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Investigation of Analgesic Effects of Venlafaxine, Atomoxetine and Trazodone Alone and in Combination in Acute Pain Models of the Rats

Münteha Zeynep Kemerli [1], Mustafa Kemal Yıldırım [2], Ziad Joha [3]*, Ahmet Şevki Taşkıran [4], İhsan Bağcivan[3]

[1]Drug Application and Research Center, Erciyes University, 38039 Kayseri, Türkiye
[2]Departments of Pharmacology, School of Medicine, Sivas Cumhuriyet University, Sivas, Türkiye
[3]Departments of Pharmacology, School of Pharmacy, Sivas Cumhuriyet University, Sivas, Türkiye
[4]Departments of Physiology, School of Medicine, Sivas Cumhuriyet University, Sivas, Türkiye

ABSTRACT:
Purpose: Poorly controlled pain is linked to several other undesirable outcomes. These outcomes are upsetting to patients, their families, and society as a whole. Although opioids and non-steroidal anti-inflammatory drugs are the cornerstone of the nociceptive pain treatment, the use of these drugs is restricted due to their side effects. Therefore, it is essential to develop new treatment alternatives for pain. Our study aimed to examine the pain relief effectiveness of Venlafaxine, Atomoxetine and Trazodone at 3 different doses alone, and in combination with each other in an acute pain model.
Material and Methods: The analgesic effectiveness of Venlafaxine, Atomoxetine, and Trazodone at three different doses alone and in combination in an acute pain model in rats was examined using the hot plate and tail flick methods. Experiments were conducted on 138 adult male Wistar albino rats.
Results: Venlafaxine and Trazodone, Venlafaxine showed dose-dependent analgesic effect when compared to the control. When Venlafaxine at dose of 2 mg/kg were was combined with Atomoxetine at doses of 1, 3 and, 6 mg/kg, the analgesic effects were significantly increased compared to these drugs alone. When Venlafaxine at dose of 2 mg/kg were was combined with trazodone at doses of 4, 12 and 24 mg/kg, the analgesic effects were significantly increased compared to these drugs alone.
Conclusion: All in all, our data suggest these combinations may offer a beneficial treatment option for acute pain in future.
Keywords: *Acute Pain, Venlafaxine, Atomoxetine, Trazodone, Hot Plate, Tail Flick, Analgesic Effect*

**Corresponding author: Ziad Joha, email: zead-geha@hotmail.com*

INTRODUCTION

When the pain is untreatable, it can have a negative impact on a person's quality of life. In addition, if the pain is severe, it can negatively affect mental functions and social communication. The most common method used to control pain is the use of analgesic drugs (Shipton et al., 2018). Pain relievers are divided into two main groups as opioid and non-opioid drugs. The use of opioid drugs is restricted due to their side effects such as addictive potential, sedation, and tolerance (Jamison and Mao, 2015). Non-steroidal anti-inflammatory drugs can cause stomach upsets, acute kidney failure, and articular cartilage deterioration. Therefore, it is essential to develop new treatment alternatives for pain (Hart and Huskisson, 2012). Adjuvant analgesics are described as medicines with a main purpose apart from pain which have analgesic effects in some painful circumstances. Since there is no analgesic drug with ideal properties, it is important to use adjuvant drugs in the clinic in order to reduce the analgesic dose and provide pain control with less

fewer side effects (Lussier et al., 2004). Antidepressants, antiarrhythmics, and antispasmodics are examples of analgesic adjuvants. Antidepressant drugs show their analgesic effects at lower doses than they are used for antidepressant effects. The analgesic effects of tricyclic antidepressants are stronger than the analgesic effects of selective serotonin reuptake inhibitors. However, selective serotonin reuptake inhibitors have fewer side effects (Rummans, 1994). Antidepressants are used for their analgesic effects in postherpetic neuralgia and diabetic neuropathy. Antidepressant medicines produce pain relief faster than antidepressant effects, and analgesia can be achieved with lower plasma concentrations. The analgesic efficacy of many antidepressant drugs has been proven in experimental acute pain models and in different pain models. The studies are continuing rapidly in order to use more antidepressant drugs as pain relievers in the clinic (Fornasari, 2017).

Venlafaxine (a serotonin noradrenaline re-uptake inhibitor), Atomoxetine (a selective noradrenaline re-uptake inhibitor) and Trazodone (a serotonin receptor modulator) are antidepressant drugs that affect the serotonergic and noradrenergic systems. It was proven that Venlafaxine has analgesic effect by several studies conducted using methods for testing analgesics such as tail immersion test, formalin test, paw withdrawal test and Von Frey filament test (Bonnefont et al., 2005; Cegielska-Perun et al., 2012; Gültekin and Ahmedov, 2006; Hajhashemi et al., 2014). However, studies showing the analgesic effects of Atomoxetine and Trazodone in an acute pain model are not sufficient. Drug combination studies for Venlafaxine and other antidepressant drugs are insufficient as well. This study aimed to investigate the pain relief effectiveness of Venlafaxine, Atomoxetine and Trazodone at 3 different doses alone, and in combination with each other in an acute pain model using hot plate and tail flick methods.

MATERIALS AND METHODS

Animals

Experiments were conducted on 138 adult male Wistar albino rats weighing 200-300 g. The rats were accommodated to the environment under temperature and humidity-controlled conditions (21 ± 1 ˚C , %63–%68 humidity) , four six in each cage, and maintained with 12-hour dark/12-hour light cycles with sufficient food and water. Each experimental group had 6 rats. Each experimental group had 6 rats. Experiment protocols were approved by Sivas Cumhuriyet University Animal Ethics Committee (Ethical Number: 65202830-050.04.04-254). The experiment protocols also conformed to the Guide for the Care and Use of Laboratory Animals, 8th Edition published by the National Academies Press (US), 2011, the guidelines from Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes. The animals were habituated to laboratory conditions prior to testing. All experiments were performed blindly between 9 and 17 hours.

