

Effect of Vortioxetine on Pilocarpine Induced Status Epilepticus in Sprague Dawley Rats

Shreya Hegde¹, Sharath Kumar C¹, Amrita Parida^{1,2*}, Jagnoor Singh Sandhu^{2,3}, Manju V⁴

¹Department of Pharmacology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka-576104, India

²Center for Animal Research, Ethics and Training (CARET), Manipal Academy of Higher Education, Manipal, Karnataka-576104, India

³Central Animal Research Facility, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka-576104, India

⁴Dr. TMA Pai Rotary Hospital, Karkala, Manipal Academy of Higher Education, Manipal, Karnataka-576104, India

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ABSTRACT

Background: Status epilepticus (SE) is a frequently encountered medical emergency that may not respond to existing antiepileptic medications, underscoring the urgency for exploring alternative treatment options. Vortioxetine, a novel multimodal antidepressant, modulates several serotonin receptors and has shown anticonvulsant potential in other seizure models. However, its role in SE remains unexplored.

Objective: The study assessed the impact of vortioxetine on seizure severity, onset latency, and 24-hour survival in a rodent model of status epilepticus using lithium-pilocarpine.

Methods: Twenty-four male Sprague Dawley rats were randomized into four groups: (1) disease control (distilled water), (2) standard treatment (diazepam, 5 mg/kg), (3) vortioxetine 10 mg/kg, and (4) vortioxetine 20 mg/kg. All groups received lithium chloride and pilocarpine to induce SE. Modified Racine scale was used to score the seizure severity. Latency to stage 4 seizures and SE, seizure scores, and 24-hour survival rates were assessed. The mean differences between groups was analyzed by one-way ANOVA. This was followed by Tukey's post hoc test to see the intergroup differences.

Results: All animals in the disease control and low-dose vortioxetine groups progressed to stage 5 seizures and SE, with 33.3% and 16.7% mortality, respectively. In the high-dose vortioxetine group, 83.3% developed SE with no mortality. Diazepam significantly delayed seizure onset, reduced severity, and prevented SE. Vortioxetine at both doses showed only marginal increases in seizure latency and no significant reduction in seizure severity or SE incidence compared to control.

Conclusion: Vortioxetine did not exhibit significant protective effects against lithium-pilocarpine-induced SE in Sprague Dawley rats at the doses tested. Its limited efficacy may be due to the complex pathophysiology of SE and the acute nature of the model. Further studies are warranted to explore its role in chronic epilepsy models or as adjunctive therapy.

Keywords: Vortioxetine, epilepsy, serotonin, pilocarpine model, anticonvulsant, rodent

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INTRODUCTION

Status epilepticus is a frequently encountered medical condition with an approximate yearly incidence of 1.3 to 74 cases/1,00,000 adults.¹ Conventionally, it was defined as either a single continuous seizure episode over thirty minutes or a series of seizure episodes without regaining consciousness between the episodes in a thirty-minute duration.² The current operational definition is "Continuous seizures lasting 5 minutes or longer, or two or more separate seizures with incomplete recovery of consciousness between them".^{3,4} The condition is linked to a high risk of mortality if not managed promptly. The pharmacological management of status epilepticus (SE) includes the use of specific antiseizure medications such as benzodiazepines, levetiracetam, fosphenytoin, and sodium valproate. However, a quarter of SE patients remain refractory to these

drugs, and this condition is termed as "refractory status epilepticus".⁵ These cases are managed with general anesthetic agents. Current medications are associated with distinct neurological and systemic side effects that can compromise patients' quality of life. Therefore, the currently approved drugs for SE are limited by their effectiveness and potential side effects, driving the need for better alternative agents.

Newer antidepressants agents which inhibit the reuptake of neurotransmitters like serotonin and norepinephrine are being studied for the management of epilepsy. This could be linked to the shared underlying pathological mechanisms between epilepsy and depression. These factors encompass neuroinflammation, disrupted monoaminergic and other neurotransmitter transmission, HPA axis dysregulation, and impaired neurogenesis.⁶ In animal models (genetically

