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A Study Investigating the Synergistic Analgesic Effects of Nefopam and Medetomidine in a Multimodal Pain Management Approach in Mice

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ABSTRACT

This study explored the type of analgesic interaction between nefopam and medetomidine and evaluated their safety profiles in a mouse model as no previous studies had examined their pharmacological interaction at the antinociceptive level. Adult male and female mice (n=6-7 per group) were administered ascending/descending doses of nefopam or medetomidine alone or in a combination via intraperitoneal injection. Analgesic efficacy was determined using the hot plate test (55°°C) and writhing reflex technique. The ED50 values were calculated via the up-and-down method, isobolographic analysis assessed drug interaction types and LD50 values were derived to assess acute toxicity. Nefopam alone exhibited an ED50 of 5.66 mg/kg intraperitoneal (I.P.), while medetomidine showed an ED50 of 93.05 mg/kg I.P. Combined administration of nefopam with a fixed medetomidine dose (0.65 mg/kg) reduced the ED50 of nefopam by 44%. At the double ED50 dosage for each drug, concurrent intraperitoneal injection of the two drugs completely inhibits the writhing reflex (100%) elicited by acetic acid compared with each drug alone and with the control group. Isobolographic analysis confirmed synergetic interaction between two drugs at 1:1 and 0.5:0.5 of ED50 ratios, with interaction indices (y) of 0.92 and 0.58, respectively. The LD50 values were 78.46 mg/kg (nefopam) and 1230.75 µg/kg (medetomidine), yielding therapeutic indices (LD50/ED50) of 14 and 13, indicative of wide safety margins. These findings demonstrate a potent synergistic analgesic effect between nefopam and medetomidine, allowing for significant dose reductions without losing efficacy. This combination's favorable safety profile supports its clinical potential as a non-opioid alternative for acute pain management.

Keywords: Isobolographic analysis, Medetomidine, Mice model, Nefopam, Synergistic analgesic.

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INTRODUCTION

Effective pain management remains a fundamental challenge in both clinical and experimental pharmacology **(Mao, 2012; Barrett, 2015; Taneja *et al.*, 2017).** Although opioid analgesics are widely used due to their strong efficacy, their adverse effects such as respiratory depression and addiction potential necessitate the exploration of alternative or adjunctive analgesic strategies, offering a pathway to effective pain control with fewer risks **(Tick *et al.*, 2018).** A number of non-opioid analgesics are used together in multimodal antinociceptives to provide a supra-additive (synergistic) or additive impact **(Li , 2019).** Among these alternatives, medetomidine and nefopam have garnered attention for their distinct mechanisms of action and potential for combined use. Medetomidine, a potent and selective α2-adrenergic agonist, is widely recognized for its potent analgesic and sedative effects, which are primarily caused by inhibiting norepinephrine release in the central nervous system **(Li, 2019).** Medetomidine effectively reduced the experience of pain by inhibiting the spinal cord and brainstem generation of nociceptive neurotransmitters **(Vranken, 2009).** Bradycardia and hypotension are two cardiovascular side effects that typically limit its clinical use **(Vranken, 2009).**

In contrast, Nefopam is a centrally acting, non-opioid, non-steroidal analgesic where Nefopam belongs to the category of centrally acting non-opioid analgesics **(Vranken, 2009; Petroianu *et al.*, 2023).** This dual mechanism makes nefopam effective in both acute and chronic pain models and offers a versatile alternative to traditional analgesics **(Rai *et al.*, 2017).** Medetomidine as α2-adrenergic activity may enhance nefopam monoaminergic effects, potentially leading to

synergistic analgesia. Such a combination could reduce the required dose of each drug, minimize side effects while maintain or even enhancing the therapeutic efficacy **(Vranken, 2009).**

This hypothesis is supported by previous studies of a synergistic combination of medetomidine with opioids **(Salarpour *et al.,* 2022)** and nefopam with acetaminophen **(Li *et al.,* 2018)** and caffeine **(ALqaysi and ALabbas, 2024).** In this study, the analgesic effects of medetomidine and nefopam alone and in combination were investigated. Utilizing the hot plate test and the writhing technique to investigate the drug combination's cerebral and visceral antinociceptive effects, since the two tests have been utilized as standard screening tools in the development of novel analgesic combinations **(Yin *et al.,* 2016)** and employing isobolographic analysis, we sought to determine the nature of their interactions and explore their potential for synergistic analgesia.