Drugs

Venlafaxine hydrochloride, Atomoxetine hydrochloride and Trazodone hydrochloride were used in the study. These agents were obtained from Sigma-Aldrich company. Venlafaxine hydrochloride, Atomoxetine hydrochloride and Trazodone hydrochloride were prepared by dissolving them in sterile 0.9% NaCl solution. Solutions were freshly prepared on the days of experimentation. Atomoxetine hydrochloride (1, 3, 6 mg/kg), Trazodone hydrochloride (4, 12, 24 mg/kg), Venlafaxine hydrochloride (2, 10, 20, 30 mg/kg), 2 mg/kg Venlafaxine + 1 mg/kg Atomoxetine, 2 mg/kg Venlafaxine + 3 mg/kg Atomoxetine, 2 mg/kg Venlafaxine + 6 mg/kg Atomoxetine, 20 mg/kg Venlafaxine + 1 mg/kg Atomoxetine, 20 mg/kg Venlafaxine + 3 mg/kg Atomoxetine, 20 mg/kg Venlafaxine + 6 mg/kg Atomoxetine, 2 mg/kg Venlafaxine + 4 mg/kg Trazodone, 2 mg/kg Venlafaxine + 12 mg/kg Trazodone, 2 mg/kg Venlafaxine + 24 mg/kg Trazodone, 20 mg/kg Venlafaxine + 4 mg/kg Trazodone, 20 mg/kg Venlafaxine + 12 mg/kg Trazodone and 20 mg/kg Venlafaxine + 24 mg/kg Trazodone were administered intraperitoneally before the analgesia tests.

Analgesia Tests

Thermal pain was assessed using standard tail flick test (May TF 0703 Tail beat unit, Commat) and hot plate test (May AHP 0603 Analgesic HP, Commat) instruments. In the tail flick procedure the radiant heat source was applied to a 3 cm distal region of the rats' tails after saline or test drugs were injected intraperitoneally. After applying radiant heat, tail-flick latencies (TFL) were obtained. To avoid tissue harm, a 15-second cutoff time was chosen. Rats that did not reply after 15 seconds were removed from the experiment. The spinal mechanism is principally involved in the nociceptive response in the tail flick method (Kanaan et al., 1996; Ramabadran et al., 1989). In the hot plate procedure the rats were placed on a hot plate (May AHP 0603 Analgesic Hot Plate; Commat) with the temperature set at 53 0.5 ° C. The time it took for the first sign of paw licking or jumping response to avoid overheating was taken as an indicator of pain threshold to avoid overheating. To avoid damaging, a 15-second cutoff time was chosen. The spinal and supraspinal mechanisms are involved in the nociceptive response in the hot plate method (Kanaan et al., 1996).

Protocol

138 rats were randomly divided into 23 groups. Each group includes six rats. Saline was applied to the rats in the control group. Drugs were administered alone and in combination at different doses. The analgesic effects of Atomoxetine hydrochloride (1, 3, 6 mg/kg), Trazodone hydrochloride (4, 12, 24 mg/kg), Venlafaxine hydrochloride (2, 10, 20, 30 mg/kg), 2 mg/kg Venlafaxine + 1 mg/kg Atomoxetine, 2 mg/kg Venlafaxine + 3 mg/kg Atomoxetine, 2 mg/kg Venlafaxine + 6 mg/kg Atomoxetine, 20 mg/kg Venlafaxine + 1 mg/kg Atomoxetine, 20 mg/kg Venlafaxine + 3 mg/kg Atomoxetine, 20 mg/kg Venlafaxine + 6 mg/kg Atomoxetine, 2 mg/kg Venlafaxine + 4 mg/kg Trazodone, 2 mg/kg Venlafaxine + 12 mg/kg Trazodone, 2 mg/kg Venlafaxine + 24 mg/kg Trazodone, 20 mg/kg Venlafaxine + 4 mg/kg Trazodone, 20 mg/kg Venlafaxine + 12 mg/kg Trazodone and 20 mg/kg Venlafaxine + 24 mg/kg Trazodone were considered at 0, 15, 30, 60, 90, and 120 minutes using tail-flick and hot-plate tests.

Data Analysis and Statistical Analysis

To calculate the percentage maximal antinociceptive effects (%MPE), the following equation was used to convert lick/escape latencies (hot-plate) and tail withdrawal latencies (tail-flick) to percent antinociceptive effects: % MPE = {(test latency – baseline)/(cutoff – baseline(}*100 (Demirkazik et al., 2019).

The anti-nociceptive effects of the drugs were measured as tail flick and hot plate latencies for each rat in each group and converted to %.MPE. The findings were evaluated using one-way ANOVA and repeated measures ANOVA followed by a Tukey post hoc test (SPSS 14.0 for Windows) for multiple comparisons between groups. All results are presented as a mean ± SEM. The significance level was determined as $p < 0.05$.

RESULTS

The Antinociceptive Effects of Different Doses of Venlafaxine in the Acute Pain Model

The Antinociceptive effect of Venlafaxine at doses of 2, 10, 20, 30 mg/kg on acute pain was investigated by assessing anti-hyperalgesic responses for these doses of Venlafaxine at 15, 30, 60, 90, and 120 minutes using tail flick and hot plate tests. In these two tests, there were significant differences between the anti-hyperalgesic responses of venlafaxine at doses of 10, 20, 30 mg/kg and the control group. ($p < 0.05$). On the other hand, there was no significant difference between Venlafaxine at dose of 2 mg/kg and the control group. ($p > 0.05$). Venlafaxine at doses of 10, 20, 30 mg/kg showed increasing antinociceptive efficacy over time in both the hot plate and tail flick methods. In the tail flick method, no significant differences were observed between the doses ($p > 0.05$), except for 30 mg/kg venlafxine at 15th minute (Figure 1A). In the hot plate method, there was a significant difference between Venlafaxine at dose of 30 mg/kg and the other doses of this drug ($p < 0.05$) (Figure 1B).

