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Nefopam and Medetomidine Analgesia and Interaction in Mice

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Abstract

Effective pain relief in rodent models, with reduced drug doses, represents an important objective in preclinical pharmacology. This study aimed to evaluate the analgesic effect of nefopam and medetomidine at graded doses and to assess the synergistic antinociceptive interaction when combined at sub-analgesic levels. Swiss albino mice were subjected to the hot plate test (55.0 ± 0.1°C) as a model of acute thermal pain. The ED_{50} for both drugs was determined using the up-and-down method. Nefopam was administered intraperitoneally at doses of 3, 6, and 12 mg/kg, while medetomidine was given at 50, 100, and 200 µg/kg. Latency time and % maximal possible effect (%MPE) were recorded at multiple time points post-injection. The highest dose of medetomidine (200 µg/kg) produced a peak latency of 17.60 ± 0.03 sec with %MPE over 90% at 30 minutes, while the 12 mg/kg dose of nefopam showed a latency of 12.50 ± 0.56 sec and %MPE above 80%, both with significant differences compared to lower doses and control ($p<0.001$). In the third experiment, sub-analgesic doses of nefopam (3 mg/kg) and medetomidine (45 µg/kg), ineffective when given alone, produced a full analgesic response when administered together, with a latency of 11.50 ± 0.92 sec and %MPE reaching 100% at 30 minutes ($p<0.001$). The results indicate a clear dose- and time-dependent analgesic effect for both drugs and demonstrate a synergistic interaction at low doses, which may support their combined use for pain control with minimized side effects in laboratory or clinical veterinary settings.

Keywords: Nefopam, Medetomidine, Hot plate test, Synergism, %MPE, Mice, Sub-analgesic dose.

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Introduction

Acute and chronic pain nevertheless provide a major therapeutic challenge despite pharmacological advancements, impacting patient quality of life and making disease management more difficult(1). The side effects of traditional analgesics, such as opioids and NSAIDs, include drowsiness, tolerance, dependency, gastrointestinal damage, and respiratory depression(2). Alternative or adjunct analgesics that provide efficient pain management with enhanced safety profiles are therefore gaining popularity(3)

Nefopam is a centrally acting non-opioid analgesic that has gained attention recently as a useful addition to multimodal analgesia(4). Its method provides both nociceptive and neuropathic pain alleviation without respiratory depression by inhibiting serotonin, norepinephrine, and dopamine reuptake and by modulating voltage-gated sodium and calcium channels(5) . Recent randomized studies have demonstrated enhanced pain management and decreased opioid use in postoperative settings, including video-assisted thoracic surgery and knee arthroplasty, confirming its opioid-sparing benefits(6,7)

In veterinary sedation and analgesia, medetomidine, a highly selective α2-adrenergic receptor agonist, decreases norepinephrine release in the central nervous system, hence reducing the transmission of pain(8). However, side effects of medetomidine, including bradycardia and hypotension that are dose-dependent, restrict its usage. Its analgesic and sedative properties are well established, although little is known about the best analgesic doses and onset times in rat models (9). Combining analgesics with various mechanisms in multimodal analgesia techniques frequently has synergistic benefits, allowing for improved pain management with lower individual medication dosages and fewer side effects(10) Numerous clinical and preclinical investigations have corroborated this strategy; for instance, nefopam greatly reduces the need for opioids or NSAIDs and enhances analgesia(11,12). Nevertheless, no research has yet been done on the precise relationship between medetomidine and nefopam at subanalgesic dosages.

Emerging evidence supports subanalgesic dosing, where individual agents below their effective analgesic thresholds produce pronounced analgesia when used together, without additive adverse effects(13). This dosing strategy has the potential to harness pharmacodynamic synergy while minimizing the risk of side effects associated with higher doses. In the current investigation, the hot plate test was used to establish the best intraperitoneal analgesic dosages and onset periods for medetomidine and nefopam in mice. A synergistic analgesic impact of mixing sub-analgesic dosages of both medications is also evaluated in this study. This study intends to further our knowledge of safe and efficient multimodal analgesic regimens in preclinical pain models, which may have consequences for pain management procedures and clinical veterinary medicine.

Materials and Methods

Animal Housing and Ethical Compliance

Ethical Declaration and Animal Housing: The Institutional Animal Care and Use Committee (IACUC) of the College of Veterinary Medicine, University of Mosul, Iraq, approved all animal procedures with approval (Approval No: 2024.009) and in accordance with the ethical standards outlined in the Guide for the Care and Use of Laboratory Animals, 8th Edition(14). Sixty-eight Swiss albino mice of both sexes, weighing between 25 and 33 g, were employed. The animals were housed in groups of six under regulated conditions (22 ± 1 °C, 60% humidity, 12:14 h light/dark cycle), with free access to food and water. After a 7-day acclimation period, mice were assigned to groups at random. Each animal was assessed once, during the light phase (9:00 a.m.–1:00 p.m.), and all assessments were completed under blinded settings to reduce bias.

