

Original Article

Investigating the role of brivaracetam in pain management: Insights from a vincristine-induced neuropathic pain model in rats

Vasanth K. S.¹, Manimekalai K.¹, Santhanalakshmi P.¹

¹Department of Pharmacology, Mahatma Gandhi Medical College and Research Institute affiliated with Sri Balaji Vidyapeeth deemed to be University, Puducherry, India.

***Corresponding author:**

K. S. Vasanth,
Department of Pharmacology,
Mahatma Gandhi Medical
College and Research Institute
affiliated with Sri Balaji
Vidyapeeth deemed to be
University, Puducherry, India.

vasanththedoctor@gmail.com

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ABSTRACT

Objectives: Neuropathic pain, characterised by abnormal pain processing, often arises due to nerve injury or chemotherapy-induced neurotoxicity. Current pharmacological interventions, including anticonvulsants and antidepressants, provide partial relief with adverse effects. Brivaracetam (BRV), a synaptic vesicle 2A ligand, has demonstrated neuroprotective effects in preclinical models. This study explores its potential analgesic properties in a vincristine-induced neuropathy model.

Materials and Methods: Rats were administered vincristine (0.1 mg/kg, intraperitoneally) for 10 days to induce neuropathy. BRV (10 mg/kg and 20 mg/kg) was administered daily for 14 post-induction. Behavioural assessments, including the von Frey filament test and hot plate test, were performed to evaluate mechanical and thermal hyperalgesia.

Results: Vincristine treatment resulted in significant hyperalgesia and nociceptive responses in the control group. BRV-treated rats exhibited significant improvement in pain thresholds compared to the control group ($P < 0.05$). This demonstrates the substantial antinociceptive properties. Furthermore, the comparative analysis indicated that BRV provides similar levels of pain relief as gabapentin, supporting its potential utility in pain management.

Conclusion: This study demonstrates BRV's potential in mitigating vincristine-induced neuropathic pain, warranting further clinical investigations. Its multimodal action could offer a novel approach to neuropathic pain treatment.

Keywords: Brivaracetam, Gabapentin, Hot plate, Peripheral neuropathy

INTRODUCTION

Peripheral neuropathy is commonly characterised by tactile allodynia. Tactile allodynia is characterised by pain in response to stimuli that are ordinarily non-painful stimuli, such as gentle touch or pressure, and is frequently seen in patients with neuropathic pain.^[1] Peripheral neuropathy is a disorder that damages the nerve cells and fibres in the extremities. There are various theories for the cause of neuropathic pain. Peripheral neuropathies can be broadly classified based on the type of nerve fibres affected: motor neuropathy (affecting muscle control), sensory neuropathy (causing altered sensations such as pain or numbness), autonomic neuropathy (involving involuntary functions like heart rate and digestion) or mixed neuropathies involving multiple types of nerves.^[2] The most common signs and symptoms of peripheral

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neuropathy are numbness and paraesthesia, accompanied by weakness, discomfort and loss of deep tendon reflexes.^[3] Neuropathic pain develops rapidly and progressively, taking months to years to show visible signs and symptoms. Neuropathic pain, showing distinct clinical features, can affect the central and peripheral nervous systems. Peripheral nerves comprise single or combined sensory, motor and autonomic functions. Neuropathic pain can affect the axons and the encasing myelin sheaths.^[4,5] Peripheral neuropathies are commonly categorised based on the underlying pathology into axonopathies and demyelinating neuropathies. In axonopathies, the primary damage occurs to the axons, often leading to a 'dying-back' pattern of nerve fibre degeneration. In contrast, demyelinating neuropathies involve damage to the myelin sheath surrounding the axon, resulting in slowed nerve conduction and characteristic conduction block patterns on nerve conduction studies.^[5] The categorisation of neuropathic pain shows definitive clinical and physiologic characteristics. Most diabetic patient have a chance of developing foot ulcers at least once in their lifetime. Diabetic peripheral neuropathy is one of the most common and serious complications of long-standing diabetes mellitus. It significantly increases the risk of foot ulceration due to impaired sensation and delayed wound healing. In severe or untreated cases, this may progress to infected ulcers and gangrene, often necessitating lower-limb amputation. These complications not only impair quality of life but also increase healthcare burden and mortality. Furthermore, neuropathic pain and decreased sensation may be associated with a variety of undesirable outcomes, such as depression, lower quality of life and restrictions in daily activities.