*Author for Correspondence: amrita.parida@manipal.edu

Table 1: Different groups and treatment given

Group	Treatment given (through intraperitoneal injection)
Group 1 (Disease control)	Distilled water
Group 2 (Standard treatment group)	Diazepam (5mg/kg)
Group 3 (Test drug: lower dose)	Vortioxetine (10mg/kg)
Group 4 (Test drug: higher dose)	Vortioxetine (20 mg/kg)

epilepsy-prone rats and pilocarpine-induced SE in Wistar rats), reduced serotonergic and noradrenergic activity correlates with both increased seizure susceptibility and depression-like behaviors, emphasizing the role of serotonergic pathways in seizure vulnerability and psychiatric comorbidities associated with epilepsy.⁷ In patients diagnosed with temporal lobe epilepsy (TLE), positron emission tomography studies have shown reduced binding to 1A subtype of serotonin receptors in the lateral region of temporal lobe cortex,⁸ and in related animal models decreased postsynaptic 5-HT_{1A} signaling appears to result from lower extracellular serotonin rather than receptor loss.⁹ Enhanced stimulation of 5-HT_{1A} receptor signaling has been associated with both anticonvulsant and antidepressant outcomes, suggesting that these receptors have a suppressive function in the manifestation of seizures and depressive symptoms.¹⁰ Though older antidepressants are known to lower seizure threshold, there is no evidence to suggest that the newer agents precipitate seizures and may in fact elevate seizure thresholds in various experimental epilepsy models.¹¹⁻¹⁴

Vortioxetine is a novel antidepressant with multimodal activity that inhibits serotonin reuptake and interacts with various serotonin receptors—acting as a 5-HT_{1A} agonist, a 5-HT₃, 5-HT₇, and 5-HT_{1D} antagonist, and a partial agonist at the 5-HT_{1B} receptor.¹⁵ It is indicated for therapy of Major Depressive Disorder in adults.¹⁶ Nevertheless, the precise mechanism through which vortioxetine exerts its effects remains unclear. Due to its direct modulatory effects on the various serotonin receptors, its pharmacological actions are different from the other SSRIs. SSRIs desensitize presynaptic 5-HT_{1A} receptors creating negative feedback that may dampen their antidepressant efficacy. The 5-HT_{1A} receptors are located pre-synaptically, hence its inactivation creates negative feedback and is possibly responsible for their reduced antidepressant effects. With vortioxetine, this

desensitization is not seen, since it is an agonist of 5-HT_{1A} receptor.¹⁷ Yang et al, in their study demonstrated that stimulation of 5-HT₇ receptors in epileptic rats was associated with rise in frequency of seizures, which was effectively reduced by administering a 5-HT₇ receptor antagonist.¹⁸

Given the novel mechanism of action of vortioxetine, its possible role in epilepsy should be thoroughly assessed. Although few studies suggest its effectiveness in absence seizures and generalized tonic-clonic seizures (GTCS), it has not demonstrated efficacy in models of status epilepticus. Therefore, this study aimed to evaluate the effects of vortioxetine in a lithium-pilocarpine-induced status epilepticus (SE) model using Sprague Dawley rats.

MATERIALS AND METHODS

Materials

The drugs required namely, pilocarpine nitrate, lithium chloride (Sigma) and atropine sulphate (Merck Life Sciences Private Limited) were purchased from Durga Laboratories, Mangalore. Diazepam- 10mg/2mL injection (Brand name: Calmpose) and Vortioxetine-20 mg tablets (Brand name: Brintellix) were procured from hospital pharmacy.

Experimental Animals

An approval from the Institutional Animal Ethics Committee was sought prior to initiation of the study. The guidelines set by the Committee for the Control and Supervision of Experiments on Animals; India were followed during the conduct of the study. Twenty four Sprague Dawley rats of male gender, each around 250 grams in weight, were utilized. Three rats were housed in each cage. The study was carried out under controlled conditions with a 12-hour alternating light and dark cycle. Ambient conditions were maintained at 25 ± 3°C and approximately 50% relative humidity. A standard rat pellet diet from VRK Nutritional Solutions (Pune, India) was supplied, with drinking water available at all times.

Procedure

The 24 rats were randomly allotted into four groups, each containing six animals through simple randomization technique (Table 1). Prior to the experiment, all animals underwent a rotarod test to evaluate motor coordination. Since every rat showed normal neuromuscular function, no animals were excluded from the study.