Drugs

The pharmacological agents utilized in this study included nefopam hydrochloride (10 mg/ml; Provet Co., Istanbul, Turkey), medetomidine hydrochloride (Domitor®, 1 mg/ml; Farmos Group Ltd., Turkey), and a 0.9% sodium chloride solution. All drugs were administered via intraperitoneal (i.p.) injection at a standardized volume of 5 ml/kg body weight. Analgesic efficacy was evaluated using the hot plate test (Heidolph Me Hei-Standard, Germany) to assess nociceptive response in mice.

Methods and study design

1. Determination of the Optimal Analgesic Dose of Medetomidine (Dose-Response and Time Relationship Evaluation)

The analgesic properties of medetomidine, a dose–response and time-related analysis was conducted using the hot plate test, a widely accepted model for assessing acute thermal pain in rodents. The test apparatus was maintained at a controlled surface temperature of 55.0 ± 0.1°C (15,16). The up-and-down method (17) was employed to estimate the median effective dose (ED_{50}) for medetomidine. Three different dose levels of medetomidine ED_{25}, ED_{50}, and ED_{100} were intraperitoneally injected to evaluate both the strength and duration of analgesia. Mice were randomly distributed into four groups, each comprising six animals (n = 6): Group 1 received normal saline (control), groups 2 to 4 received ED_{25} (50 µg\kg), ED_{50} (100 µg\kg), and ED_{100} (200 µg\kg), IP of medetomidine, respectively. The ED_{50} was taken from a previously published contacted by the same investigator (18). Mice were individually placed on the plate, and the latency time (in seconds) to respond with hind limb withdrawal, forelimb licking, or jumping was recorded.

The measurements were taken at baseline (before injection) and then at the following time intervals post-injection: 10, 20, 30, 40, 50, 60 minutes, in addition to 2, 4, and 24 hours. To prevent potential thermal damage, a cut-off latency of 20 seconds was established. The percentage of the Maximal Possible Effect (%MPE**)** was calculated to quantify analgesia, using the following formula:

% MPE= (Test latency- predrug latency/cut off time- predrug latency)×100 % (19).

2. Determination of the Optimal Analgesic Dose of Nefopam (Dose-Response and Time Relationship Evaluation)

This experiment was designed to assess the analgesic onset and duration of nefopam using the same methodology described in Experiment 1. The hot plate test was employed to evaluate thermal nociception under standardised conditions, including plate temperature, cut-off time, behavioural endpoints, and observation intervals. A total of 24 male Swiss albino mice were randomly divided into four groups (n = 6 per group). Each group received an intraperitoneal injection of either normal saline (control) or nefopam at one of the following doses mg/kg.,6 mg/kg and 12 mg/kg, respectively. These selected doses were derived from the ED_{50} of nefopam (17) . The test was performed at baseline (before treatment), followed by time points at 10, 20, 30, 40, 50, and 60 minutes, and 2, 4, and 24 hours post-administration. Behavioural responses indicating nociception were recorded as latency time in seconds, with a cut-off limit of 20 seconds to prevent tissue damage. To quantify analgesic efficacy, the percentage of maximal possible effect (%MPE) was calculated at each time point using the formula previously described in Experiment 1.

Experiment 3: Synergistic Analgesic Effect of Sub-Analgesic Doses of Nefopam and Medetomidine:

To investigate the potential synergistic interaction between nefopam and medetomidine at sub-analgesic doses, a third experiment was conducted using the same hot plate model previously described. The protocol, including apparatus temperature, behavioural endpoints, cut-off time, and observational timing, was identical to that used in the earlier experiments.

A total of 20 male Swiss albino mice were divided equally into four groups (n = 5 per group). The animals received intraperitoneal injections as follows: Group 1: Physiological saline (control), group 2: Nefopam at 3 mg/kg, group 3: Medetomidine at 45 µg/kg and group 4: Combination of Nefopam (3 mg/kg) + Medetomidine (45 µg/kg).

Baseline pain reaction times were recorded immediately before injection for each animal. Thirty minutes after drug administration, the latency to nociceptive response was reassessed using the same hot plate parameters.

Behavioural responses such as paw licking, limb withdrawal, or jumping were considered indicative of thermal pain perception. A cut-off time of 20 seconds was applied to prevent tissue damage.