The Antinociceptive Effects of Different Doses of trazodone in the Acute Pain Model

The Antinociceptive effect of Trazodone at doses of 4, 12, 24 mg/kg on acute pain was investigated by assessing anti-hyperalgesic responses for these

doses of Trazodone at 15, 30, 60, 90, and 120 minutes using tail flick and hot plate tests. In these two tests, there were significant differences between the anti-hyperalgesic responses of Trazodone at doses of 4, 12, 24 mg/kg and the control group ($p < 0.05$). The antinociceptive effects of Trazodone at doses of 4, 12, 24 mg/kg reached their peak at the 60-min in both the hot plate and tail flick tests. In the hot plate method, no significant differences were observed between the doses ($p > 0.05$), except for 24 mg/kg Trazodone at 15th and 120th minutes (Figure 2B). In the tail flick method, there was a significant difference between Trazodone at dose of 24 mg/kg and the other doses of this drug ($p < 0.05$) (Figure 2A).

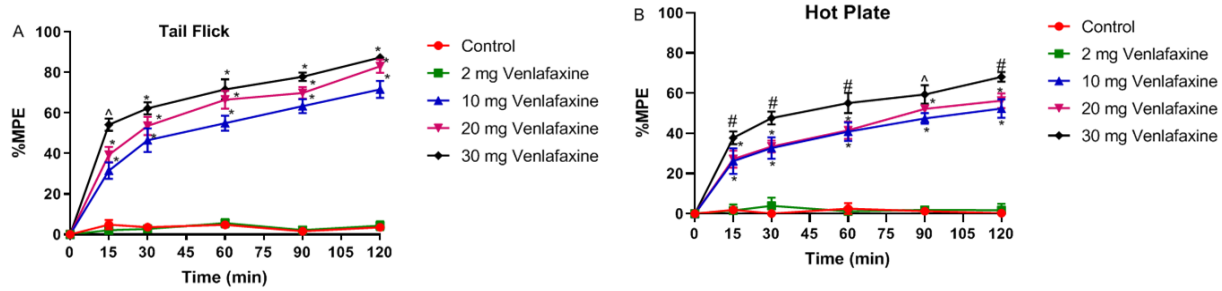

Figure 1: The analgesic effects of various doses of Venlafaxine on rats evaluated by tail flick test (A) and hot plate test (B). The response time was measured as a percentage maximum possible effect (%MPE). The drug was administered intraperitoneally. Each point represents the mean ± SEM of % MPE for 6 rats. (*) There was a significant analgesic effect compared to the control group (*$p < 0.05$). (^) There was a significant analgesic effect compared to the control group and this analgesic effect was significantly higher than that of 10 mg/kg venlafaxine (^$p < 0.05$). (#)There was a significant analgesic effect compared to the control group and this analgesic effect was significantly higher than that of 10 and 20 mg/kg venlafaxine groups (#$p < 0.05$).

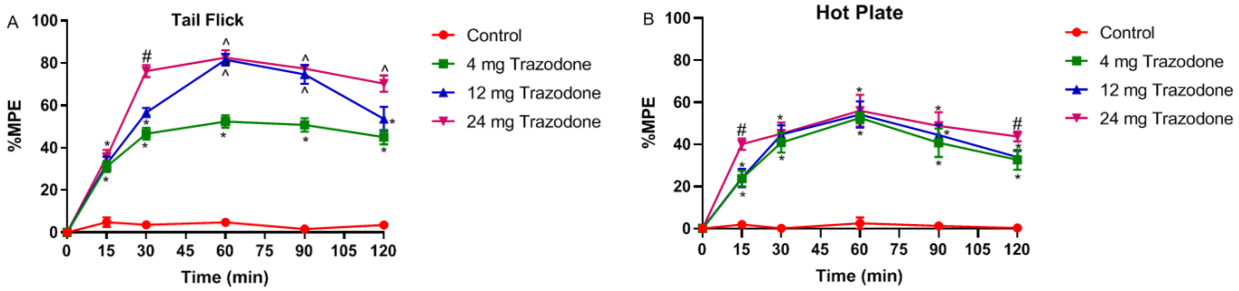

Figure 2: The analgesic effects of various doses of trazodone on rats evaluated by tail-flick test (A) and hot-plate test (B). The response time was measured as a percentage maximum possible effect (%MPE). The drug was administered intraperitoneally. Each point represents the mean ± SEM of % MPE for 6 rats. (*) There was a significant analgesic effect compared to the control group (*$p<0.05$) (^). There was a significant analgesic effect compared to the control group and this analgesic effect was significantly higher than that of 4 mg/kg trazodone (^$p <0.05$). (#)There was a significant analgesic effect compared to the control group and this analgesic effect was significantly higher than that of 4 and 12 mg/kg trazodone groups (#$p <0.05$).

The Antinociceptive Effects of Different Doses of Atomoxetine in the Acute Pain Model

The Antinociceptive effect of Atomoxetine at doses of 1, 3, 6 mg/kg on acute pain was investigated by assessing anti-hyperalgesic responses for these doses of Atomoxetine at 15, 30, 60, 90, and 120 minutes using tail flick and hot plate tests. In these two tests, there were significant differences between the anti-hyperalgesic responses of Atomoxetine at doses of 1, 3, 6 mg/kg and the

control group. ($p < 0.05$). Atomoxetine at doses of 1, 3, 6 mg/kg showed increasing antinociceptive efficacy over time in both the hot plate and tail flick methods. In the tail flick method, no significant differences were observed between the doses ($p > 0.05$) (Figure 3A). In the hot plate method, there was a significant difference between this drug at dose of 6 mg/kg and at dose of 1 mg/kg ($p < 0.05$) (Figure 3B).