Induction of Status Epilepticus: Each rat was administered lithium chloride at a dose of 3 mEq/kg through intraperitoneal route. Pilocarpine hydrochloride (30 mg/kg,

Table 2: Percentage of rats exhibiting various stages of seizures

Groups	% (n) of rats showing stage 4 (N=6)	% (n) of rats showing stage 5 (N=6)	% (n) of rats showing SE (N=6)	% (n) Mortality after 24 hours (N=6)
Group 1 (Disease control)	100	100	100	33.33 (2)
Group 2 (Standard treatment group)	33.33 (2)	0	0	0
Group 3 (Vortioxetine 10mg/kg)	100	100	100	16.66 (1)
Group 4 (Vortioxetine 20mg/kg)	100	83.33 (5)	83.33 (5)	0

i.p.) was injected 18 to 20 hours following the lithium chloride injection. Atropine sulfate (1 mg/kg, i.p.) was given thirty minutes prior to pilocarpine hydrochloride administration, to reduce the peripheral muscarinic actions of pilocarpine. Diazepam (3mg/kg; ip) and vortioxetine in dose of 10mg/kg and 20mg/kg i.p. were given to group 3 and 4 respectively, 24 hours prior to administration of pilocarpine injection. Drug dosages were determined using data from earlier research.^{19,20} For monitoring, each rat was kept in different cage.

Seizure Monitoring and Scoring

The time taken to get first seizure attack was noted in all animals. This indicated the latency of onset of seizures. The latency of onset of seizures was compared between control and treatment groups.

Severity Assessment, Observation, and Management

The severity of seizures was evaluated using a modified version of Racine's scale, with scores defined as follows: Seizure activity was evaluated using a slightly modified version of the Racine scale, with the following stages:²¹

1. Facial automatisms
2. Head nodding
3. Wet dog shakes and forelimb clonus
4. Tonic-clonic seizures accompanied by forelimb rearing
5. Rearing followed by loss of balance and GTCS.

The stage was recorded at the onset of the first seizure episode and used to compare outcomes across different experimental groups. The time taken to reach stage 4 seizures (characterized by tonic-clonic convulsions accompanied by forelimb rearing) was monitored. Rats that progressed to stage 4 seizures were closely observed for an additional hour after the onset of these convulsions. When the seizure activity was continuous or intermittent and persisted for at least 30 min, SE was considered. One hour after the appearance of stage 4/5 seizures, diazepam was administered to manage SE at a dose of 10 mg/kg, intraperitoneally. Additional doses were administered as and when needed till the seizures ceased to improve survival rates. The survival status of the animals, whether

they recovered or succumbed, was documented 24 hours post-experiment. The rats with status epilepticus were housed and maintained singly. Survival after 24 hours was also assessed and noted accordingly. Overall, the key parameters assessed included the latency to the first seizure episode (stage 4 or 5), outcome in terms of recovery or mortality, seizure severity score, and 24-hour survival rate.

Post Induction Care

Following seizure induction, rats were placed in individual, husk-free cages for 1–2 days, during which they were monitored until salivation subsided and recovery signs appeared. Two hours after receiving diazepam, the rats were administered 2 mL of normal saline. Close monitoring was conducted for at least a week following induction, as the rats did not consume food and exhibited signs of depression. Thereafter, to reduce the risk of dehydration and mortality, 0.9% saline was given through oral route (two times a day) every day for one week. Animals experiencing stage four and/or stage five seizures are at risk of developing repetitive seizures in the following days and were treated with sodium valproate 400mg/kg to prevent development of seizures. All surviving rats getting repeated seizures after seven days post-induction were subjected to euthanasia. At a dose of 120 mg/kg, thiopentone sodium given intraperitoneally was used for this purpose. The remaining animals were returned to the animal house. Since the initial results were not encouraging and it is single dose acute study, we did not proceed with histopathological examination of the tissues.

Statistical Analysis

“One-way ANOVA”, followed by “Tukey’s” post hoc test for multiple group comparisons was used for analysis of the data. Data analysis was done with SPSS software (version 20), and a *p*-value of less than 0.05 was indicative of statistical significance.