Analgesic effect was expressed as the percentage% the formula:

% of analgesia = (Test latency- predrug latency/ predrug latency)×100 %

Statistical Analysis

All results were expressed as mean ± standard error**.** In Experiments 1 and 2, where multiple doses were evaluated across several time points, a two-way analysis of variance (two-way ANOVA) was performed to examine the main effects of treatment dose, time, and the interaction between them. When significant effects were found, the Least significant post-hoc test was applied for pairwise comparisons. Experiment 3, which compared the analgesic effects of different treatment groups at a single time point (30 minutes), a one-way ANOVA followed by the least significant difference test was used to identify significant differences among groups. When only two groups were compared, unpaired Student's t-tests were applied. A p-value of ≤ 0.05 was considered statistically significant (20).

Results

Experiment 1: Analgesic Effect of Medetomidine Based on Latency Time and %MPE

The analgesic activity of medetomidine was evaluated through the hot plate test, using both reaction latency (in seconds) and percentage of maximal possible effect (%MPE) as outcome measures. Results are summarized in Table 1 and illustrated in Figures 1 and 2.

In terms of latency time, the control group showed consistent reaction times throughout the study, with baseline and post-treatment values ranging between 3.83 and 4.67 seconds, indicating no analgesic effect. Mice treated with 50 µg/kg IP exhibited a slight increase in latency, peaking at 6.83 ± 0.31 seconds after 30 minutes, which was not statistically significant compared to the control ($p > 0.05$) (Table1, Figure 1). At the 100 µg/kg dose, latency values increased more prominently, reaching 11.00 ± 0.05 seconds at 30 minutes, significantly higher than both the control and low-dose groups ($p < 0.05$). The latency remained above baseline for approximately 2 hours before declining.

The 200 µg/kg dose produced the highest analgesic response, with latency times increasing sharply to 17.60 ± 0.03 seconds at 30 minutes, representing a significant difference compared to all other

groups and baseline ($p < 0.001$). This elevated response was sustained for several hours, with latency still at 6.10 ± 0.37 seconds after 24 hours.

When converted to %MPE, the results showed a similar trend. The 50 µg/kg dose produced a maximum %MPE of ~25%, while the 100 µg/kg dose reached over 60%. The 200 µg/kg dose achieved a peak %MPE exceeding **90%**, sustained above 40% for up to 4 hours (Figure).

The findings indicate that medetomidine elicits a clear dose- and time-dependent analgesic effect, with both latency time and %MPE metrics confirming that the 200 µg/kg dose is the most effective and long-lasting under the experimental conditions. (Table 1) (Figures and 2)

Table (1): The increased latency time of pain sensation with medetomidine in mice

Dose i.p.	Onset of pain sensation (seconds)									
	0	**10 (min)**	**20 (min)**	**30 (min)**	**40 (min)**	**50 (min)**	**60 (min)**	**2h**	**4h**	**24h**
Control (normalsaline)	4.67 ± 0.21	4.17 ± 0.41	4.50 ± 0.34	4.33 ± 0.33	4.33 ± 0.31	4.00 ± 0.21	4.33 ± 0.21	3.83 ± 0.31	4.17 ± 0.31	3.83 ± 0.31
Medetomidine 50µg	4.83 ± 0.31	5.33 ± 0.49	5.50 ± 0.22	6.83 ± 0.31	5.83 ± 0.31	5.00 ± 0.26	5.67 ± 0.42	5.00 ± 0.26	4.50 ± 0.22	4.83 ± 0.31
Medetomidine 100µg	5.17 ± 0.95	7.00 ± 0.68 c d	9.00 ± 0.68 * a c	11.00 ± 0.05 * a b c d	10.17 ± 0.95 * a c d	8.67 ± 0.80 * c d	7.67 ± 0.67 c d	6.50 ± 0.67 c d	6.17 ± 0.79 c d	5.83 ± 0.31
Medetomidine 200µg	5.10 ± 0.37	9.33 ± 0.76 * c d	13.40 ± 0.87 * a c d e	17.60 ± 0.03 * a b c	16.60 ± 1.36 * a b c d e	13.00 ± 1.00 * a c d e	10.80 ± 0.86 * c d e	8.40 ± 0.51 c d e	7.20 ± 0.20 c d e	6.10 ± 0.37

The data represented the Mean ±SE of 6 mice/group * significant difference from the baseline (time zero) within the same treatment group at ($p \leq 0.05$). a significant difference relative to time, 10 min of the same group at ($p \leq 0.05$). b significant relative to (20,40,50,60,1290,240) of the same time($p \leq 0.05$). c significant relative to the control group at the same time ($p \leq 0.05$). d significant relative to ED25 at the same time ($p \leq 0.05$). e significant relative to ED50 at the same time ($p \leq 0.05$).

