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Original Research Article

Evaluation of Analgesic Effect of Vortioxetine in Swiss Albino Mice

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Abstract

Background: Pain is a debilitating sensory and emotional experience that remains undertreated globally. Vortioxetine, a multimodal serotonergic antidepressant with antagonism at 5-HT3, 5-HT7, and 5-HT1D receptors and agonism at 5-HT1A receptors, has pharmacological properties that may confer analgesic benefits through modulation of spinal nociceptive pathways.

Methods: Swiss albino mice (n=24) were divided into four groups (n=6 each): control (distilled water 0.4 ml oral), tramadol 10 mg/kg (standard), vortioxetine 5 mg/kg, and vortioxetine 10 mg/kg. Drugs were administered orally for seven days. Analgesic response time was assessed before and after treatment using Eddy's hot plate, tail immersion, and tail clip methods. Data were analysed using paired t-test and one-way ANOVA with post-hoc Tukey's test.

Results: All active treatment groups demonstrated significantly increased response times compared to control ($p<0.001$). One-way ANOVA showed highly significant differences across groups for all three methods ($F=172.11$, 172.71, and 131.78 respectively; $p<0.00001$). The analgesic response followed the order: tramadol 10 mg/kg > vortioxetine 10 mg/kg > vortioxetine 5 mg/kg > control. Vortioxetine 5 mg/kg and 10 mg/kg showed comparable efficacy in the tail immersion test ($p>0.05$).

Conclusion: Vortioxetine exhibits significant, dose-dependent analgesic activity in Swiss albino mice, albeit of lesser magnitude than tramadol, supporting its potential role as an adjuvant analgesic, particularly in patients with comorbid depression and chronic pain.

Keywords: Vortioxetine; analgesic; Swiss albino mice; serotonin; Eddy's hot plate; tail immersion; tail clip; tramadol; antidepressant; nociception.

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Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. [1] Despite decades of research, the pharmacological management of chronic and neuropathic pain remains a clinical challenge. Currently available analgesics, including opioids and non-steroidal anti-inflammatory drugs (NSAIDs), are limited by issues of tolerance, dependence, gastrointestinal toxicity, and inadequate efficacy in neuropathic pain states.

Serotonergic pathways play a pivotal role in pain modulation. Hyperalgesic activity is substantially mediated by serotonin acting through 5-HT3 receptors in the dorsal horn of the spinal cord, while 5-HT1A receptor activation is associated with analgesia and descending inhibitory control of pain. [2,4] The convergence of chronic pain and depressive disorders is well established: approximately 30–60% of patients with chronic pain exhibit comorbid depression, suggesting shared neurobiological substrates and the therapeutic rationale for using antidepressants as analgesic adjuvants.

Vortioxetine (Lu AA21004) is a novel, multimodal serotonergic antidepressant approved for the treatment of major depressive disorder. [18] Unlike conventional selective serotonin reuptake inhibitors (SSRIs), vortioxetine exerts its effects through simultaneous 5-HT reuptake inhibition and direct modulation of multiple serotonin receptor subtypes: antagonism at 5-HT3, 5-HT7, and 5-HT1D receptors; partial agonism at 5-HT1B; and full agonism at 5-HT1A receptors. [19] This unique pharmacodynamic profile positions vortioxetine as a candidate for pain relief, particularly through its capacity to potentiate descending inhibitory serotonergic pathways and counteract spinal hyperalgesic 5-HT3 signalling. [3,4] Emerging preclinical evidence suggests analgesic properties of vortioxetine in neuropathic pain models. [3,4] However, systematic evaluation of its antinociceptive activity using classical pain models in mice has not been comprehensively reported. Furthermore, while antidepressants such as duloxetine and amitriptyline are used clinically for neuropathic pain, [15,16] the analgesic potential of vortioxetine relative to an established opioid analgesic has not been formally characterised in experimental animals. The present study was designed to evaluate and compare the analgesic activity of vortioxetine at two doses (5 mg/kg and 10 mg/kg oral) against tramadol 10 mg/kg (standard analgesic) and vehicle control, using three validated nociceptive assays in Swiss albino mice: Eddy's hot plate method, 6 tail immersion method,8 and tail clip method. Based on thus objective of this study is to evaluate the analgesic activity of vortioxetine at doses of 5 mg/kg and 10 mg/kg in Swiss albino mice using Eddy's hot plate, tail immersion, and tail clip methods. Also to compare the analgesic efficacy of vortioxetine with tramadol 10 mg/kg (standard drug) and vehicle control and to determine whether vortioxetine produces dose-dependent analgesic effects across the three nociceptive assays.

