity.**

The local committee of the animal care and use at the College of Veterinary Medicine University of Baghdad provided this ethical approval (number P.G.2271 at 10. Sep.2025).

**Animals**

Twenty-four adult Himalayan male cats (Toms) were recruited for this study. All animals were clinically evaluated by physical examination, vaccinated, and treated with anthelmintics and anti-parasitics. The cats were housed in individual cages for a two-week acclimatization period prior to the experiment. Animals were fasted for 3-4 hours prior to anesthesia (8). All housing and treatment protocols were performed in accordance with approved ethical guidelines for animal welfare.

**Experimental Design and Anesthetic Protocol**

The cats were randomly divided into three equal groups (n=8).

**Control Group (A):** Animals were administered an intramuscular (IM) injection mixture of xylazine (0.5mg/kg B.W.) and ketamine (5 mg/kg B.W.).

**Tramadol Group (B):** Animals were administered an IM injection of tramadol (4mg/kg B.W.) as a preemptive treatment. The xylazine-ketamine anesthetic mixture was injected 10 minutes later.

**Nefopam Group (C):** For subjects in the Nefopam Group (C), a preemptive dose of nefopam (2 mg/kg B.W.) was delivered via intramuscular injection. Following a 10-minute interval to allow for initial systemic absorption, the xylazine-ketamine anesthetic combination was administered.

**Surgical Procedure**

In order to establish a uniform pain model, a standardized surgical defect was created in the tibia of each subject while under the influence of general anesthesia.

**Data Collection and Monitoring**

To assess the anesthetic profile, several key parameters were monitored, including the interval to induction, the overall duration of anesthesia, and the time required for complete recovery. Post-operative pain was assessed daily using a multidimensional composite pain scale. Time to return to normal appetite and gait were also recorded. Blood samples were collected before surgery and on days 1, 3 and 7 post-operatively for serum Creatinine analysis.

**Statistical Analysis**

All data are expressed as mean ± standard error (SE). Statistical comparisons among groups were performed using one-way analysis of variance (ANOVA) followed by the Least Significant Difference (LSD) test for post-hoc comparisons. A P-value ($P<0.05$) was considered statistically significant.

## RESULT AND DISCUSSION

**Anesthetic Course**

In particular, the preemptive analgesics significantly modified the anesthesia course. Induction time was faster in the Nefopam group (2.12±0.12 min) and the Tramadol group (2.75±0.16 min), both these being faster compared to the Control group (4.50±0.18 min) ($P<0.05$). The longest duration of anesthesia was prolonged in the Tramadol cohort (51.25±0.81 min, $P<0.05$). The recovery was significantly faster for both Tramadol (31.25±0.82 min) and Nefopam (30.63±1.50 min) compared to the Control group (43.38±0.98 min) ($P<0.05$). The recovery in the Control group was observed to be painful. The times to return to normal appetite were markedly shorter with Tramadol (171.87±2.97 minutes) and Nefopam (175.62±5.03 minutes) compared to Control (247.37±5.62 minutes) ($P<0.05$). The time to return to normal gait was also significantly shorter for both Tramadol and Nefopam (2.37 days in both groups) compared to 4.62 days in the Control group ($P<0.05$). Both preemptive groups displayed significantly lower pain scores than the Control group on every post-operative day. In patients receiving Tramadol and Nefopam, evidence of pain completely resolved by day 5, but persisted up until day 6 in patients receiving Control treatment. Differences in pain scores at any time point between Tramadol and Nefopam groups were not statistically significant (table 1).

**Table 1.** Anesthetic course parameters (induction, duration, recovery)/minutes.

| Time/min. / Groups | Induction | Duration | Recovery |
|---|---|---|---|
| **Control** | 4.50±0.18a | 16.00±0.53c | 43.38 ± 0.98 a |
| **Tramadol** | 2.75±0.16b | 51.25±0.81a | 31.25 ± 0.82 b |
| **Nefopam** | 2.12±0.12c | 46.25±1.25b | 30.63 ± 1.50 b |
| **LSD** | 0.47 | 2.69 | 6.00 |

- Means with a different small letter in the same column are significantly different ($P<0.05$)

**Clinical Summary and Other Data**

The preemptive administration of either tramadol or nefopam significantly accelerated the return to normal appetite compared to the Control group ($P < 0.05$). Cats in the Tramadol group showed the earliest return to appetite at (171.87±2.97 minutes), followed by the Nefopam group at (175.62±5.03 minutes). In contrast, cats in the Control group required a significantly longer duration (247.37±5.62 minutes) to begin eating post-operatively. No significant difference was observed between the two analgesic groups regarding this metric (table 2).

**Table 2.** Comparison between appetite return time after recovery among the groups

| Mean ± SE of the minutes of normal appetite return post anesthesia | |
|---|---|
| **Time / Groups** | Appetite return |
| **Control** | 247.37±5.62 a |
| **Tramadol** | 171.87±2.97 b |
| **Nefopam** | 175.62±5.03 b |
| **LSD** | **13.78** |

- ($P<0.05$).
- Time in minutes starting from recovery time ( table 1)

**Time to Return to Normal Gait**

In terms of functional recovery, both preemptive groups showed significantly faster return to normal gait and weight-

bearing compared to the Control group (P<0.05). Tramadol and nefopam-treated cats walked normally again in (2.37±0.26 days) and (2.37±0.18 days), respectively, compared to (4.62 ± 0.18) days for the Control group. The results of this study support the proposition that preemptive analgesic regimes may be very successful at limiting surgical trauma-induced disability and, hence, are accepted as vital to preventing and alleviating surgical trauma-induced injury in the mobility of the cat as indicated in Table (3).