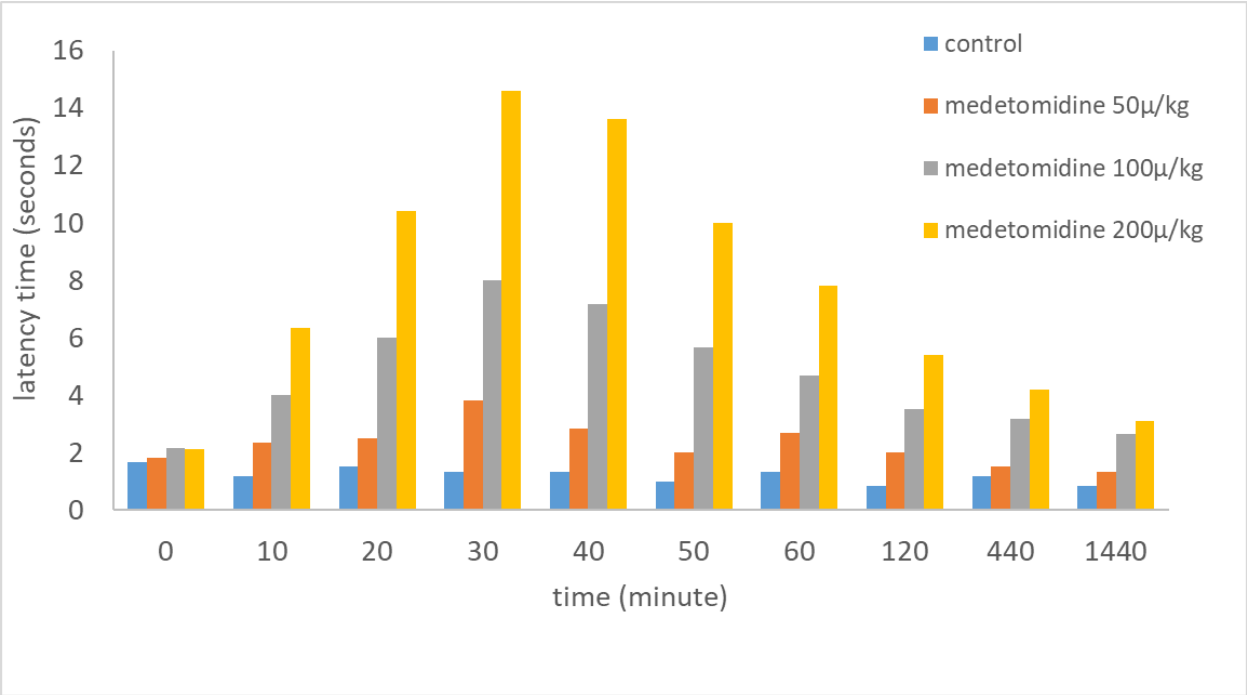

Figure 1: Relief of acute pain with medetomidine at different doses and different times

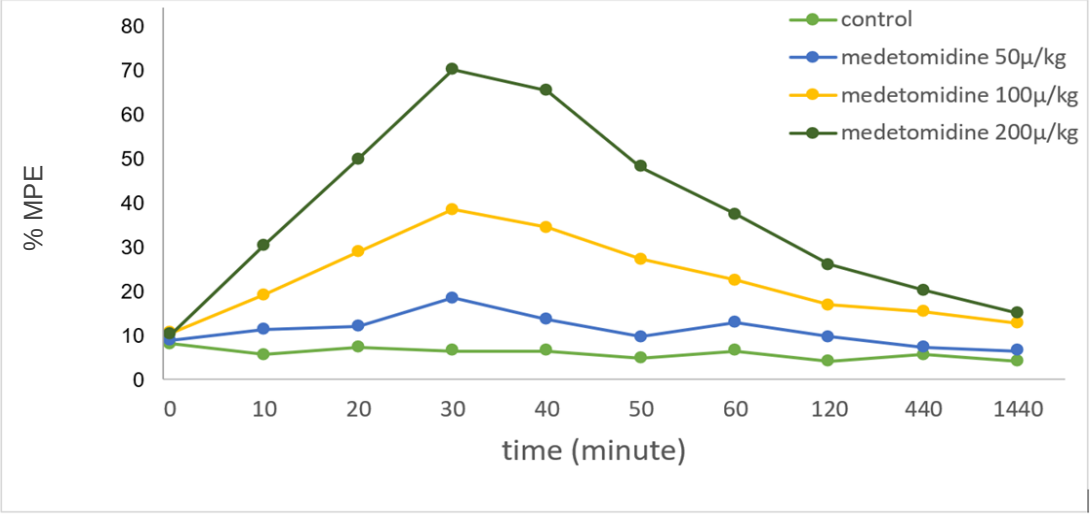

Figure 2 : Percentage of maximal possible effect (%MPE) for medetomidine doses over time. Values were calculated using the formula: %MPE = [(post-treatment latency - baseline latency) / (cut-off time - baseline latency)] × 100. Cut-off time = 20 s.