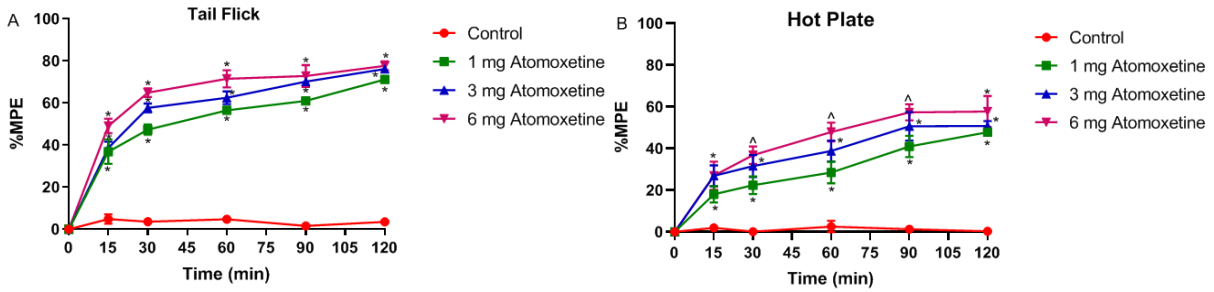

Figure 3: The analgesic effects of various doses of Atomoxetine on rats evaluated by tail-flick test (A) and hot-plate test (B). The response time was measured as a percentage maximum possible effect (%MPE). The drug was administered intraperitoneally. Each point represents the mean ± SEM of % MPE for 6 rats. (*) There was a significant analgesic effect compared to the control group (*p<0.05). (^) There was a significant analgesic effect compared to the control group and this analgesic effect was significantly higher than that of 1 mg/kg Atomoxetine (^p <0.05).

The Antinociceptive Effects of combinations of venlafaxine at ineffective dose (2 mg/kg) plus different doses of Atomoxetine in the Acute Pain Model

It was examined whether there was a potentiation effect between the ineffective dose of venlafaxine and different doses of Atomoxetine. So these combinations (2 mg/kg venlafaxine +1 mg/kg Atomoxetine, 2 mg/kg venlafaxine +3 mg/kg Atomoxetine and 2 mg/kg venlafaxine +6 mg/kg Atomoxetine) were appalied to rats. The antinociceptive effect of these combinations were investigated by assessing anti-hyperalgesic responses for these combinations at 15, 30, 60, 90, and 120 minutes using tail flick and hot plate tests. In the tail flick method, the antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 3 mg/kg Atomoxetine at the 15th minute was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 3 mg/kg Atomoxetine alone ($p < 0.05$). The antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 6 mg/kg Atomoxetine at the 15th 30th, 60th and 90th minutes was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 6 mg/kg Atomoxetine alone ($p < 0.05$) (Figure 4). In the hot plate method, the antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 1 mg/kg Atomoxetine at the 30th and 60th minutes was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 1 mg/kg Atomoxetine alone ($p < 0.05$). The antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 3 mg/kg Atomoxetine at the 15th minute was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 3 mg/kg Atomoxetine alone ($p < 0.05$). The antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 6 mg/kg Atomoxetine at the 15th 30th, and 120th minutes was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 6 mg/kg Atomoxetine alone ($p < 0.05$) (Figure 4).

The Antinociceptive Effects of combinations of Venlafaxine at ineffective dose (2 mg/kg) plus different doses of Trazodone in the Acute Pain Model

It was examined whether there was a potentiation effect between the ineffective dose of venlafaxine and different doses of Trazodone. So these combinations (2 mg/kg venlafaxine +4 mg/kg Trazodone, 2 mg/kg venlafaxine +12 mg/kg Trazodone and 2 mg/kg venlafaxine +24 mg/kg Trazodone) were appalied to rats. The antinociceptive effect of the combinations were was investigated by assessing anti-hyperalgesic

responses for these combinations at 15, 30, 60, 90, and 120 minutes using tail flick and hot plate tests. In the tail flick method, the antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 4 mg/kg Trazodone at the 15th minute was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 4 mg/kg Trazodone alone ($p<0.05$). The antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 12 mg/kg Trazodone at the 15th and 30th minutes was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 12 mg/kg Trazodone alone ($p < 0.05$). The antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 24 mg/kg Trazodone at the 15th minute was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 24 mg/kg Trazodone alone ($p < 0.05$) (Figure 5). In the hot plate method, the antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 4 mg/kg Trazodone at the 15th and 60th minutes was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 4 mg/kg Trazodone alone ($p < 0.05$). The antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 12 mg/kg Trazodone at the 15th and 60th minutes was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 12 mg/kg Trazodone alone ($p < 0.05$). The antinociceptive effect of the combination of 2 mg/kg Venlafaxine + 24 mg/kg Trazodone at the 15th minute was significantly higher than that of 2 mg/kg Venlafaxine alone and that of 24 mg/kg Trazodone alone ($p < 0.05$) (Figure 5).