MATERIALS AND METHODS

Animals housing and Ethical approval

The experimental procedures in this study were conducted in strict accordance with ethical principles for animal research and the guidelines set forth in the Guide for the Care and Use of Laboratory Animals. The study protocol was thoroughly reviewed and approved by the Scientific Committee of the Department at the College of Veterinary Medicine, University of Mosul, Iraq. The Animal Ethics Committee (IACUC) (approval no.: 2024.007). The animals were Swiss albino mice aged 8-12 weeks old (n=78; male and/or female) obtained from the animal house of the College of Veterinary Medicine, University of Mosul. The animal weights ranged between 25 and 32 g. The animals were group-housed (6 mice per cage) under standard environmental conditions (22±1°C, humidity 60±5%, 12 h light/dark cycle) with free access to a standard commercial diet and water ad libitum. Mice were randomly assigned to treatment groups, and experiments were performed blind for pharmacological conditions. After a 7-day adaptation period, all experiments were performed during the light phase.

Drugs

Nefopam chlorohydrate (10 mg/ml) was supplied by Provet Co. (Istanbul, Turkey), and Medetomidine HCl (Domitor, 1 mg/ml) was obtained Farmos Group Ltd., Turkey). They were dissolved in NaCl solution (0.9% sterile saline). Both medications were given intraperitoneal (i.p.) at a fixed amount of 5 ml / kg of body mass (volume of administration) for the hot plate apparatus (Heidolph Me Hei-standard, Germany) and writhing reflex test.

The protocol of methods

Experiment 1: Estimation of ED_{50} for medetomidine and nefopam each alone

Depending on up-and-down technique **(Dixon, 1980).** The analgesic ED50 of either nefopam or medetomidine was assessed for each drug alone using a hot plate apparatus and six mice for each drug. The temperature of the hot plate was set to be 55 + 0.5°C **(Shaban *et al.,* 2020).** The individual mouse was placed on the metal hot plate surface before administration of each drug and the latency time, which is defined as the duration required to detect a nociceptive activity, encompassing forepaw withdrawal, hind paw licking, and/or leaping, was recorded. The cut-off point time was 20 seconds to prevent tissue injury **(Thanoon and Faris, 2023; Shaban *et al.,* 2024),** then latency time was recorded 30 minutes after injection of each drug by placing the same mouse on the hot plate. The initial dose of nefopam and medetomidine was 10 mg/kg and 200 µg/kg i.p., respectively. The dosages were selected based on initial testing for medetomidine and from a previous study for nefopam **(Girard *et al.,* 2016).** The rise or fall in the subsequent dosages of nefopam and medetomidine by 2.5 mg/kg and 50 µg/kg, respectively. The ED50 value was estimated using the formula:

$ED_{50} = Xf + Kd$ **(Dixon, 1980)**

Experiment 2: Determination of the Median Effective Dose for Nefopam Combined with a fixed dose of Medetomidine (the effect of medetomidine on the ED_{50} of nefopam)

In this work, the ED_{50} of nefopam was determined using seven mice. The first dose 2.5 mg/kg of nefopam and the individual ED_{50} dose of medetomidine were given to the first mouse. Thirty minutes following the intraperitoneal injection of both doses, the latency time was recorded on the hot plate. When paired with the fixed ED_{50} dosage of medetomidine simultaneously, the successive dosages of nefopam increment and decrement by 2.5 mg/kg. The effect of medetomidine on the nefopam ED_{50} value was evaluated using the ED_{50} equation.