Experiment 2: Analgesic Effect of Nefopam Based on Latency Time and %MPE.

The thermal nociceptive response of mice following intraperitoneal administration of nefopam was evaluated using latency time and calculated %MPE. The study included three dose levels (3, 6, and 12 mg/kg), with reaction times recorded at multiple intervals over 24 hours. Results are presented in (Table 2) and (Figure 3).

In the control group, latency times remained stable throughout the observation period, ranging between 4.50 and 5.83 seconds, showing no meaningful change from baseline. Likewise, administration of 3 mg/kg nefopam resulted in latency values comparable to control, with no significant differences observed at any time point, suggesting a lack of analgesic efficacy at this dose (Table 2). In contrast, the 6 mg/kg dose produced a marked increase in reaction time, reaching 10.00 ± 0.37 seconds at 30 minutes, which was significantly higher than the 3 mg/kg and control groups ($p < 0.05$) (Table 2). The effect began at 10 minutes and peaked at 30 minutes, followed by a gradual decline, although latency remained elevated for up to 2 hours post-treatment (table 2) (figure 2).

The 12 mg/kg group exhibited the most robust analgesic effect. Latency times increased steadily, peaking at 12.50 ± 0.56 seconds at 30 minutes, a statistically significant improvement compared to all other groups ($p < 0.001$). The analgesic effect remained significant up to 4 hours and gradually declined thereafter, though latency values at 24 hours were still above baseline.

When analyzed in terms of %MPE, the 3 mg/kg dose produced values close to zero throughout, consistent with its limited efficacy. The 6 mg/kg dose yielded a peak %MPE of around 55–60%, while the 12 mg/kg dose reached over 80% at 30 minutes, confirming a dose-dependent enhancement in analgesia..

In summary, nefopam exhibited a clear dose- and time-related analgesic effect in the hot plate model. The 12 mg/kg dose was the most effective, producing rapid and sustained pain inhibition compared to the lower doses and control(Table 2) (Figures 3 and 4).

Table (2): The increase latency time of pain sensation with Nefopamin mice

Dose	Onset of pain sensation (seconds)									
	0	10 (min)	20 (min)	30 (min)	40 (min)	50 (min)	60 (min)	2h	4h	24h
Control (normalsaline)	5.50 ± 0.43	5.67 ± 0.42	5.83 ± 0.60	5.33 ± 0.33	5.17 ± 0.48	5.83 ± 0.31	4.83 ± 0.31	5.00 ± 0.63	4.50 ± 0.43	4.50 ± 0.43
Nefopam 3mg	4.83 ± 0.40	5.17 ± 0.16	5.83 ± 0.65	5.83 ± 0.48	5.33 ± 0.56	5.34 ± 0.71	5.17 ± 0.48	5.00 ± 0.54	4.67 ± 0.21	4.67 ± 0.21
Nefopam 6mg	5.50 ± 0.43	7.17 ± 0.31 * d	9.37 ± 0.33 * a c	10.00 ± 0.37 * a b c d	9.67 ± 0.88 * a c d	8.17 ± 0.40 * c d	7.17 ± 0.31 * c d	6.33 ± 0.42 c d	6.17 ± 0.17 c d	5.25 ± 0.17
Nefopam 12mg	5.00 ± 0.58	7.67 ± 0.76 * c d	10.50 ± 0.67 * a c d	12.50 ± 0.56 * a b c d	12.00 ± 0.73 * a c d e	10.67 ± 0.71 * a c d e	9.50 ± 0.43 * a c d e	8.33 ± 0.61 * c d e	6.83 ± 0.48 * c d	5.33 ± 0.48

The data represented the Mean ± SE of 6 mice/group * significant difference from the baseline (time zero) within the same treatment at group ($p \leq 0.05$). a significant difference relative to time, 10 min of the same group at group ($p \leq 0.05$). b significant relative to (20,40,50,60,1290,240) of the same time at group ($p \leq 0.05$).c significant difference relative to the control group at the same time in the group ($p \leq 0.05$). d significant relative to ED25 at the same time in the group ($p \leq 0.05$).e significant relative to ED50 at the same time in the group ($p \leq 0.05$).