Globally, 2.4% of the human population suffers from neuropathic pain; in older age groups, the prevalence reaches up to 8.0%.^[6] Insulin-dependent and non-insulin-dependent diabetes mellitus are both associated with diabetic neuropathic pain, which affects approximately 50% of individuals with diabetes, often correlating with disease duration and glycaemic control.

Recent research indicates that peripheral nociceptive input alone is insufficient to sustain chronic neuropathic pain at the level of the posterior horn of the spinal cord. Instead, the persistence of pain involves central sensitisation and facilitative input from supraspinal structures such as the brainstem and thalamus, which modulate descending pain pathways.^[7] Hence, for researchers and physicians, understanding the mechanism involved in the evolution of peripheral neuropathy is a complex part, and therefore, treating neuropathic pain remains a challenging task.^[7,8]

Peripheral neuropathy is most commonly associated with diabetes mellitus, but other significant contributing factors include chronic alcohol consumption, chemotherapy-induced neurotoxicity (e.g. vincristine, taxanes and

isoniazid), nutritional deficiencies such as Vitamin B12 deficiency and certain infections or autoimmune conditions.^[9] Chemotherapy-induced peripheral neuropathy should be monitored since cancer patients suffering from pain should be eased by the medication and not subjected to any neuropathic pain with chemotherapy.

Although medications such as gabapentin and pregabalin^[10] are commonly prescribed for the management of peripheral neuropathic pain, clinical evidence suggests that they often provide only partial symptom relief and are associated with adverse effects such as sedation, dizziness and cognitive impairment, which may limit long-term adherence and overall patient satisfaction. It is imperative to look for more treatment modalities to improve the patient's outcome in peripheral neuropathy. Levetiracetam (LEV), an approved newer antiepileptic drug, has been proven in so many studies to be effective in neuropathic pain as compared with the standard drug gabapentin.^[11] Brivaracetam (BRV) is a next-generation anticonvulsant structurally related to LEV and is approved for the treatment of focal (partial-onset) seizures, with or without secondary generalisation, in patients with epilepsy. It exhibits a high affinity for synaptic vesicle protein 2A (SV2A), a mechanism thought to contribute to both its antiepileptic and potential antinociceptive properties.^[12] BRV is generally regarded as a safe and well-tolerated antiepileptic drug, demonstrating robust efficacy in controlling seizures across diverse patient populations.

BRV is a novel anti-epileptic drug that binds selectively to synapse protein SV2A and acts by inhibiting the sodium channel, altering the release of glutamate and GABA across the synapses.^[13] LEV, the newer antiepileptic drug, has an antinociceptive effect, considering the similarities between the pathophysiological phenomenon and mechanism observed in epilepsy and neuropathic pain models. Hence, the present study was planned to evaluate the antinociceptive efficacy of BRV in rat models for peripheral neuropathy using the *in vivo* nociceptive behavioural model, Eddy's hot-plate test.

MATERIALS AND METHODS

Animals

The study was conducted at the Central Animal Facility of Mahatma Gandhi Medical College and Research Institute (MGMCRI), Puducherry, which is registered with the Committee for Control and Supervision of Experiments on Animals (CCSEA), Government of India. Wistar albino rats weighing 180–200 g were procured from a CCSEA-approved animal breeding centre and housed in the central animal house of MGMCRI. The animals were quarantined for 1 week before the study's commencement to adapt to the new environment. The animals were housed in polypropylene

cages under standard laboratory conditions (12-h light/dark cycle, temperature $22\pm 2^\circ\text{C}$ and relative humidity $55\pm 10\%$) with free access to standard pellet diet and water ad libitum. The experimental protocol was approved by the Institutional Animal Ethics Committee. All efforts were made to minimise the number of animals used and to reduce their pain and discomfort, following the principles of ethical animal research and the CCSEA guidelines.