Experiment 3: Determine the sort of interaction between nefopam and medetomidine at the antinociceptive level using isobolographic assay

The first doses of nefopam and medetomidine, which were identified in experiment 1, were given to six mice at 5.66 mg/kg and 93.05 µg/kg, respectively. The kind of antinociceptive interaction between two medications was ascertained by isobolographic analysis using their individual and combined ED50s. At 1.41 mg/kg and 23.27 µg/kg, respectively> the ED50 values for nefopam and medetomidine increased and dropped in a 1:1 ratio. Using diagram paper, calculate the ED50 values for medetomidine and nefopam on the Y and X

axes, respectively. Then, using the isobolographic analysis, draw a straight diagonal line that connects the two. A synergistic or antagonistic interaction was indicated if the combination's ED50 value was determined to be over or beneath the line, respectively. Conversely, additive (no interaction) is represented by a location on the diagonal **(Tallarida, 2011; Hasan, 2018).** We used another 6 mice to evaluate the sort of antinociception interaction between nefopam and medetomidine at a ratio of 0.5:0.5 of each ED50; the initial doses were 3 mg/kg and 46 µg/kg, respectively. The increases and decreases in the next doses were 0.73 and 11.5 µg/kg, respectively.

Experiment 4: LD50 of nefopam and medetomidine in mice

The median fatal dosage (LD_{50}) of nefopam and medetomidine was found using 7 and 8 mice, respectively and the up and down technique. Each drug's subsequent dosages showed a consistent decline and rise. The first dose was based on preliminary trials for medetomidine and along with the previous studies for nefopam .The later increase and decrease dose of each drug was based on a constant value **(Dixon, 1980).** The therapeutic index for medetomidine and nefopam was evaluated to detect the safety margin for each drug by using the formula:

Therapeutic index = LD_{50} / ED_{50}

Experiment 5: Evaluate the antinociceptive effect of a single intraperitoneal injection of medetomidine or nefopam, either alone or in combination, on the incidence of abdominal cramping in the acetic acid writhing assay (visceral pain)

Twenty mice were used to evaluate the impact of each drug, either separately or in a combination on the visceral pain generated by acetic acid in the writhing test protocol **(Ghias Uddin *et al.,* 2014; Naser *et al.,* 2020).** The mice were randomly split into four distinct groups of five mice each. The control group was intraperitoneally (I.P.) injected with normal saline. In contrast, mice in groups 2 and 3 were given separate intraperitoneal treatment with either nefopam (11.2 mg/kg) or medetomidine (186 µg/kg) at double the ED50 dose. The mice in the fourth group were given a double ED50 dose of nefopam and medetomidine concurrently. Thirty minutes later, the mice within each group were individually injected with 1% acetic acid at 0.1 ml/10 gm. The onset and the total number of the abdominal stretches (writhes) were measured immediately following injection of acetic acid over a 30-minute period. The procedure involved recording a video for each mouse individually by placing each animal in a separate plastic cage box. The following mathematical formula was used to estimate the percentage of writhing number reduction.

% reduction in writhes = [(Mean writhes (control) − Mean writhes (treated)) / Mean writhes (control)] × 100

Statistical analysis

Results are reported as mean ± SEM. The data were analyzed using a statistical program (SPSS version 16), Statistical analyses were performed using one-way ANOVA followed by LSD test, with $p < 0.05$ considered statistically significant.

RESULTS

1. Experiment 1: Median Effective Dose (ED_{50}) Determination

1.1. Determination of ED_{50} of Nefopam for acute pain analgesia by Up-and-Down method

The ED_{50} of nefopam that produce analgesia 30 minutes after intraperitoneal injection was 5.66 mg/kg of body weight. Administration of varying doses of nefopam induced signs of reduced mobility, analgesia and sedation in the tested animals (**Table1)**.

1.2.Determination of ED_{50} of Medetomidine for acute pain analgesia by Up-and-Down method

The ED_{50} of medetomidine for acute pain analgesia in 50% of animals 30 minutes after IP injection was 93.05 µg /kg of body weight. Clinical signs included analgesia, sedation, reduced mobility, and recumbency (**Table1)**.

Table 1: ED_{50} of Nefopam or Medetomidine alone via Intraperitoneal Injection in Mice.