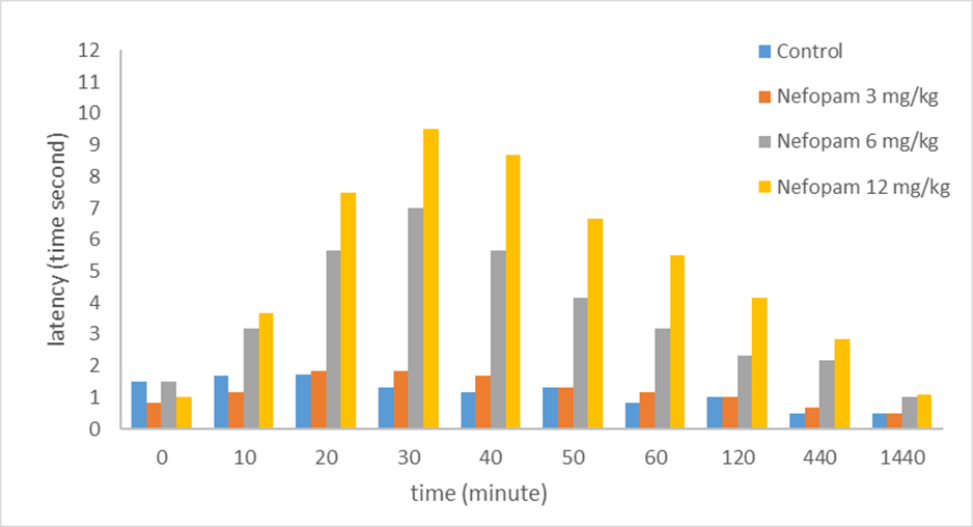

Figure 3: Relief of acute pain with medetomidine at different doses and different times

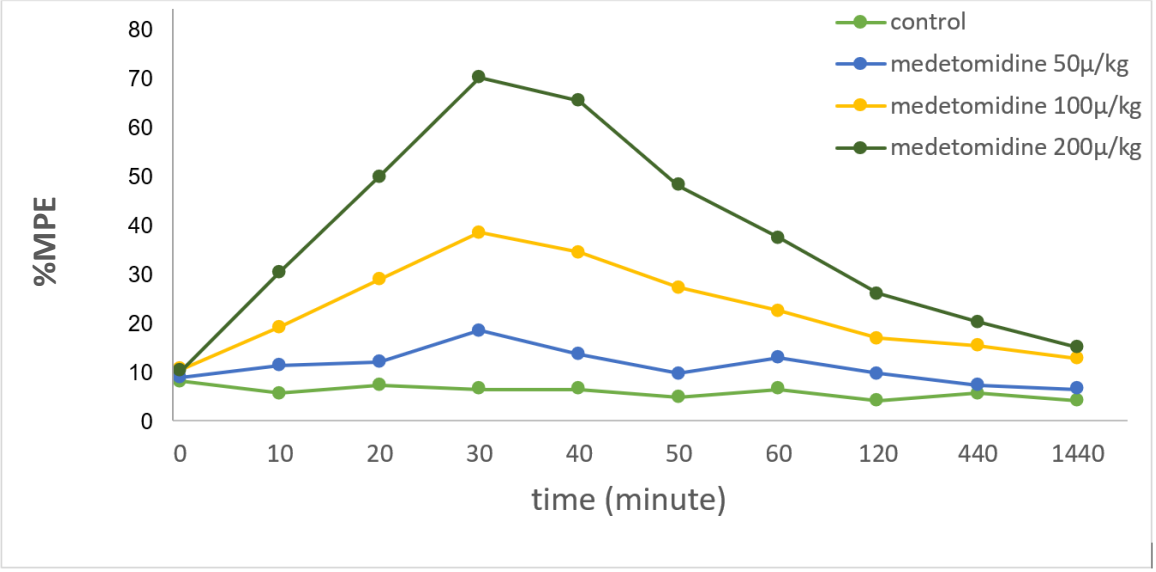

Figure 4: Percentage of maximal possible effect (%MPE) for medetomidine doses over time. Values were calculated using the formula: %MPE = [(post-treatment latency - baseline latency) / (cut-off time - baseline latency)] × 100. Cut-off time = 20 s

Experiment 3: Analgesic Synergy of Sub-Analgesic Doses of Nefopam and Medetomidine

In the control group (physiological saline), latency time remained unchanged between baseline and 30 minutes post-injection (4.00 ± 0.36 s), indicating no analgesic effect. (Table 3)

Mice treated with nefopam 3 mg/kg alone showed a non-significant increase in latency time from 4.33 ± 0.33 **s** at baseline to 4.83 ± 0.30 **s** after 30 minutes ($p > 0.05$). Similarly, the group that received medetomidine at 45 µg/kg exhibited only a slight increase from 4.60 ± 0.24 **s** to 5.20 ± 0.20 **s**, which was not statistically different from baseline or control ($p > 0.05$). These findings confirm that neither dose individually achieved a measurable analgesic response.