RESULTS

Seizure Staging and Mortality

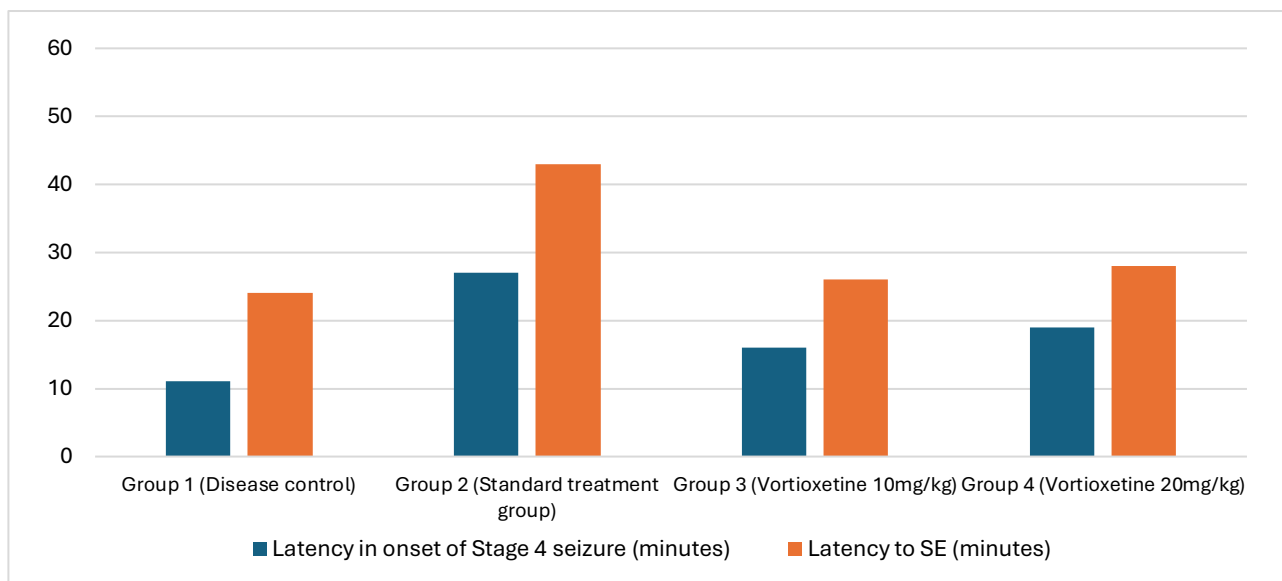


Figure 1: The latency for seizure onset and status epilepticus development

Table 3: Seizure score

Groups (n = 6 in each group)	Mean seizure score (Mean \pm SD)
Group 1 (Distilled water) Control	5
Group 2 (Diazepam)	3*
Group 3 (Vortioxetine 10mg/kg)	5
Group 4 (Vortioxetine 20mg/kg)	4 \pm 1.1

* $p < 0.001$ when compared with Group 1. One-way ANOVA followed by Tukey's post-hoc test was used to compare the means of different groups.

The results showed that all animals in the disease control group (Group 1) exhibited both stage 4 and stage 5 seizures, and 100% developed status epilepticus (SE), with a 24-hour mortality rate of 33.33% (Table 2). In contrast, the standard treatment group (Group 2; diazepam) showed a marked reduction in seizure severity, with only 2 rats (33.33%) reaching stage 4, and none progressing to stage 5 or developing SE. All animals in this group survived at 24 hours post-induction. In the vortioxetine-treated groups, both doses (10 mg/kg and 20 mg/kg) resulted in all rats reaching stage 4 seizures. In Group 3 (10 mg/kg), all animals also progressed to stage 5 and developed SE, with 1 mortality (16.66%). Group 4 (20 mg/kg) showed a slight improvement: while 100% reached stage 4, 5 out of 6 animals (83.33%) reached stage 5 and developed SE. However, no mortality was observed in this group. There was no statistically significant difference between the control and the group 3 and 4 values.

Latency to Seizure and SE Onset

Figure 1 summarizes the latencies to the onset of stage 4 seizures and SE. The disease control group showed the shortest latency to stage 4 seizures (11 minutes) and SE onset (24 minutes). Diazepam treatment significantly prolonged both latencies to 27 and 43 minutes, respectively. Vortioxetine treatment led to moderate increases in latency compared to control: Group 3 exhibited latencies of 16 minutes (stage 4) and 26 minutes (SE), while Group 4 showed 19 minutes (stage 4) and 28 minutes (SE). However, these increases were not statistically significant compared to standard treatment group.

Seizure Severity Score

The mean seizure score in the disease control group was 5. Diazepam treatment significantly reduced the seizure severity to a mean score of 3 ($p < 0.05$ vs. control). Vortioxetine at 10 mg/kg did not reduce seizure severity (mean score remained 5), while the higher dose (20 mg/kg) showed a slight numerical reduction to 4 ± 1.1 , which was not statistically significant (table 3).