Parameters	Values of Nefopam	Values of Medetomidine
ED_{50} (analgesia)	5.66 mg/kg	93.05 µg/kg
Dose Range	5–10 mg/kg	50–200 µg/kg
Starting Dose	10 mg/kg	200 µg/kg
Final Dose	7.5 mg/kg	50 µg/kg
Dose Increment/Decrement	2.5 mg/kg	50 µg/kg
The quantity of mice	6 adult Mice (**XXOXOX**)	6 adult Mice (**XXOXXO**)
Observed Effects	Reduced mobility, sedation,analgesia and recumbency.	Analgesia, calmness, Reduced movement, recumbency

X: Analgesia observed, O: No analgesia observed.

1.3.Determination of the Median Effective Dose for Nefopam Combined with a fixed dose of Medetomidine

The ED_{50} of nefopam when co-administered with a fixed dose of medetomidine was (0.65 mg/kg I.P.), which decreased by 44% compared with the individual ED50 of nefopam. Observed signs included sedation, reduced mobility, calmness and analgesia **Table2.**

Table 2: ED_{50} of Nefopam with Fixed-Dose Medetomidine (0.65 mg/kg).

Parameter	Value/Details
ED_{50} (nefopam + medetomidine)	0.65 mg/kg (44% reduction vs. alone)
Dose Range	2.5–10 mg/kg
Starting Dose	10 mg/kg
Final Dose	5 mg/kg
Dose Increment/Decrement	2.5 mg/kg
The quantity of Mice	7 adult Mice (**XXXOXOX**)
Observed Effects	Analgesia, sedation, reduced Mobility and calmness

X: Analgesia observed, O: No analgesia observed.

2. Experiment 2: Isobolographic Analysis of Drug Interaction

2.1. Interaction Analysis at a 1:1 Ration of ED50 doses of nefopam and medetomidine

The ED_{50} values for nefopam and medetomidine when co-administered at 1:1 ratio was 2.62mg/kg and 43.28 µg/kg, respectively. This represents a 54% reduction in nefopam's ED_{50} and a 53 % reduction in medetomidine 's ED_{50}. Isobolographic analysis confirmed a synergistic interaction (Y-index= 0.80 mean less than 1) and the combination's ED_{50} located under the connective line **(Table 3 and Fig.1).**

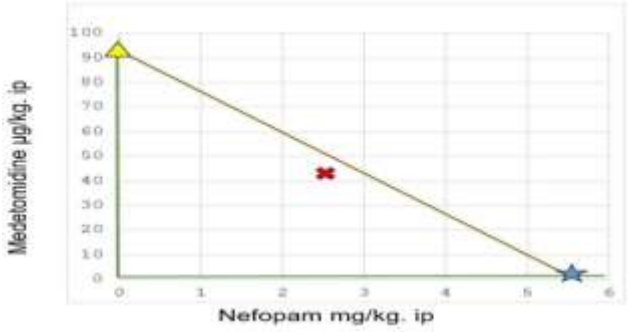

Fig.1: Isobolographic analysis of nefopam and medetomidine interaction at 1:1 ratio in mice.

The ED50 of each drug connected by diagonal line. (X) 1:1 point represented the ED50 combination of two drugs, fall down under the diagonal line, indicated synergism interaction.

Table 3: Interaction Analysis at 1:1 ED_{50} Ratio (Nefopam : Medetomidine).

Parameters	Nefopam	Medetomidine
Combined ED_{50}	2.62 mg/kg	43.28 µg/kg
Dose Range	1.41–5.66 mg/kg	23.24–93.05 µg/kg
Starting Dose	5.66 mg/kg	93.05 µg/kg
Final Dose	1.41 mg/kg	23.24 µg/kg
Dose Increment/Decrement	1.41 mg/kg	23.27 µg/kg
The quantity of Mice	6 Mice (**XXOXXO**)	6 Mice (**XXOXXO**)
% Reduction in ED_{50}	54%	53 %
Interaction Index (*Y*)	0.92	