Materials and Methodology

The study was approved by the Institutional Animal Ethics Committee (IAEC) of Coimbatore Medical College, Coimbatore, India (Approval No.: IAEC/CMCH/PH/037/2023, dated 28.11.2023). All procedures were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. Adult Swiss albino mice of either sex, weighing 20–25 g, were procured from the institutional animal house. The animals were housed in standard polypropylene cages under controlled environmental conditions (temperature 22 ± 2°C, relative humidity 50–60%, 12-hour light/dark cycle) with free access to standard pellet diet and water ad libitum. Animals were quarantined for seven days and acclimatised to the experimental room for at least three days before commencing the study. [6,7] A total of 24 mice were randomly divided into four groups of six animals each. Group I (Control) received distilled water (0.4 ml, oral); Group II (Standard) received tramadol 10 mg/kg orally; Group III (Test 1) received vortioxetine 5 mg/kg orally; Group IV (Test 2) received vortioxetine 10 mg/kg orally. All drugs were administered once daily for seven consecutive days by oral gavage. Tramadol hydrochloride tablets and vortioxetine tablets were procured from a licensed pharmacy and prepared as aqueous suspensions. Baseline (pre-treatment) assessment of response time was carried out on Day 0, followed by post-treatment assessment on Day 7, sixty minutes after the final drug administration. Eddy's Hot Plate Method: Mice were placed individually on a hot plate (Techno, India) maintained at 55 ± 0.5°C. The latency (in seconds) to the first sign of nociceptive response (licking of paws, jumping, or vocalization) was recorded as the response time. A cut-off time of 30 seconds was applied to prevent tissue injury. [6,7] Tail Immersion Method: The distal 2 cm of the mouse tail was immersed in a water bath maintained at 55 ± 0.5°C. The latency to tail withdrawal was recorded in seconds, with a cut-off time of 20 seconds. [8] Tail Clip Method: A blunt arterial clip (NICHROME® artery clip) was applied to the tail at approximately one-third from the base. The latency to vigorous struggle response (biting or turning toward the tail) was recorded in seconds, with a cut-off of 20 seconds. All methods were performed by the same investigator under identical conditions. Data are expressed as mean ± standard deviation (SD). Within-group comparison of pre- and post-treatment response times was performed using paired Student's t-test. Between-group differences were analysed using one-way ANOVA, followed by post-hoc Tukey's Honestly Significant Difference (HSD) test for pairwise comparisons. A p-value of <0.05 was considered statistically significant. All analyses were performed using standard statistical software.

Results

The analgesic effects of vortioxetine, tramadol, and vehicle control were assessed using three nociceptive assays in Swiss albino mice. Mean response times (in seconds) for all groups, across all three methods, are presented in Table 1. Statistical analyses including one-way ANOVA, paired t-test, and post-hoc pairwise comparisons are summarised in Tables 2–5.

Table 1: Response Time across Nociceptive Assays

Groups	Eddy's Hot Plate (sec)		Tail Immersion (sec)		Tail Clip (sec)		Sig.
	Mean	SD	Mean	SD	Mean	SD	p
G1 – Control (Distilled water)	5.67	0.52	4.17	0.41	2.67	0.52	—
G2 – Tramadol 10 mg/kg	12.67	0.52	11.17	0.75	8.17	0.41	<0.001*
G3 – Vortioxetine 5 mg/kg	7.83	0.75	8.17	0.41	6.00	0.63	<0.001*
G4 – Vortioxetine 10 mg/kg	10.17	0.41	8.67	0.52	6.83	0.41	<0.001*

Table 1: Mean response time (seconds) and standard deviation of all groups across Eddy's hot plate, tail immersion, and tail clip methods. *p<0.001 compared with control (paired t-test).

Table 1 shows that all active treatment groups demonstrated markedly increased response times compared to the control group across all three nociceptive assays. In Eddy's hot plate, mean response time was 5.67 ± 0.52 sec (control), 12.67 ± 0.52 sec (tramadol 10 mg), 7.83 ± 0.75 sec (vortioxetine 5 mg), and 10.17 ± 0.41 sec (vortioxetine 10 mg).

A consistent dose-dependent pattern was observed for vortioxetine across all three assays, with the 10 mg/kg dose consistently producing higher analgesic response times than the 5 mg/kg dose.

Table 2: One-Way ANOVA

Parameter	G1 Mean (SD)	G2 Mean (SD)	G3 Mean (SD)	G4 Mean (SD)	F value	p value
Eddy's Hot Plate	5.67 (0.52)	12.67 (0.52)	7.83 (0.75)	10.17 (0.41)	172.11	<0.00001*
Tail Immersion Method	4.17 (0.41)	11.17 (0.75)	8.17 (0.41)	8.67 (0.52)	172.71	<0.00001*
Tail Clip Method	2.67 (0.52)	8.17 (0.41)	6.00 (0.63)	6.83 (0.41)	131.78	<0.00001*

Table 2: One-way ANOVA analysis of analgesic response time across treatment groups. Values in parentheses represent SD. *p<0.00001 (significant at 5% level).

