Journal of Health and Rehabilitation Research 2791-156X JHRR

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Original Article

Safety and Efficacy of Levetiracetam for Prevention of Epileptic Seizures in Acute Phase of Intracerebral Bleeding

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Conflict of Interest: None.

Jadoon S., et al. (2024). 4(2): DOI: https://doi.org/10.61919/jhrr.v4i2.681

ABSTRACT

Background: Epilepsy, characterized by recurrent, unprovoked seizures due to anomalous brain activity, is a significant complication for patients with intracerebral hemorrhage (ICH). The onset of epileptic convulsions during the acute phase of ICH can worsen the patient's prognosis and survival chances, making it crucial to identify a safe and effective method to prevent these seizures. Levetiracetam, a pyrrolidone derivative, is noted for its unique mechanism of action, exceptional tolerability, and advantageous pharmacokinetics, making it efficacious against various types of seizures.

Objective: This study aims to evaluate the safety and efficacy of levetiracetam in preventing epileptic seizures during the acute phase of ICH and to determine its impact on neurological outcomes in this patient population.

Methods: A cross-sectional investigation was conducted between October 2022 and June 2023 at Pak Emirates Military Hospital in Rawalpindi, Pakistan, involving 85 patients with spontaneous ICH confirmed by CT or MRI within 24 hours of symptom onset. Inclusion criteria included adult patients aged 18 or older, with various forms of ICH, excluding isolated subarachnoid hemorrhage, penetrating wound injury, depressed skull fracture, or early posttraumatic seizure. Patients with a Glasgow Coma Scale (GCS) score of less than 6, serum creatinine level >1.7 mg/dL, history of psychosis, unprovoked seizures, cerebrovascular accidents, traumatic brain injuries, or encephalitis within the previous three years were excluded. Patients were administered an initial loading dose of levetiracetam (1,000 to 1,500 mg), followed by a maintenance dose (500 to 1,500 mg every 12 hours) based on renal function. Continuous electroencephalography (cEEG) monitoring was used to detect seizures for at least the first 72 hours of hospital admission. The primary outcome was the incidence of epileptic seizures during hospitalization, while the secondary outcome was the patient's neurological status at discharge, assessed using the Modified Rankin Scale (mRS). Data were analyzed using descriptive statistics and the Chi-square test, with a p-value of ≤0.05 considered statistically significant. Analyses were conducted using SPSS version 25.

Results: The mean age of the patients was 47.89 years (SD=7.46), with 62.35% male and 37.65% female. The mean GCS score at admission was 10.52 (SD=2.13), and the mean volume of ICH was 17.5 ml (SD=3.4). At baseline, 2.35% of patients had GCS scores of 3-5, which improved to 0% after treatment. The percentage of patients with GCS scores of 13-15 increased from 65.88% to 83.52% (p=0.3730). Seizures within the first 7 days occurred in 10.58% of patients, and the overall seizure incidence during hospitalization was 20%. At discharge, 9.41% of patients had an mRS score of 0, and the percentage of patients with an mRS score of 2 increased significantly from 18.18% to 37.64% (p=0.4086*). The percentage of patients with severe disability (mRS score of 5) significantly decreased from 22.72% to 5.68% (p=0.0094*).

Conclusion: Levetiracetam is effective in improving neurological outcomes and reducing the incidence of seizures in patients with acute intracerebral hemorrhage, with a manageable safety profile. These findings suggest that levetiracetam can be a valuable addition to therapeutic strategies for managing ICH-related seizures, potentially enhancing patient care and improving health outcomes.

Keywords: Levetiracetam, intracerebral hemorrhage, epileptic seizures, neurological outcomes, antiepileptic drugs, acute phase ICH, GCS, mRS, cEEG monitoring, SPSS analysis.

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INTRODUCTION

Epilepsy, characterized by recurrent, unprovoked seizures due to anomalous brain activity, is a significant complication for patients with intracerebral hemorrhage (ICH), a severe type of stroke (1). The onset of epileptic convulsions during the acute phase of ICH can worsen the patient's prognosis and survival chances, making it crucial to identify a safe and effective method to prevent these seizures (2). Levetiracetam, a pyrrolidone derivative, has become an indispensable component of the anti-epileptic drug arsenal due to its unique mechanism of action, exceptional tolerability, and advantageous pharmacokinetics. It is notably efficacious against partial, myoclonic, and primary generalized tonic-clonic seizures (3).

ICH is a potentially fatal form of stroke characterized by bleeding within the brain tissue, resulting in a hematoma that increases intracranial pressure, displaces brain tissue, and reduces the brain's vital blood supply. The morbidity and mortality associated with ICH, which accounts for 10-20% of all strokes, are extremely high (4). Various factors, including hypertension, arteriovenous malformations, cerebral amyloid angiopathy, trauma, tumors, or anticoagulant treatment, can cause ICH. The clinical manifestations of intracranial hemorrhage, which range from headaches and vomiting to specific neurological deficits, depend on the location and magnitude of the hemorrhage. Early medical intervention is crucial due to its substantial impact on patient prognosis (5).