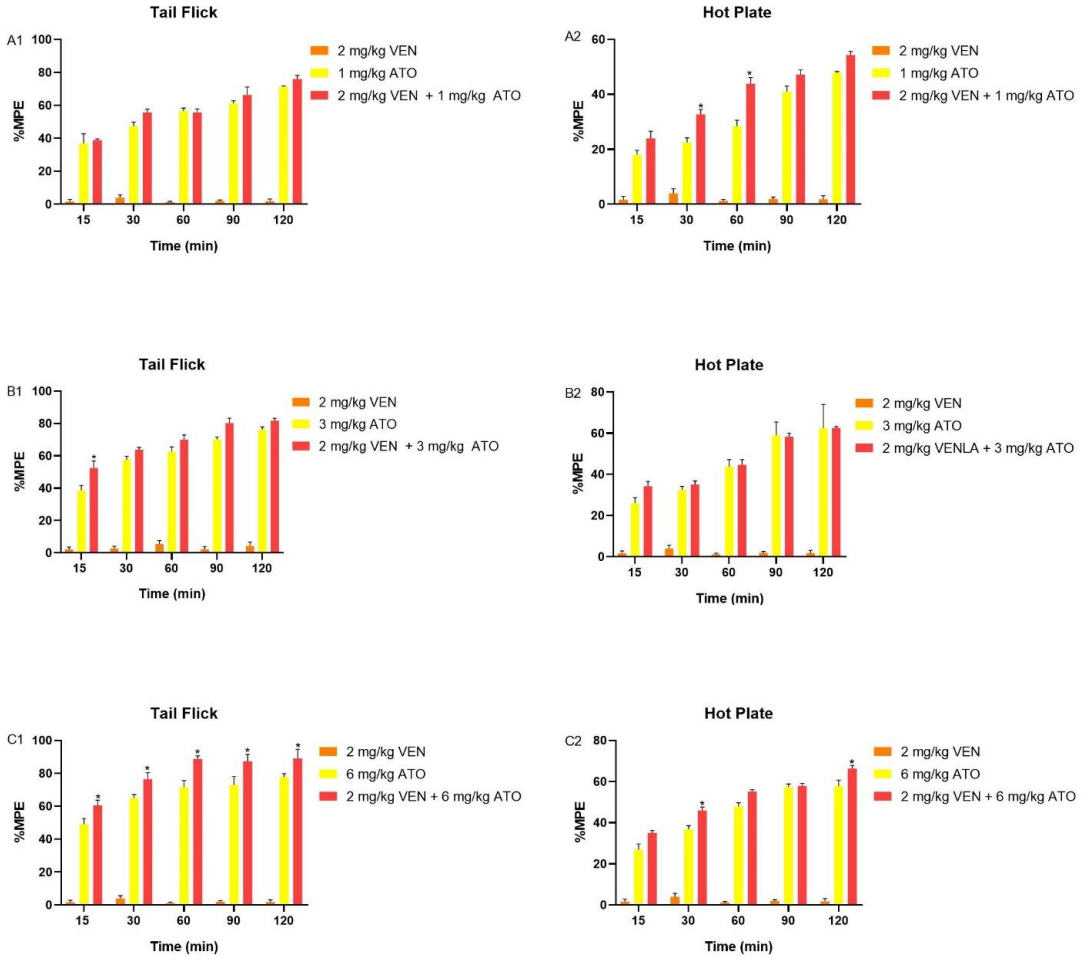

Figure 4: The analgesic effects of combinations of venlafaxine at ineffective dose (2 mg/kg) plus different doses of Atomoxetine on rats evaluated by tail-flick test (A1, B1, C1, D1) and hot-plate test (A2, B2, C2, D2). The response time was measured as a percentage maximum possible effect (%MPE). The drugs was administered intraperitoneally. Each point represents the mean ± SEM of % MPE for 6 rats. (*) The analgesic effect of the combination was significantly higher compared to 2 mg/kg Venlafaxine alone and Atomoxetine alone (*$p<0.05$).