Drugs, chemicals and equipment

- Rats were procured from the Biogen lab, Bangalore
- BRV and vincristine were procured from Sigma Aldrich Company, Bangalore
- Gabapentin was purchased from a local pharmacy
- All other chemicals and reagents used in the study were of analytical grade and were procured from SD Fine Chemicals, Chennai, India.

Ethical clearance

The study was approved by the Institutional Animal Ethics Committee (IAEC) of the Mahatma Medical College and Research Institute, Puducherry. (Letter No: 04/IAEC/MG/04/2023-I).

Grouping and experimental design

After 1 week of acclimatisation, 30 healthy male Wistar albino rats (weighing 180 ± 20 g) were randomly assigned to 5 groups ($n = 6$ per group). The antinociceptive effects of the test and standard drugs were evaluated using Eddy's hot plate test, a widely accepted method for assessing thermal nociception in neuropathic pain models. All the rats were fed with standard chow and RO water ad libitum.

Induction of peripheral neuropathy

Peripheral neuropathy was induced by administering vincristine at a dose of $50 \mu\text{g}/\text{kg}$ intraperitoneally, once daily for 10 consecutive days, following the established protocol described by Siau and Bennett (2006).^[14]

Treatment

Following neuropathy induction, the animals were divided into 5 groups ($n = 6$ each) and treated as follows:

- Group I (normal control): Received distilled water (DW) orally for 10 days
- Group II (neuropathic control): Continued to receive vincristine ($50 \mu\text{g}/\text{kg}$, i.p.) for 14 days
- Group III (standard treatment): Received gabapentin ($60 \text{ mg}/\text{kg}$, p.o.) for 14 days
- Group IV (BRV1 - low dose): Treated with BRV ($0.3 \text{ mg}/\text{kg}$, i.p.) for 14 days

- Group V (BRV2 - high dose): Treated with BRV ($3 \text{ mg}/\text{kg}$, i.p.) for 14 days.

All the drugs were dissolved in DW and administered according to the body weight using an intraperitoneal route for vincristine and BRV, followed by gabapentin using an oral gavage needle between 9 and 10 am till the end of the study period. The behavioural tests (hot-plate test) were assessed starting from day 0 (before treatment) and subsequently on days 1, 3, 6, 9, 12, 15, 18 and 21. On day 22, the animals were sacrificed.^[15]

Study parameters

Behavioural tests

Behavioural pain tests (thermal hyperalgesia) were carried out 30 min after administration of Vincristine. The rats were acclimatised to the experimental room, and the surface of each piece of equipment was used 30 min before each test to reduce fear and anxiety in the animals.

Thermal hyperalgesia test

Thermal hyperalgesia was assessed using a hotplate test model. The development of thermal hypersensitivity associated with neuropathic pain was measured chronologically using the paw withdrawal latency (PWL) of the rat placed on the surface of the hotplate maintained at $55^\circ\text{C} \pm 0.5^\circ\text{C}$. The PWL was recorded as the time taken by each rat to either lick its hind paw or jump from the hot plate surface, indicating a nociceptive response. A cutoff time of 30 s was imposed on each animal to avoid paw tissue injury.

Statistical analysis

The collected data were entered into Microsoft Excel 2013 and subsequently analysed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 26.0. Statistical comparisons between groups were performed using one-way ANOVA, followed by the Bonferroni *post hoc* test. $P < 0.05$ was considered statistically significant.

RESULTS

Animal characteristics

Description of the Wistar albino rat sample

A total of 30 healthy male Wistar albino rats, each weighing between 180 and 200 g at the start of the experiment, were included in the study. The rats were housed in groups of six, providing an environment conducive to social interaction while allowing for easy monitoring of health and behaviour. Throughout the acclimatisation period and subsequent experimental phases, the animals exhibited normal feeding

and grooming behaviours, indicating their well-being. All animals remained healthy with no significant adverse reactions noted from the vincristine treatment before establishing neuropathy.