**Table 3.** Statistical comparison of restoration of functional gait in the experimental groups.

| Mean ± SE of the minutes of normal appetite return post anesthesia | |
|---|---|
| Time<br>Groups | Gait |
| Control | 4.62±0.18 a |
| Tramadol | 2.37±0.26 b |
| Nefopam | 2.37±0.18 b |
| LSD | 0.62 |

- (P<0.05).
- Time in minutes starting from recovery time ( table 1)

**Safety and Hemodynamic Effects**

The preplanned agents used induced divergent cardiovascular responses. Subjects in the Tramadol group had a marked decline of heart rate towards the subnormal level after 70 minutes' anesthetic maintenance. The Nefopam group, by contrast, showed a marked increase of systolic blood pressure in certain intra-operative intervals. For clinical safety, renal function was unaffected; serum creatinine concentrations did not differ significantly across cohorts at any post-surgical stage. Also, all creatinine values were systematically maintained within the physiological reference parameters for cats (Table 4).

**Table 4.** Post-operative serum creatinine levels Blood biochemistry

| Blood biochemistry<br>Mean ± SE of the levels of ( Creatinine ) mg/dL | | | | |
|---|---|---|---|---|
| **Groups** | **Day0** | **Day1** | **Day3** | **Day7** |
| **Control** | 0.94 ± 0.9 Aa | 1.12 ± 0.15 Aa | 1.12 ± 0.15 Ab | 1.09 ± 0.1 Aa |
| **Tramadol** | 0.98 ± 0.06 Aa | 1.04 ± 0.06 Aa | 0.90 ± 0.03 Aa | 1.01 ± 0.04 Aa |
| **Nefopam** | 0.76 ± 0.04 Aa | 0.96 ± 0.11 Aa | 0.87 ± 0.03 Aa | 0.97 ± 0.05 Aa |
| **LSD** | 0.2346 | | | |
| All differences were not significant<br>Reference Range : ≤ 2 mg/dl [9] | | | | |

Our results provide innovative medical rationale for the practical application of nefopam to preoperative management in cats and demonstrate an analgesic response similar to that currently reported to accompany the acute orthopedic pain of tramadol. This significant improvement in recovery-parameters for all cases in both preventive and control patients demonstrates that early analgesia is important to prevent trauma. These strategies are instrumental in minimising the central sensitization and 'wind-up' phenomena in the cat and hence, they comprise the key elements crucial to maintain the postoperative recovery status of the cat (10).

It is accepted that appetite restoration is the critical indication of new anesthetic in feline care and is a strong clinical indication in perioperative pain. According to our study, feeding was resumed much earlier in both of the preemptive cohorts (171.87±2.97 min; 175.62±5.03 min), and the control group had only a gradual restart (247.37±5.62 min). From a physiologic perspective, acute pain acts as an acute stressor; this catabolic stimulus can inhibit the hypothalamic appetites of animals. The strong analgesia of nefopam and tramadol probably mitigated this surgical stress response and allowed for the rapid recovery of physiologic homeostasis. The current results are supported by Steagall et al., (11) in that they report that pet cats experience pain relief and are able to change their nursing and feeding habits as a result and therefore achieve clinical recovery faster. Against the control group (4.62±0.18 days), the faster weight bearing and functional gait in nefopam (2.37±0.18 d) or tramadol (2.37±0.26 d) rates forms an impressive relative comparison to prove effective perioperative analgesia. In orthopedic environment, postoperative lameness is often exacerbated by 'wind up' and central sensitization of dorsal horn neurons. In this sense, one would arguably expect that the induction of tibial deficiency and its subsequent clinical phenotypic effects would be controlled by analgesics at the time of N-methyl-D-aspartate (NMDA) receptor stimulation. This drug blockade itself maintains motor capability and allows mobility earlier in life. Such findings are in agreement with the findings of Abed et al., (12), which classified restoration of gait into one of the top clinical markers to determine the impact of analgesic protocol and overall outcome in small animal practice of orthopedic metric of orthopedic treatments. In comparing analgesic parity for nefopam with tramadol, we demonstrate a key insight. These are precisely the reasons that corroborating that nefopam, a drug that is nonopioid, as a potential alternative to the pain treatment in cats providing clinicians very suitable alternatives that are safe or available for using as a substitute for other traditional synthetic opioids. That decision is particularly poignant in a world where clinical interest in opioid-dependent protocols is growing. The findings here are consistent with those of earlier studies conducted in dog models receiving nefopam, while also having postoperative analgesia comparable to that suggested for tramadol (13).

Antitrapylic activity was favored the individual pharmacological candidates owing to the risk profile. The bradycardia observed in the tramadol group is a well-defined phenomenon; it is most probably mediated by an escalation in parasympathetic tone (14). Under nefopam conditions we would likely have triggered the hypertensive response through

the inhibition of norepinephrine reuptake alone (15). While such physiological sequelae warrant rigorous clinical surveillance, the principal safety result was no nephrotoxic cues. Serum creatinine in all study groups exhibits good stability, suggesting significant renal safety for the tested doses. Not only these observations are consistent with classical assumptions and knowledge about toxico-clinical conditions, most doses in this study were much higher than those presented in these data sources (16).

Nevertheless, limitations have been identified in this study including the one-size-fits-all pain model of healthy subjects. Similarly, the results might not be applicable to other clinical pain syndromes or to a cat with comorbidity. Additionally, it is generally required that further studies be conducted particularly for the pharmacokinetic modelling of metabolic status and clearance of nefopam of cats. Yet veterinary medicine has so far not covered all of these variables, and literature on them is rather limited. These therapeutic regimens for managing postoperative pain without reliance on old-fashioned opioid-assisted approaches may become available more simply by incorporating nefopam in the clinic setting of cats.

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