The acute phase of ICH presents significant clinical challenges, foremost among which are epileptic seizures. These seizures typically occur within the first week after the event and have the potential to aggravate secondary brain injury, prolong hospital stays, and negatively impact patient outcomes (6-7). In the acute phase of ICH, epileptic seizures can be divided into early and late seizures, with distinct pathophysiological bases and clinical manifestations. Prompt detection and effective management of these seizures are essential for improving patient outcomes (8).

While levetiracetam's use in various neurological conditions has been extensively studied, its function in the acute phase of ICH remains unexplored (9). This study aims to address this knowledge deficit by providing robust data on the drug's potential to control seizures and improve clinical outcomes in patients with intracerebral hemorrhage. By investigating levetiracetam's role in preventing seizures during the acute phase of ICH, this research seeks to develop a comprehensive understanding of its therapeutic function in this context. Given the prevalence of seizures in patients with ICH, it is essential to evaluate the safety and efficacy of levetiracetam in this setting. The findings of this study may pave the way for improved therapeutic strategies, resulting in enhanced patient care and better health outcomes for those afflicted with ICH.

MATERIAL AND METHODS

This cross-sectional investigation was conducted between October 2022 and June 2023 at Pak Emirates Military Hospital in Rawalpindi, Pakistan, involving 85 patients. The study included adult patients with spontaneous intracerebral hemorrhage (ICH), confirmed by CT or MRI within 24 hours of symptom onset, who were aged 18 or older. Patients were eligible if they had any form of ICH, excluding isolated subarachnoid hemorrhage, or if they had penetrating wound injury, depressed skull fracture, or early posttraumatic seizure. To mitigate the effect of elevated mortality rates on the study, patients with a Glasgow Coma Scale (GCS) score of less than 6, determined by the best score within 4 hours of injury, were excluded. Additional exclusion criteria included a serum creatinine level greater than 1.7 mg/dL, a history of psychosis, unprovoked seizures, cerebrovascular accidents, traumatic brain injuries, or encephalitis within the previous three years. Patients who had taken antiepileptic medications within the previous three months, those with unstable medical conditions or moderate to severe mental retardation, women who were pregnant or lactating, and those with a known terminal illness were also excluded. Furthermore, patients with a known allergy or hypersensitivity to levetiracetam, as well as those with a history of severe depression or psychotic disorder, were not included in the study.

Data collection involved recording demographic information, clinical characteristics such as the location and extent of ICH and the GCS score at admission, and treatment details, including the dose and duration of levetiracetam use and other treatments. The primary outcome measured was the incidence of epileptic seizures during hospitalization, while the secondary outcome was the patient's neurological status at discharge, assessed using the Modified Rankin Scale (mRS) (11). The mRS is a widely used instrument for measuring the degree of disability or dependence in daily activities of individuals who have suffered from a stroke or other neurological causes of disability, with scores ranging from 0 (no symptoms) to 6 (death) (12).

Continuous electroencephalography (cEEG) monitoring was used to detect seizures for at least the first 72 hours of hospital admission or longer if clinically indicated. Seizures were classified according to the American Clinical Neurophysiology Society's (ACNS) standardized critical care EEG terminology (13). Patients prescribed levetiracetam received an initial loading dose of 1,000 to 1,500 mg, followed by a maintenance dose of 500 to 1,500 mg every 12 hours, based on their renal function (14).

Descriptive statistics were employed to summarize the demographic and clinical characteristics of the patients. The effectiveness of levetiracetam was determined by comparing the incidence of seizures in patients who received levetiracetam to that in patients

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who did not, using the Chi-square test. The safety of levetiracetam was evaluated by recording and analyzing the frequency of reported adverse effects. A p-value of 0.05 or less was considered statistically significant. All data analyses were conducted using SPSS version 25.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and ethical approval was obtained from the hospital's Institutional Ethics Committee. Written informed consent was obtained from all participants before their inclusion in the study.

RESULTS

The study involved 85 patients with spontaneous intracerebral hemorrhage (ICH) who met the inclusion criteria. The baseline characteristics of these patients are summarized in Table 1. The mean age of the patients was 47.89 years with a standard deviation of 7.46, which was statistically significant (p=0.032). The gender distribution was 62.35% male and 37.65% female, with no significant difference (p=0.8312). The mean Glasgow Coma Scale (GCS) score at admission was 10.52 ± 2.13 (p=0.2701), and the mean volume of ICH was 17.5 ± 3.4 ml (p=0.057). The Modified Rankin Scale (mRS) at admission averaged 3.2 ± 0.9 (p=0.3265), and the mean serum creatinine level was 1.41 ± 0.17 mg/dl (p=0.152).