X: Analgesia observed, O: No analgesia observed

2.2. Interaction Analysis at a 0.5:0.5 Ration of ED50 doses of nefopam a Medetomidine

At a 0.5:0.5 ED50 ratio, the ED_{50} values were 1.7 mg/kg (nefopam) and 25.99 µg/kg (medetomidine), with 70% and 72% reductions, respectively. isobolographic analysis confirmed synergistic interaction (Y- index= 0.58) **(Table 4 and Fig. 2).**

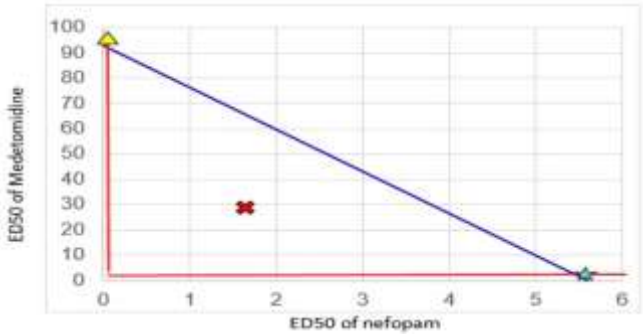

Fig. 2: Isobolographic analysis of nefopam and medetomidine interaction at 0.5:0.5 ratio in mice.

Table 4: Interaction Analysis at 0.5:0.5 ED_{50} Ratio (Nefopam: Medetomidine).

Parameters	Nefopam	Medetomidine
Combined ED_{50}	1.7 mg/kg	25.99 µg/kg
Dose Range	1.5–3 mg/kg	23–46 µg/kg
Starting Dose	3 mg/kg	46 µg/kg
Final Dose	2.25 mg/kg	34.5 µg/kg
Dose Increment/Decrement	0.75 mg/kg	11.5 µg/kg
The quantity of Mice	6 Mice (**XXOXOX**)	6 Mice (**XXOXOX**)
% Reduction in ED_{50}	70 %	72%
Interaction Index (*Y*)	.58	

X: Analgesia observed, O: No analgesia observed

The ED50 of each drug connected by diagonal line. (X) 0.5:0.5 point represented the ED50 combination of two drugs, fall down under the diagonal line, indicated synergism interaction.

3. Experiment 3: Median Lethal Dose (LD50) determination

3.1. Determination of LD50 for nefopam

The LD_{50} of nefopam was 78.46 mg /kg (IP). Clinical signs included discomfort, piloerection, hunched posture, lacrimation, prostration, tail rigidity, rapid respiration /pulse, urination/defecation, convulsions and death **(Table 5).**

Table5: LD_{50} of Nefopam or Medetomidine via Intraperitoneal Injection in Mice.

Parameter	Values/of Nefopam	Values of Medetomidine
LD_{50}	78.46 mg/kg	1230.75 µg/kg
Dose Range	40–80 mg/kg	1250 – 625 µg/kg
Starting Dose	40 mg/kg	625 µg/kg
Final Dose	80 mg/kg	1250 µg//kg
Dose Increment/Decrement	10 mg/kg	125 µg/kg
The quantity of Mice	7 Mice (OOOXOOO)	8 Mice (OOOOXOOO)
Observed effects	Discomfort, piloerection, convulsions, respiratory distress, death	Ataxia, lethargy, cardiorespiratory depression, death

X: Analgesia observed, O: No analgesia observed

3.2. Determination of LD50 for Medetomidine

The LD_{50} of medetomidine was 1230.75 µg/ kg (IP). Clinical signs included ataxia, piloerection, lethargy, lacrimation, prostration, recumbency, immobility, urination /defecation, muscle relaxation, respiratory/cardiac depression, convulsions and death Table 5. While therapeutic index value was 13.85 and 13.22 for nefopam and medetomidine, respectively (**Table 6)**.