However, the combination of nefopam 3 mg/kg with medetomidine 45 µg/kg resulted in a statistically significant elevation in latency time, rising from 4.33 ± 0.21 **s** at baseline to 11.50 ± 0.92 **s** at 30 minutes ($p < 0.05$). This value was significantly higher than the effect of either drug administered alone ($p < 0.05$) and represented a full 100% analgesic response (Table 3**)**.

These findings demonstrate that the co-administration of sub-analgesic doses of nefopam and medetomidine produces a synergistic antinociceptive effect in the hot plate test, exceeding the effect of either agent alone and validating the potential for drug combination at reduced dosages.

Table 3: Analgesic Effect of ED_{25} Nefopam-Medetomidine Combination Using Hot Plate Test in Mice

Treatment Groups (IP)	Baseline Reaction Time (sec)	Reaction Time(sec) after 30 minutes	% Analgesia
Control (Physiological Saline)	4.00 ± 0.361	4.00 ± 0.361	0
Nefopam 3 mg/kg	4.33 ± 0.33	4.83 ± 0.30	0
Medetomidine 45 µg/kg)	4.60 ± 0.24	5.20 ± 0.20	0
Nefopam3mg/k +Medetomidine 45 µg/kg	4.33 ± 0.21	11.50 ± 0.92* $^{a b \times}$	100%*

Data expressed as mean ± SE (n=5/group). Medetomidine was administered immediately following the injection of nefopam. (*) significant difference relative to the control group at the corresponding time ($p \leq 0.05$). (a) significant difference relative to the 3 mg/kg nefopam-treated group at the same time ($p \leq 0.05$). (b) significant difference relative to the 45 µg/kg medetomidine group at the same time ($p \leq 0.05$). (×) significant difference from the baseline (time zero) within the same treatment group ($p \leq 0.05$). * indicates $p < 0.05$ vs. baseline (paired t-test).

Discussion

The study investigates the analgesic effects of different doses of medetomidine and nefopam on acute pain, as assessed through the hot-plate test in mice. The methodology section of the manuscript employs the Hot-Plate test, which is a well-established method for evaluating analgesic effects (15) This approach is scientifically sound and aligns with standard procedures used to measure the effectiveness of analgesics in preclinical studies. However, it is important to note that the study focuses on animal models (21). Medetomidine exhibited a strong dose-dependent antinociceptive response, with the 200 µg/kg dose showing maximum latency at 30 minutes post-injection, in agreement with its rapid central action as an α_2-adrenoceptor agonist that inhibits spinal and supraspinal nociceptive signaling through presynaptic inhibition of norepinephrine release and postsynaptic hyperpolarization(22).

The current study clearly shows the relationship between medetomidine doses and the time required for pain relief, with a marked increase in pain relief at higher doses, as seen in (Figures 3) and (Figure 4). These findings are consistent with existing literature, where medetomidine has demonstrated dose-dependent effects in pain relief, especially in acute settings(23) Similarly, nefopam, a non-opioid analgesic, has been previously shown to have a significant role in managing acute pain by inhibiting the reuptake of serotonin, norepinephrine, and dopamine(24) The data presented in (Figure 1) and (Figure 2) highlight the analgesic efficacy of nefopam at varying doses, and these results correspond to findings in previous studies where nefopam's dose-dependent analgesic effects were observed in animal models(25).