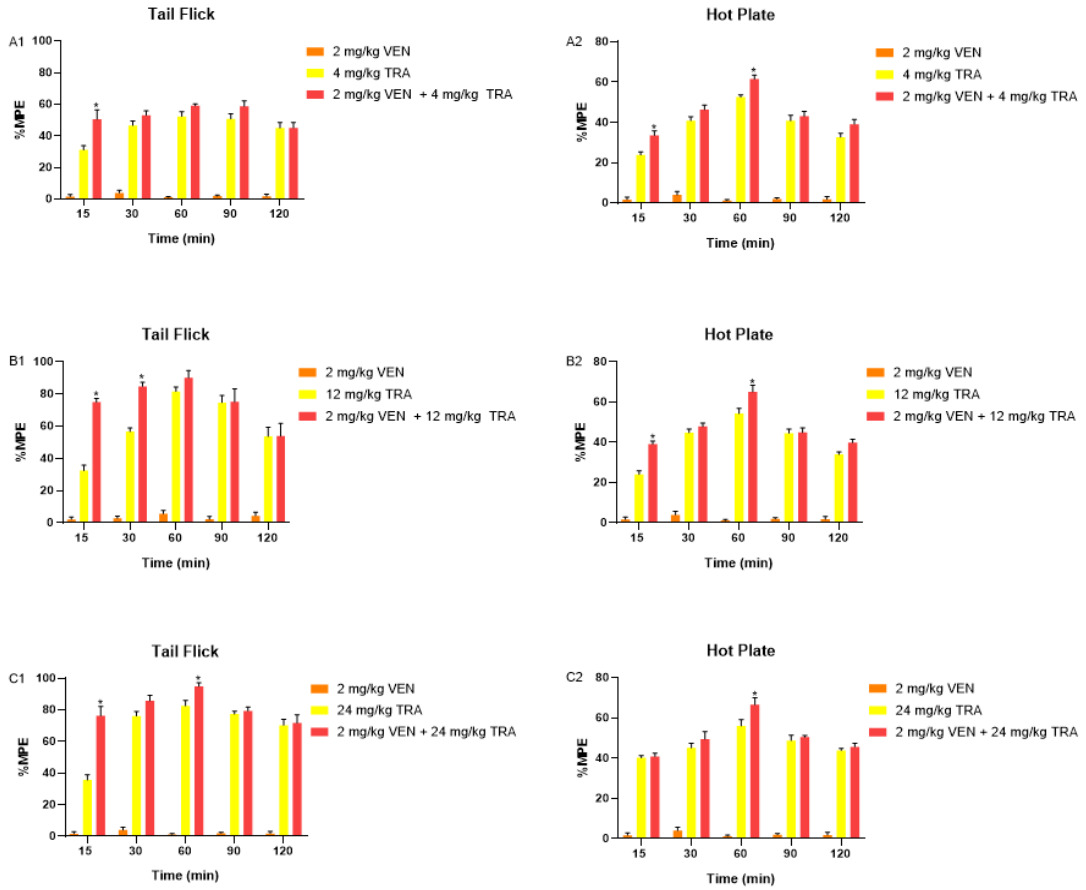

Figure 5: The analgesic effects of combinations of venlafaxine at ineffective dose (2 mg/kg) plus different doses of trazodone on rats evaluated by tail-flick test (A1, B1, C1, D1) and hot-plate test (A2, B2, C2, D2). The response time was measured as a percentage maximum possible effect (%MPE). The drugs was administered intraperitoneally. Each point represents the mean ± SEM of % MPE for 6 rats. (*) The analgesic effect of the combination was significantly higher compared to 2 mg/kg Venlafaxine alone and trazodone alone (*p<0.05).

The Antinociceptive Effects of combinations of venlafaxine at submaximal dose (20 mg/kg) plus different doses of Atomoxetine in the Acute Pain Model

It was examined whether there was a potentiation effect between the submaximal dose of venlafaxine and different doses of Atomoxetine. So these combinations (20 mg/kg venlafaxine +1 mg/kg Atomoxetine, 20 mg/kg venlafaxine +3 mg/kg Atomoxetine and 20 mg/kg venlafaxine +6 mg/kg Atomoxetine) were appalied to rats. The antinociceptive effect of these combinations were investigated by assessing anti-hyperalgesic responses for these combinations at 15, 30, 60, 90, and 120 minutes using tail flick and hot plate tests. In the hot plate test, the antinociceptive effect of the combination of 20 mg/kg Venlafaxine + 6 mg/kg Atomoxetine at the 120th minutes was significantly higher than that of 20 mg/kg Venlafaxine alone and that of 6 mg/kg Atomoxetine alone ($p < 0.05$) (Figure 6).

The Antinociceptive Effects of combinations of Venlafaxine at submaximal dose (20 mg/kg) plus different doses of Trazodone in the Acute Pain Model

It was examined whether there was a potentiation effect between the submaximal dose of venlafaxine and different doses of Trazodone. So these combinations (20 mg/kg venlafaxine +4 mg/kg Trazodone, 20 mg/kg venlafaxine +12 mg/kg Trazodone and 20 mg/kg venlafaxine +24 mg/kg Trazodone) were appalied to rats. The antinociceptive effect of the combinations were investigated by assessing anti-hyperalgesic responses for these combinations at 15, 30, 60, 90,

and 120 minutes using tail flick and hot plate tests. In the tail flick method, the antinociceptive effect of the combination of 20 mg/kg Venlafaxine + 12 mg/kg Trazodone at the 15th minute was significantly higher than that of 20 mg/kg Venlafaxine alone and that of 12 mg/kg Trazodone alone ($p<0.05$). The antinociceptive effect of the combination of 20 mg/kg Venlafaxine + 24 mg/kg Trazodone at the 15th and 90th minutes was significantly higher than that of 20 mg/kg Venlafaxine alone and that of 24 mg/kg Trazodone alone ($p < 0.05$) (Figure 7). In the hot plate method, the antinociceptive effect of the combination of 20 mg/kg Venlafaxine + 12 mg/kg Trazodone at the 15th minutes was significantly higher than that of 20 mg/kg Venlafaxine alone and that of 12 mg/kg Trazodone alone ($p < 0.05$). The antinociceptive effect of the combination of 20 mg/kg Venlafaxine + 24 mg/kg Trazodone at the 90th and 120th minutes was significantly higher than that of 20 mg/kg Venlafaxine alone and that of 24 mg/kg Trazodone alone ($p < 0.05$) (Figure 7).