Table 6: Therapeutic index (TI) value of nefopam and medetomidine in mice:

Drug	Therapeutic index value
Nefopam	14
Medetomidine	13

4. Experiment 4: The antinociceptive effects of nefopam and medetomidine alone or in a combination in the acetic acid writhing assay (visceral pain)

Treatment with a twofold dosage of ED_{50} for nefopam (11.2 mg/kg) and medetomidine (186 µg/kg) , administered individually , significantly increased the onset and decreased the frequency of abdominal stretches (writhes) compared to the acetic acid control group .The percentage % of reduction in the writhes significantly reduction by 54% and 66% ,respectively .While the combination of medetomidine and nefopam significantly prevent the incidence of abdominal stretching (writhing reflex) induced by acetic acid by 100% , in comparison with control ,medetomidine and nefopam groups , respectively **(Fig. 3)** .The findings demonstrated a synergistic antinociceptive impact of the novel combination at the level of visceral hyperalgesia**.**

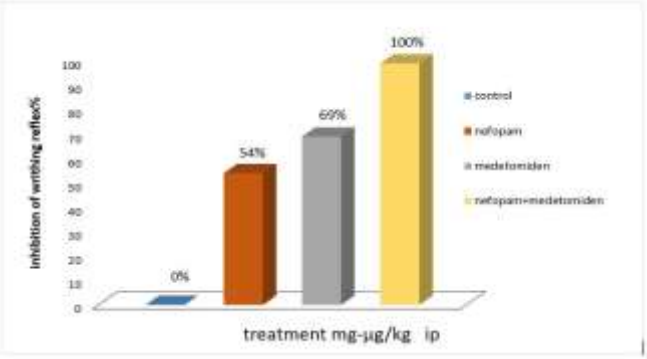

Fig.3: The figure shows the percentage reduction in the number of writhing for nefopam, medetomidine, or both.

DISCUSSION

Mice and rats are widely used in biomedical research due to their physiological and genetic similarities to humans, well-characterized behaviors, and ease of handling, making them invaluable models for studying disease mechanisms, drug efficacy, and toxicity **(Abdul Hameed & Naser, 2025; Aremu et al., 2024; Baker *et al.*, 2025).** The primary objective of this work was to elucidate the impact of medetomidine on the analgesic efficacy of nefopam in a mouse model, as no prior research has demonstrated the antinociceptive effect of nefopam in conjunction with medetomidine. The fundamental purpose of creating combination

analgesics is to improve their potency and efficacy and hence lower their doses **(Raffa, 2001).** According to the current study, nefopam and medetomidine as a combination worked in concert to enhance antinociceptive activity and decrease pain behavior. This finding is consistent with the results of previous clinical trials that indicated a combination of nefopam with ketoprofen **(Girard *et al.,* 2016)** and with paracetamol **(Al-Awwady *et al.,* 2020)** produced effective synergistic analgesia. In the present study, we used a hot plate device (thermal stimuli) to assess the antinociceptive action of nefopam and medetomidine each alone or as a combination form, as they achieved their analgesic effect through their effect on the central nervous system **(Kim and Abdi, 2014).** While the impact of the novel combination on the visceral pain level was evaluated using the writhing reflex test.

Based on the up-and-down method, the individual ED50 values for medetomidine and nefopam were 93.05 µg/kg and 5.66 mg/kg IP, respectively. These values matched those of previous studies for nefopam **(Girard *et al.,* 2016)** and medetomidine **(Kanda *et al.,* 2020).** In the hot plate test, the two drugs interacted synergistically on the level of analgesia at 1:1 and 0.5:0.5 of each drug's ED50, according to the isobolographic analysis, which was accompanied by a significant reduction in the ED50 dose of each drug **(Tallarida, 2011).** This result was confirmed by the interaction index, or Y value, being less than one **(Miranda *et al.,* 2014).** Isobolographic analysis is a powerful method for evaluating drug interactions in analgesia, determining whether combined drugs act synergistically, additively, or antagonistically. By plotting dose-response curves and calculating the theoretical additive line, it quantifies deviations that indicate synergy. The Y-value (interaction index) is key—values <1 suggest synergy, =1 additivity, and >1 antagonism **(Al-Jader & Taqa, 2014; Taqa, 2012).** This approach helps optimize analgesic combinations, enabling lower doses with enhanced efficacy while minimizing side effects, particularly valuable in developing non-opioid strategies. Another indicator of their synergistic interaction was the considerable decrease in the ED50 of nefopam that occurred when a fixed dose of medetomidine was administered with nefopam.