DISCUSSION

Vortioxetine, due to its novel mechanism of action, has been studied for its antiseizure activity in the past through a few epilepsy models. A study carried out by Ögün MN *et al*, vortioxetine significantly reduced the penicillin-induced epileptic discharges with no difference from diazepam (standard treatment drug) in spike activity in rats compared

to controls.¹⁴ Vortioxetine delayed epileptic seizure onset times and reduced the total spike number and seizure severity in PTZ-induced kindling rat model. Improvement in cognitive deficits was also noticed in the vortioxetine group.²²

In our earlier investigation using the maximal electroshock seizure (MES) model, vortioxetine was found to significantly reduce the incidence of tonic hind limb extension compared to the control group. Additionally, rats treated with vortioxetine exhibited a notably shorter seizure duration. The compound demonstrated efficacy in decreasing both tonic hind limb extension (THLE) and seizure duration. Notably, these effects were comparable to those observed with diazepam, the standard reference drug, with no significant differences between the two treatment groups.²⁰

Vortioxetine reduced the mean spike frequency in a penicillin-induced seizure model, according to a study by Aygun *et al*. In PTZ induced seizure model, it was found to additionally increase the latency to seizure development and decreased the seizure duration. The anticonvulsant effect of the drug was attributed to the 5HT_{1A} receptor activation. However, in WAG/Rij rats with genetic absence epilepsy, an increase in spike-wave discharges and seizure duration was seen. This effect was observed at larger doses (5 mg/kg and 10 mg/kg) and not at a lower dose (1 mg/kg).²³ Keeping in mind the efficacy of vortioxetine in epilepsy, this study sought to investigate the potential of vortioxetine to prevent SE in the lithium-pilocarpine model in Sprague-Dawley rats with a focus on behavioral outcomes and seizure latency. The results demonstrated that vortioxetine did not produce significant improvements in behavioral parameters like approach response, touch response, loud noise response, and pick-up test when compared to the disease control group indicating the inability of the drug to provide acute neuroprotection following status epilepticus. Furthermore, latency to onset of stage 4 seizure and status epilepticus was not significantly delayed in the vortioxetine-treated groups. While there was a marginal numerical improvement compared to the disease group, the difference was not statistically significant. The above findings indicate that vortioxetine at both 10 mg/kg and 20 mg/kg body weight does not show anticonvulsant effect in status epilepticus model.

There may be several reasons for the ineffectiveness of vortioxetine in this particular model of status epilepticus. SE is a complex neurological ailment involving multiple pathophysiological mechanisms. GABAergic dysfunction is more strongly linked to the onset of SE, while the serotonin system may only contribute indirectly.^{24,25} In convulsive SE, evidence from both animal and human studies suggests dynamic changes in receptor expression, particularly the internalization of GABA receptors and increased surface expression of NMDA receptors. These alterations can significantly affect drug responsiveness over time. The serotonergic system, which vortioxetine primarily targets, may not alone be enough to prevent the complex, multifactorial events that lead to SE. Moreover, sustained seizure activity induces numerous physiological disturbances such as hypoxia, hypoglycemia, hyperthermia,

and cardiovascular instability that further complicates the treatment.²⁶ Secondly, the changes produced by vortioxetine, which likely involve long-term adaptations in serotonin signaling, may not be suited for acute, rapid-onset nature of SE. The acute nature of the lithium-pilocarpine model, which induces seizures within hours of the drug's administration, might not provide enough time for vortioxetine to exert its potential neuroprotective effects. Lastly, SE usually requires high doses of antiepileptic drugs, whereas in this study, a single dose was used which might have been ineffective. EEG recordings would have been more conclusive

In a case series reported by Siwek M et al, vortioxetine was administered to treat depressive symptoms in patients of epilepsy. Complete remission of depression was seen in all cases. In all cases where the antiepileptic treatment was optimized, there were no seizures observed after switch of treatment to vortioxetine.²⁷ These findings possibly suggest that vortioxetine, while effective in treating depression, didn't precipitate seizures in epileptic patients and can safely be used in them.

Therefore, based on existing evidence from animal models, vortioxetine appears to exert beneficial effects in focal epilepsy and generalized tonic-clonic seizures; however, it has not demonstrated efficacy in models of absence seizures or status epilepticus. The findings in the current study do not rule out the possibility that vortioxetine could be effective in preventing seizure-induced neurodegeneration. Future studies can explore the long-term effect of vortioxetine in other SE models. The effect of the drug in combination with other anticonvulsant drugs can be assessed. Examining the effect of vortioxetine in chronic epilepsy models may provide more insights into its potential neuroprotective properties.

In conclusion, while vortioxetine was ineffective in preventing SE in the lithium-pilocarpine model at the doses tested, these results contribute to the broader understanding of serotonin-based therapies therapy of epilepsy. Future research is required to explore the effect of combination therapy with existing anticonvulsant drugs, testing in alternative animal models to better learn the potential scope of serotonin modulators in treating epilepsy. The search for effective treatments for status epilepticus remains critical, and serotonin-based therapies may hold promise under varied conditions.

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