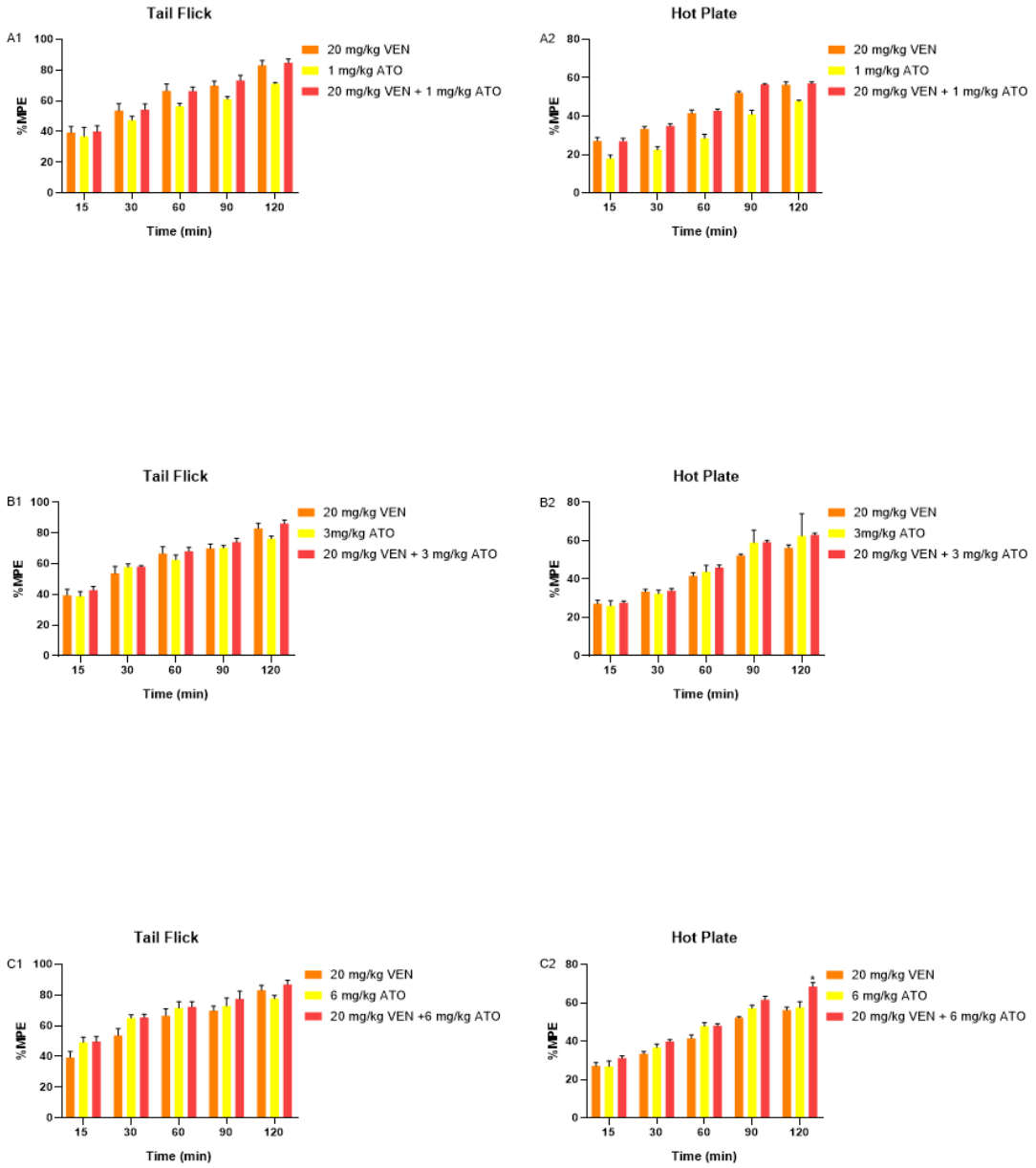

Figure 6: The analgesic effects of combinations of venlafaxine at submaximal dose (20 mg/kg) plus different doses of Atomoxetine on rats evaluated by tail-flick test (A1, B1, C1, D1) and hot-plate test (A2, B2, C2, D2). The response time was measured as a percentage maximum possible effect (%MPE). The drugs was administered intraperitoneally. Each point represents the mean ± SEM of % MPE for 6 rats. (*) The analgesic effect of the combination was significantly higher compared to 20 mg/kg Venlafaxine alone and Atomoxetine alone (*$p<0.05$).