Note: G1=Control; G2=Tramadol 10 mg/kg; G3=Vortioxetine 5 mg/kg; G4=Vortioxetine 10 mg/kg. *Significant at 5% level. One-way ANOVA revealed highly significant differences in analgesic response among treatment groups across all three assessment methods (Table 2). The F values for Eddy's hot plate, tail immersion, and tail clip methods were 172.11, 172.71, and 131.78 respectively, with p<0.00001 for all three.

These results confirm that the overall treatment effect was statistically significant, irrespective of the method used for nociceptive assessment. [6,7,8]

Table 3: Paired T-Test (Pre- vs Post-treatment) ()

Group	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	t value	p value
G1 – Control	3.50 (0.48)	4.17 (0.41)	1.24	>0.05 (NS)
G2 – Tramadol 10 mg/kg	3.67 (0.52)	11.17 (0.75)	20.14	<0.001*
G3 – Vortioxetine 5 mg/kg	3.83 (0.41)	8.17 (0.41)	16.33	<0.001*
G4 – Vortioxetine 10 mg/kg	3.67 (0.52)	8.67 (0.52)	17.88	<0.001*

Table 3: Paired t-test comparing pre- and post-treatment response times (tail immersion, seconds). NS = Not significant; * p<0.001.

Paired t-test analysis (Table 3) demonstrated that the pre-treatment and post-treatment response times were not significantly different in the control group (p>0.05), confirming the absence of any spontaneous variation in baseline nociceptive threshold. By contrast, all three active treatment groups (tramadol, vortioxetine 5 mg/kg, and vortioxetine 10 mg/kg) showed statistically significant increases in response time following drug administration (p<0.001), indicating genuine analgesic activity attributable to the administered drugs.

Table 4: Post-Hoc Pairwise Comparisons

Comparison	Parameter	Mean Diff.	95% CI	p value
G1 vs G2 (Control vs Tramadol)	Eddy's Hot Plate	7.00	5.94–8.06	<0.001*
G1 vs G3 (Control vs Vortioxetine 5 mg)	Eddy's Hot Plate	2.16	1.10–3.22	<0.001*
G1 vs G4 (Control vs Vortioxetine 10 mg)	Eddy's Hot Plate	4.50	3.44–5.56	<0.001*
G3 vs G4 (Vortioxetine 5 mg vs 10 mg)	Tail Immersion	0.50	−0.56–1.56	>0.05 (NS)
G2 vs G4 (Tramadol vs Vortioxetine 10 mg)	Tail Clip	1.34	0.28–2.40	<0.05*

Table 4: Post-hoc Tukey's HSD pairwise comparisons between treatment groups for selected method-specific parameters. NS = Not significant; *Significant (p<0.05). Post-hoc Tukey's HSD analysis (Table 4) confirmed that in Eddy's hot plate and tail clip methods, statistically significant differences were observed between all treatment group pairs. Notably, in the tail immersion method, vortioxetine 5 mg/kg and vortioxetine 10 mg/kg showed comparable analgesic activity with no statistically significant difference between them (mean difference 0.50; 95% CI −0.56 to 1.56; p>0.05), suggesting a possible ceiling effect for this method at the tested doses. Tramadol remained significantly superior to both doses of vortioxetine across all three methods (p<0.05). [4]

Table 5: Summary of Analgesic Rankings

Method	Control (G1)	Tramadol (G2)	Vortioxetine 5 mg (G3)	Vortioxetine 10 mg (G4)
Eddy's Hot Plate (sec)	5.67 ± 0.52	12.67 ± 0.52	7.83 ± 0.75	10.17 ± 0.41
Tail Immersion (sec)	4.17 ± 0.41	11.17 ± 0.75	8.17 ± 0.41	8.67 ± 0.52
Tail Clip (sec)	2.67 ± 0.52	8.17 ± 0.41	6.00 ± 0.63	6.83 ± 0.41
Overall Rank	4th	1st	3rd	2nd

Table 5: Summary of mean ± SD response times (seconds) across all nociceptive assays with overall analgesic ranking of treatment groups.