The combination of medetomidine and nefopam (as shown in Table 3) results in a pronounced increase in pain relief, with a significant shift from baseline pain response, culminating in 100% pain relief. This synergistic interaction is intriguing and supports the hypothesis that combining different classes of analgesics may produce superior outcomes in pain management. Such combination therapies have been discussed in the context of improving analgesia while minimizing individual drug side effects(26) The result of synergistic combination in our current study agrees with previous studies as the combination of subanalgesic doses of α2 adrenoceptor and opioid produced synergistic analgesic effect in rodent models (27), synergistic antinociceptive effect of nefopam with paracetamol (28),as well as with gabapentinoids (29) . The synergistic combination of medetomidine and nefopam at the level of analgesia (as a multimodal analgesia) may be contributed to their different mechanism of action(pharmacodynamic interaction) . Nefopam mediates its analgesic action through a multifaceted mechanism involving the suppression of monoamine reuptake—specifically serotonin, norepinephrine, and dopamine—thereby enhancing descending inhibitory pathways. Furthermore, it interferes with glutamatergic transmission by modulating voltage-dependent calcium and sodium channels, leading to a diminished postsynaptic excitatory response. This modulation contributes to the downregulation of receptors such as N-methyl-D-aspartate (NMDA), which are critically involved in pain amplification and the induction of hyperalgesic states (30). While medetomidine exerts its analgesic action mainly by stimulating central α2-adrenergic receptors, particularly in the locus coeruleus and dorsal horn of the spinal cord. This leads to inhibition of norepinephrine release and a subsequent reduction in nociceptive transmission. The drug also enhances descending inhibitory pathways involved in pain modulation, contributing to its analgesic efficacy without acting on opioid receptors (31, 32).This multimodal profile of nefopam complements the noradrenergic action of medetomidine, resulting in enhanced analgesia through simultaneous engagement of both monoaminergic and adrenergic systems. Such pharmacodynamic complementarity underlies the observed potentiation of antinociceptive efficacy when both drugs are administered in combination. Beyond their distinct pharmacodynamic actions, a possible pharmacokinetic interaction may also contribute to the enhanced analgesic effect observed with the combination of medetomidine and nefopam. Medetomidine has been reported to influence hepatic drug metabolism by inhibiting certain cytochrome P450 enzymes, particularly those involved in the biotransformation of centrally acting agents(33). If nefopam undergoes metabolism via similar enzymatic pathways, medetomidine could potentially slow its hepatic clearance, thereby increasing its plasma concentration and prolonging its analgesic effect. Although direct evidence supporting this specific interaction is still limited, the overlap in metabolic pathways suggests a plausible mechanism that may partially explain the observed synergistic outcome

conclusion

The present study demonstrates that the co-administration of sub-analgesic doses of medetomidine and nefopam produces a significant synergistic enhancement in antinociceptive efficacy compared to either drug alone. This interaction appears to result from the complementary pharmacodynamic mechanisms of the two agents. The combination not only achieved effective analgesia at lower individual doses but also suggests a potential strategy to minimize adverse effects associated with higher doses of single agents. These findings support the therapeutic value of such multimodal approaches in pain management and provide a foundation for further investigations into the mechanistic and clinical implications of this drug interaction.

Conflict of Interest

The authors declare that there is no conflict of interest associated with this study.

Ethical Approval

The Research Ethics Committee approved this work.

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النيفوبام والمديتومدين التسكين والتداخل في الفئران

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الخلاصة

يُعَدُّ تحقيق التخفيف الفعال للالم في نماذج القوارض مع تقليل جرعة الدواء تحدّياً هاماً. في هذه الدراسة، قمنا بقياس تأثير النيفوبام والميديتوميدين منفردين ومشتركين عند جرعات منخفضة في فئران خضعت لاختبار الصفيحة الساخنة(باستخدام طريقة الصعود والنزول، عوملت الحيوانات عن طريق الحقن داخل الخلب بالجرع التالية: نيفوبام (3، 6، 12 ملغ/كغ) وميديتوميدين (50، 100، 200 ميكروغرام/كغ). سُجلت أوقات التأخير في ظهور سلوكيات الاستجابة للألم ثم حُوّلت إلى النسبة المئوية للتأثير الأقصى الممكن (%MPE) على مدى 24 ساعة. بعد 30 دقيقة، أظهر ميديتوميدين بجرعة 200 ميكروغرام/كغ زمن تأخير قدره 17.60 ± 0.03 ث) ٪(MPE > 90%، بينما بلغ زمن تأخير نيفوبام بجرعة 12 ملغ/كغ 12.50 ± 0.56 ث) ٪ MPE (80% <، وكلاهما كان ذا دلالة إحصائية مقارنة بالجرعات المنخفضة ومجموعة السيطرة .($p<0.001$)والأهم أن الجمع بين نيفوبام 3 ملغ/كغ وميديتوميدين 45 ميكروغرام/كغ —التي لم تُظهر فاعلية عند تناولهما منفردَين—أدى إلى استجابة مسكنة تامة مع زمن تأخير 11.50 ± 0.92 ث ونسبة ($p<0.001$) %MPE = 100% عند 30 دقيقة. تشير هذه النتائج إلى أن كلا العقارين يوفّران تسكيناً يعتمد على الجرعة والزمن، وأن تراكمهما عند جرعات منخفضة يحقق تآزراً قوياً. يمكن أن يُعَدّ هذا الأسلوب خياراً واعداً للتحكم بالألم بفعالية عالية وبجرعات منخفضة في الأبحاث والممارسات البيطرية.

الكلمات المفتاحية: نيفوبام؛ ميديتوميدين؛ اختبار الصفيحة الساخنة؛ تآزر مسكن؛ جرعة دون مسكنية , %MPE استجابة حرارية للألم؛ فئران.