In addition, the novel combination prevents the abdominal constriction in the writhing test model, which is considered a sensitive method for assessing the activation of abdomen local receptors. Combining many analgesics or methods with various mechanisms or places of action is known as multimodal analgesia **(O'Neill and Lirk, 2022).** Non-steroidal and non-opioid pain reliever nefopam (a centrally acting analgesic drug) is considered safe with mild adverse effects, such as sweating and nausea **(Girard *et al.,* 2016).** These features make nefopam a great choice for multimodal pain management. Enhanced analgesic effects of nefopam by medetomidine were revealed in our novel study. This is consistent with the previous research on nefopam with a combination of ketoprofen and acetaminophen and with xylazine **(Khalil *et al.,* 2022)** and ketorolac **(Fahim and Alwan, 2022).** The synergistic antinociceptive interaction between nefopam and medetomidine may be related to their different mechanisms of action (pharmacodynamic interaction). Nefopam is a non-opioid, non-steroidal analgesic belonging to the benzoxazocine class. Unlike traditional painkillers, it exerts its central analgesic effects without binding to opioid receptors or exhibiting anti-inflammatory properties (**Petroianu *et al.,* 2023).** Increased extracellular serotonin (5-HT) and norepinephrine levels, together with decreased glutamate release in the spinal cord, were the main mechanisms by which nefopam produced its antinociceptive effects **(Girard *et al.,* 2006).**

Nefopam's analgesic effects were investigated by blocking carrier-dependent depletion of serotonin (5-HT) or norepinephrine (NE) in tissue and assessing their total contents to determine if serotonergic or noradrenergic pathways were involved **(Chae et al., 2020).** Nefopam reduced the reuptake of monoamines by neurons **(Kim and Abdi, 2014).** Synaptic glutamate release requires membrane voltage-gated Na+ and Ca++ channels, which are also blocked by nefopam **(Verleye *et al.,* 2004).** An excessive glutamate release, which is crucial for the nociception effect, has been avoided as a result. Medetomidine an α2 adrenoreceptor agonist drug, is more specific for the α2 adrenoreceptor than α1 (ratio 1620:1) **(Virtanen *et al.,* 1988).**

Alpha2-agonists work by activating receptors at different points throughout the brain and spinal cord's pain pathway to generate analgesia **(Smith and Elliott, 2001).** High concentrations of α2-adrenoreceptor binding sites are found in key pain modulation regions, particularly the brainstem (where nociceptive signal processing initiates) and the spinal cord's dorsal horn (where nociceptive fibers form synapses) **(Antal, 2025).** α2-adrenoreceptor agonists' antinociceptive effects are caused by pre- and postsynaptic inhibitory mechanisms **(Sinclair, 2003).** All these mechanisms produced a synergistic analgesic effect for the novel combination of nefopam and medetomidine at the level of central and visceral pain. The therapeutic index (TI), defined as the ratio between a drug's lethal dose (LD50) and effective dose (ED50), is a key indicator of safety (Muller and Milton, 2012). In this study, the TIs for medetomidine and nefopam were calculated as 13 and 14, respectively, reflecting a favorable safety margin for both drugs in mice. Previous research has demonstrated the analgesic efficacy and relative safety of medetomidine as an alpha-2 adrenergic agonist **(Kumar *et al.,* 2020)** and nefopam as a centrally acting non-opioid analgesic

(Kim and Abdi, 2014). Our findings provide novel quantitative evidence of their therapeutic windows, supporting their potential use in combination therapy with an acceptable margin of safety.

CONCLUSION

This study reveals a powerful synergy between medetomidine and nefopam, significantly boosting their pain-relieving effects. By targeting complementary pathways, the combination not only enhances analgesia but also maintains a strong safety profile, offering a promising alternative to opioids. These exciting findings pave the way for innovative, multimodal pain therapies that could improve patient outcomes while minimizing risks. Future research should focus on translating these results into clinical practice and uncovering the precise mechanisms behind this remarkable interaction.

Conflicts of interest

The authors declare that they have no competing interests.

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