Effects of treatments

Efficacy of gabapentin and BRV (low and high dose) in vincristine-induced neuropathic pain

The efficacy of treatment was evaluated through Eddy's hot plate test, measuring PWL in each group over the 21-day trial period. Baseline measurements taken on Day 0 indicated comparable pain thresholds across all groups before the induction of neuropathy. Following vincristine administration, the control group (Group 2) exhibited a significant reduction in PWL, confirming the successful induction of neuropathic pain.

Groups receiving gabapentin (Group 3) showed a gradual increase in PWL from Day 1 to Day 21, reaching statistical significance when compared to the control group ($P < 0.01$). Both low-dose BRV (Group 4) and high-dose BRV (Group 5) demonstrated notable increases in PWL compared to the control, with the high-dose group exhibiting the most significant improvement ($P < 0.001$) on the final assessment day.

The treatment effects on Day 21 are summarised as follows:

- Group III (Gabapentin, 60 mg/kg): Showed an improvement in PWL
- Group IV (BRV low dose: 0.3 mg/kg): Demonstrated significant improvement
- Group V (BRV high dose, 3 mg/kg): Produced the highest latency response, indicating superior antinociceptive activity.

The detailed time-course data comparing all groups for the acute post-treatment assessment (0 min) is presented in Figure 1. The antinociceptive effect was consistently observed across all subsequent time points (20 min, 60 min, and 90 min), as further illustrated in Figures 2-4, respectively.

Comparative analysis

Comparative evaluation of BRV and gabapentin in neuropathic pain management

On comparing the efficacy of BRV against gabapentin, statistical analysis revealed significant difference in PWL improvements between the two active treatment groups (Gabapentin vs. high-dose BRV, $P > 0.05$). However, both treatments were significantly more effective than the control group and were able to ameliorate pain behaviours in the model of vincristine-induced neuropathy.

Summary of findings

The findings of this study indicate that both BRV, at low and high doses, and gabapentin possess antinociceptive properties in the context of vincristine-induced neuropathic pain. These findings support the potential of BRV as an effective therapeutic candidate for the management of neuropathic pain, particularly in chemotherapy-induced models. However, further preclinical and clinical investigations are warranted to validate its efficacy, explore underlying mechanisms and assess its translational applicability.

DISCUSSION

A broad spectrum of ailments originating from injuries or disorders of the somatosensory nerve system, primarily involving the peripheral and central nervous system, has been designated as pain caused by neurons. Neuropathic pain is characterised by a range of symptoms including dysesthesia (unpleasant abnormal sensations), hyperalgesia (increased sensitivity to painful stimuli) and allodynia (pain due to normally non-painful stimuli), which significantly impair patients' quality of life.^[16]

Neuropathic inflammation associated with damage to the peripheral nerves is likely to be the most problematic kind since it frequently responds poorly to therapy, making it particularly difficult to manage clinically.^[17]

Neuropathic pain is managed using a variety of pharmacological agents, including antidepressants, anticonvulsants and opioids. Among anticonvulsants, racetams – a class used mainly in epilepsy – exert their effects through a distinct mechanism involving SV2A modulation, which may also confer antinociceptive properties, as observed in preclinical pain models.^[18]

Compared to LEV, BRV is a different racetam anticonvulsant that has gained popularity due to its higher antiseizure effectiveness and less off-target effects. In 2004, BRV was originally described as a configurational derivative of LEV, except for one propyl group that set it apart from the parent molecule.^[19,20]

This study compared the antinociceptive effect of BRV by inducing peripheral neuropathy using vincristine for 10 days. And then, the standard drug (Gabapentin) and test drug (BRV 1 and 2) were administered for 14 days. The drug was withdrawn after the 14th day, and animals were observed and evaluated from day 0 till the 21st day. The BRV doses (0.3 mg/kg and 3 mg/kg) were selected based on prior experimental models assessing seizure and neuropathic behaviour. In a landmark study by Tai and Truong (2007), BRV showed maximal anti-seizure and anti-myoclonic efficacy in rats at 0.3 mg/kg with no significant dose-dependent improvement beyond that dose. This potency is