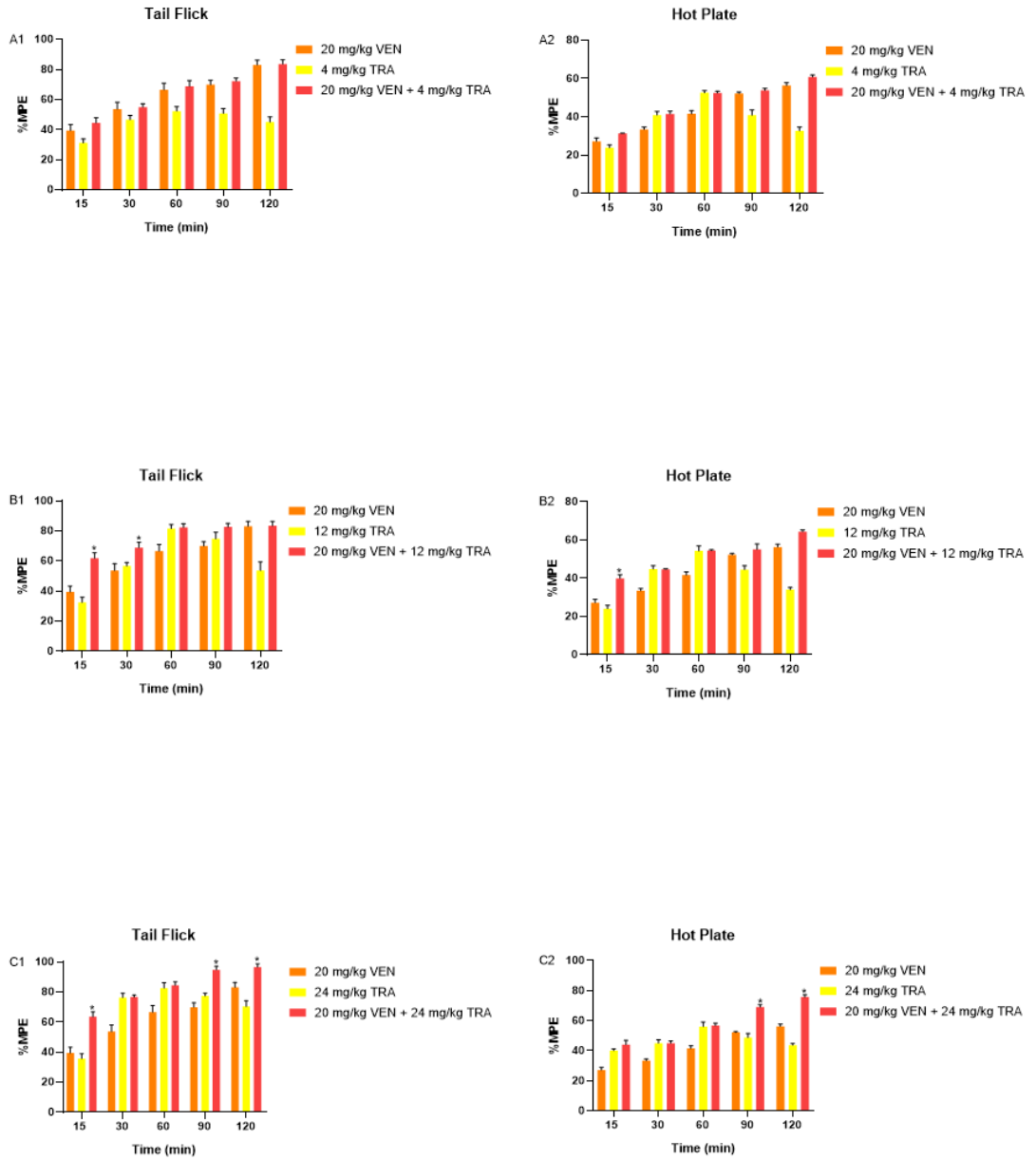

Figure 7: The analgesic effects of combinations of venlafaxine at submaximal dose (20 mg/kg) plus different doses of trazodone on rats evaluated by tail-flick test (A1, B1, C1, D1) and hot-plate test (A2, B2, C2, D2). The response time was measured as a percentage maximum possible effect (%MPE). The drugs was administered intraperitoneally. Each point represents the mean ± SEM of % MPE for 6 rats. (*) The analgesic effect of the combination was significantly higher compared to 20 mg/kg Venlafaxine alone and trazodone alone (*p<0.05).

DISCUSSION

Up to now the antinociceptive effects of Atomoxetine and Trazodone alone and the antinociceptive effects of combinations between Venlafaxine and Atomoxetine and between Venlafaxine and Trazodone in an acute pain model have not been investigated. The Antinociceptive Activity of these medications were investigated in this study at various doses alone and in combination. The antinociceptive efficacy of Venlafaxine, Trazodone and Atomoxetine has been demonstrated at different doses. The antinociceptive effect of Venlafaxine was more than the antinociceptive effect of Trazodone and Atomoxetine. The antinociceptive effect of Venlafaxine and Atomoxetine increased over time in both the hot plate and tail flick tests. The antinociceptive effect of Trazodone increased with time until the 60th minute and then it started to decrease. Venlafaxine and Atomoxetine may have a longer duration of

antinociceptive effect because they inhibit the reuptake of monoamine and serotonin, whereas Trazodone acts at the receptor level. Like Venlafaxine, Trazodone inhibits thee the reuptake of serotonin, but this inhibition is much less than Venlafaxine (Florkowski et al., 2005). When Venlafaxine was added to Atomoxetine at a dose of 2 mg/kg, the effect was significantly increased. Thus, we thought that there was a possible potentiation between the two drugs in our study. Venlafaxine and Atomoxetine increase noradrenaline by increasing the noradrenaline re-uptake inhibition so they can produce antinociceptive effect. The noradrenaline system is thought to be involved in pain suppression, according to studies (Chen et al., 2021). The descending inhibitory noradrenergic pathways from the locus coeruleus are thought to generate pain inhibition via noradrenergic receptors in dorsal horn neurons.

Venlafaxine at an ineffective dose may strengthen the noradrenaline re-uptake inhibitory mechanism of the other drug and contributed to the antinociceptive activity (Taylor and Westlund, 2017). We observed similar results for the combination of trazodone and low-dose venlafaxine. An ineffective dose of Venlafaxine may strengthen the serotonin re-uptake inhibitory mechanism of the other drug and contributed to its antinociceptive activity. Spinal inhibitory interneurons and descending pathways play an important role in endogenous pain modulation by inhibiting or facilitating pain transmission. These neurons of descending pathway project to the dorsal horn of spinal cord and modulate the pain response by releasing serotonin which binds to serotonin receptor subtypes (Neugebauer, 2020; Tao et al., 2019). Activation of 5-HT1 and 5-HT2 receptors leads to pain inhibition, but activation of 5-HT3 receptors leads to pain facilitation (Cortes-Altamirano et al., 2018). The increase in the antinociceptive effect of the combination of Venlafaxine and Trazodone may be due to increased serotonin levels (Ozdemir et al., 2019). In the tail flick and hot plate tests, the combination of Venlafaxine and Atomoxetine increased the antinociceptive effect more than Venlafaxine alone or Atomoxetine alone. In the combination of Venlafaxine and Trazodone, the clinical use of Venlafaxine and Trazodone may increase the risk of serotonin syndrome, since serotonin levels will be increased and serotonin receptors will be more activated. As a result, patients should be closely monitored when taking these drugs in combination (Scotton et al., 2019). It was observed that the combination of different doses of Trazodone and Atomoxetine with Venlafaxine at dose of 20 mg/kg increased the antinociceptive effect less than the combination with 2 mg/kg Venlafaxine. This is a more fruitful result because the high doses of drugs can cause more side effects and rapid development of tolerance. Other analgesia studies have been performed on venlafaxine. According to these studies, it has been shown that the antinociceptive effect of venlafaxine drug may be via the opioidergic, noradrenergic and serotonergic systems (Grothe et al., 2004; Marchand et al., 2003; Sumpton and Moulin, 2001).

Trazodone has been reported to be effective in the treatment of migraine headaches and diabetic neuropathy (Khouzam, 2016). It was also shown that Trazodone-mediated analgesia was partially reversed by naloxone (Fernández-Dueñas et al., 2011). The antihyperalgesic effect of atomoxetine on diabetes-induced neuropathic pain has been reported, and this effect appears to be mediated via α/β-adrenergic receptors, as well as D2/D3 dopaminergic receptors (Barbaros et al., 2018). Venlafaxine, Atomoxetine demonstrated antinociceptive effects when applied alone. Venlafaxine and Trazodone, as well as Venlafaxine and Atomoxetine, were found to have greater antinociceptive effects when used in combination at lower doses compared to the application alone. In the future years, the use of these medicines as antinociceptive adjuvants in clinical acute pain therapy appears to be promising.

CONCLUSION

Venlafaxine, Atomoxetine demonstrated antinociceptive effects when applied alone. Venlafaxine and Trazodone, as well as Venlafaxine and Atomoxetine, were found to have greater antinociceptive effects when used in combination at lower doses compared to the application alone. In the future years, the use of these medicines as

antinociceptive adjuvants in clinical acute pain therapy appears to be promising.

Conflict of Interests

The authors declare that they have no conflict of interest.

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