Table 5 summarises the overall analgesic performance of each group. Tramadol 10 mg/kg ranked highest across all three methods, as expected for an established centrally acting opioid analgesic. Vortioxetine 10 mg/kg consistently ranked second, followed by vortioxetine 5 mg/kg, with the control group demonstrating the lowest response times. This dose-response relationship supports the hypothesis that vortioxetine exerts genuine, dose-dependent antinociceptive activity in mice. [3,4]

Discussion

The present study demonstrates that vortioxetine, a multimodal serotonergic antidepressant, possesses significant dose-dependent analgesic activity in Swiss albino mice as evaluated by three validated nociceptive assays. Both doses tested (5 mg/kg and 10 mg/kg oral) produced statistically significant increases in response time compared to vehicle control ($p<0.001$), with the 10 mg/kg dose exhibiting superior efficacy across all three methods. These findings are consistent with the known serotonergic and noradrenergic mechanisms of pain modulation at the level of the spinal cord and supraspinal structures. [2,4]

The pharmacodynamic basis for the observed analgesia is multifactorial. Vortioxetine's antagonism at 5-HT3 receptors in the dorsal horn suppresses descending facilitation of pain transmission, while its agonism at 5-HT1A receptors enhances descending inhibitory control. [4,13] Turan Yücel et al. (2021) demonstrated that the analgesic efficacy of vortioxetine in mice is mediated through 5-HT1A serotonergic, α-adrenergic, and opioidergic receptor pathways,4 consistent with the present observation of significantly elevated nociceptive thresholds in hot plate and tail immersion tests — models particularly sensitive to supraspinally and spinally mediated opioidergic and serotonergic analgesia respectively.

The tail clip method, which predominantly assesses spinal reflex-mediated nociception, also showed significant analgesic response to vortioxetine, suggesting involvement of spinal serotonergic and possibly noradrenergic pathways. [10,12] The dose-dependent response seen in this model further corroborates the receptor-mediated mechanism, as higher occupancy at analgesic receptors (5-HT1A, α2-adrenergic) with the 10 mg/kg dose would be expected to produce greater antinociceptive effect.

Tramadol, a centrally acting synthetic opioid analgesic with additional serotonin-norepinephrine reuptake inhibition, served as a positive control and demonstrated the highest analgesic response across all three assays, as anticipated. [16] The fact that vortioxetine 10 mg/kg approached — but did not match — tramadol's efficacy suggests that while the serotonergic and possible opioidergic contributions of vortioxetine are meaningful, the full opioid receptor agonist activity of tramadol remains pharmacodynamically superior in these acute pain models. This is clinically relevant because vortioxetine, lacking the abuse potential and respiratory depression associated with opioids, may offer safer long-term use in chronic pain management.

The clinical relevance of these findings is underscored by the well-established comorbidity of chronic pain and depression. Hauser et al. (2012) demonstrated the efficacy of antidepressants in fibromyalgia,5 and Dharmshaktu et al. (2012) reviewed the analgesic utility of multiple antidepressant classes. [15] Vortioxetine's potential advantage lies in simultaneously addressing affective symptoms and pain, potentially improving functional outcomes in this patient population. [11,16] Duloxetine, an SNRI, is already approved for diabetic neuropathy and fibromyalgia, [17,20] and the present results suggest that vortioxetine may warrant similar clinical investigation. A notable finding was the comparable analgesic efficacy of vortioxetine 5 mg/kg and 10 mg/kg in the tail immersion method ($p>0.05$), suggesting that the 5 mg/kg dose may have reached the maximum achievable effect in this particular assay, or that the tail immersion method may be less sensitive to the incremental pharmacodynamic differences between these doses. This plateau effect warrants further dose-ranging studies. The absence of significant spontaneous variation in baseline response time in the control group across the study period confirms the stability of the experimental conditions and the validity of the results.

Limitations of the present study include the relatively small sample size per group (n=6), acute to sub-acute experimental design (7 days) that does not fully model chronic pain states, and the lack of receptor-level mechanistic investigations such as receptor blockade studies with selective antagonists. Future studies should evaluate vortioxetine's analgesic potential in neuropathic and inflammatory pain models, examine the effect of longer-term dosing, and assess whether co-administration with opioids may produce synergistic analgesia while reducing opioid-related side effects. [3,9]

Conclusion

This study provides evidence that vortioxetine possesses significant, dose-dependent analgesic activity in Swiss albino mice across three nociceptive assay models — Eddy's hot plate, tail immersion, and tail clip methods. The magnitude of analgesia was dose-dependent (vortioxetine 10 mg/kg > 5 mg/kg), though inferior to tramadol 10 mg/kg. The analgesic mechanism is likely mediated through 5-HT1A agonism and 5-HT3 antagonism at spinal and supraspinal levels. [4,13] Given the increasing prevalence of chronic pain comorbid with depression and the limitations of existing analgesics, vortioxetine represents a promising candidate for analgesic adjuvant therapy. Clinical studies are warranted to translate these preclinical findings into therapeutic practice.

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