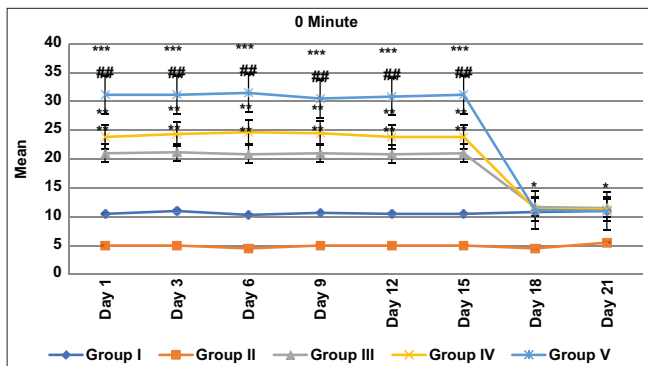


Figure 1: Comparison of antinociceptive effect of brivaracetam on Eddy's Hot Plate at 0 min. Data represent mean (%) ± scanning electron microscopy ($n=6$); * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ when compared to neuropathic control with gabapentin, brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg; ## $P<0.01$ compared to gabapentin with brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg.

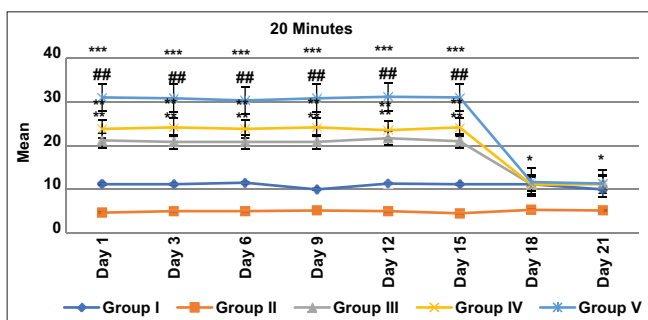


Figure 2: Comparison of antinociceptive effect of brivaracetam on Eddy's Hot Plate at 20 min. Data represent mean (%) ± scanning electron microscopy ($n=6$); * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ when compared to neuropathic control with gabapentin, brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg; ## $P<0.01$ when compared to gabapentin with brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg.

attributed to its high-affinity binding to SV2A and additional sodium channel modulation. Therefore, the selected doses in our study represent the lower yet pharmacodynamically active range validated in rodent models of CNS dysfunction.^[21] This study revealed that BRV has reduced peripheral neuropathy in Wistar albino rats. For lowering peripheral neuropathy, the racetam group of drugs LEV is useful. A study by Tsymbalyuk *et al.* reported that decreased spinal cord neuroinflammation is correlated with significant results for BRV on peripheral neuropathic behaviour. When given before the first episode of neurological pain and when the pain has become fully apparent, BRV shows positive results.^[20]

We demonstrated the development of neuropathy through Vincristine, which was administered for 10 days, and after inducing peripheral neuropathy with vincristine, the standard and test drugs were administered. After that, all the

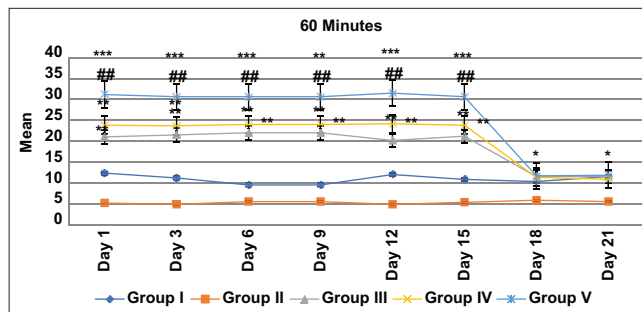


Figure 3: Comparison of antinociceptive effect of brivaracetam on Eddy's Hot Plate at 60 min. Data represent mean (%) ± scanning electron microscopy ($n=6$); * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ when compared to neuropathic control with gabapentin, brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg; ## $P<0.01$ when compared to gabapentin with brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg.

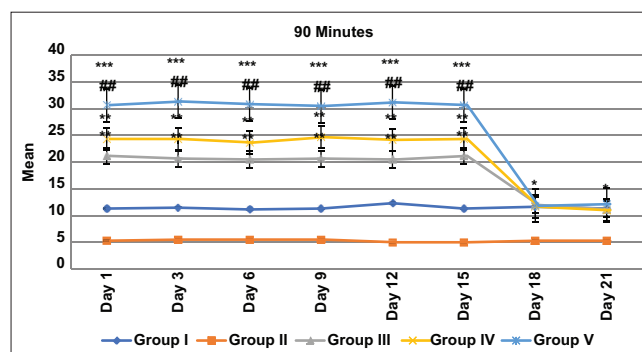


Figure 4: Comparison of antinociceptive effect of brivaracetam on Eddy's Hot Plate at 90 min. Data represent mean (%) ± scanning electron microscopy ($n=6$); * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ when compared to neuropathic control with gabapentin, brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg; ## $P<0.01$ when compared to gabapentin with brivaracetam low dose, 0.3 mg/kg and brivaracetam high dose, 3 mg/kg.

rats were evaluated for pain threshold latency using Eddy's hot plate test from Day 0 to Day 21.

The results show that groups treated with BRV with both low and high doses showed antinociceptive properties from the day of administration. Hence, the anti-nociceptive effect of BRV was evident with an increase in the time of the response of the Wistar albino rats. Vincristine was given for 14 days and was stopped for the reversal of peripheral neuropathy in Wistar albino rats.

Gabapentin and BRV treatment were given for 14 days, and the experiment was continued for 21 days to see whether there was a reduction in peripheral neuropathy compared to the disease control group. Hence, the results demonstrated that the BRV 2 (high dose) group had higher significance than the standard control. This shows that BRV has antinociceptive effects in peripheral neuropathy-affected rats.

The BRV 1 (low dose) group has also shown significant results when compared to the standard control group. Compared to the BRV 2 (high dose), the BRV 1 has less significance. It shows that a lower dose also has a significant effect, but it has a lesser effect when compared to a higher dose.

No significant effects were seen in the vincristine-induced peripheral neuropathy group, and both doses of BRV (BRV 1 and BRV 2) showed significant results. These findings showed the anti-nociceptive effects. Ozcan *et al.*^[15] reported that LEV had reduced peripheral neuropathy.

Then, all the drugs were discontinued after the 14th day, and the rats were evaluated till the 21st day with the same experiment. After withdrawing treatment drugs, when compared to the normal group rats, peripheral neuropathy was reversed in all the Vincristine-induced groups except the neuropathy control rats.

The standard, BRV1 and BRV2 group rats tests were performed in parallel to the normal control group rats, in which the rats were able to withstand the pain threshold latency in Eddy's hot plate, which was equal to that of the normal control group, whereas the neuropathic control rats could not withstand the pain threshold when compared to normal control rats.

With all these results obtained from our *in vivo* animal studies, the behavioural test shows that BRV has an anti-nociceptive effect, recommending a novel therapeutic potential in peripheral neuropathy after further clinical trials.

CONCLUSION

To summarise, the study drug v a third-generation antiepileptic racetam derivative showed better results than the standard Gabapentin and the control group in alleviating the parameters used to check the anti-nociceptive property. Both BRV groups achieved a statistical significance with $P < 0.05$ in reducing the nociception in Eddy's hot plate test. The rats were also able to withstand the pain threshold in the thermal stimuli, which also added the supporting point that BRV has an anti-nociceptive property.

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Ethical approval: The research/study was approved by the Institutional Animal Ethics Committee (IAEC) of the Mahatma Medical College and Research Institute, approval number 04/IAEC/MG/04/2023-I, dated 7th April 2023.

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