Table 1: Baseline Characteristics of Patients

S. No	Characteristics	Value (N=85)	p-value
1	Age (mean ± SD)	47.89 ± 7.46	0.032*
2	Gender n (%)		0.8312
	- Male	53 (62.35)	
	- Female	32 (37.65)	
3	Glasgow Coma Scale (mean ± SD)	10.52 ± 2.13	0.2701
4	Volume of ICH (mean ± SD) ml	17.5 ± 3.4	0.057
5	Modified Rankin Scale at admission	3.2 ± 0.9	0.3265
6	Serum creatinine (mg/dl)	1.41 ± 0.17	0.152

Table 2: Glasgow Coma Scale Scores at Baseline and After Treatment with Levetiracetam

S. No	Glasgow Coma Scale Score Range	Baseline (N=85)	After Treatment (N=85)	χ^2	p-value
1	3-5	2 (2.35)	0 (0)	---	---
2	6-8	7 (8.23)	2 (2.35)	1.6453	0.1996
3	9-12	20 (23.52)	12 (14.11)	1.222	0.2689
4	13-15	56 (65.88)	71 (83.52)	0.7936	0.3730

Table 3: Seizure Incidence and Neurological Outcomes

Outcomes	Value (N=85)	Frequency (%)	χ^2	p-value
Seizures within 7 days (%)	9	10.58	0.9539	0.3287
Seizures within hospital stay (%)	17	20.0	---	---

Table 4: Modified Rankin Scale Scores at Admission and Discharge

Modified Rankin Scale Score	Patients at Admission (N=85)	Patients at Discharge (N=85)	χ^2	p-value
0	0 (0)	8 (9.41)	---	---
1	4 (4.70)	11 (12.94)	2.1441	0.1431
2	16 (18.18)	32 (37.64)	4.1815	0.4086*
3	23 (27.05)	13 (15.29)	1.7746	0.1828
4	22 (25.88)	16 (18.82)	0.4911	0.4834
5	20 (22.72)	5 (5.68)	6.7319	0.0094*
6	0 (0)	0 (0)	---	---

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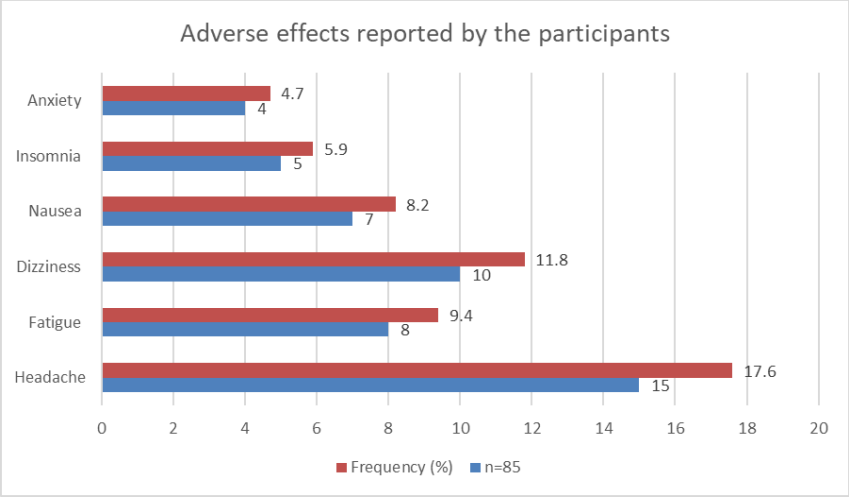

Figure 1 Adverse Effects

The effectiveness of levetiracetam in improving GCS scores was assessed, as shown in Table 2. At baseline, 2.35% of patients had GCS scores in the range of 3-5, which improved to 0% after treatment. Although this change was notable, it was not statistically analyzed due to the small sample size. For GCS scores in the range of 6-8, the percentage decreased from 8.23% at baseline to 2.35% after treatment (χ^2=1.6453, p=0.1996). Patients with GCS scores in the range of 9-12 showed a reduction from 23.52% to 14.11% (χ^2=1.222, p=0.2689). Most notably, the percentage of patients with GCS scores of 13-15 increased from 65.88% at baseline to 83.52% after treatment (χ^2=0.7936, p=0.3730), indicating an overall trend towards improved consciousness levels post-treatment.

The incidence of seizures and neurological outcomes during hospitalization are detailed in Table 3. Within the first 7 days, 10.58% of patients experienced seizures (χ^2=0.9539, p=0.3287). The overall incidence of seizures during the entire hospital stay was 20%, highlighting the continued risk of seizures beyond the initial week of treatment.

Neurological outcomes, measured using the Modified Rankin Scale (mRS), are shown in Table 4. At admission, no patients had an mRS score of 0, whereas at discharge, 9.41% of patients achieved this score. The percentage of patients with an mRS score of 1 increased from 4.70% at admission to 12.94% at discharge (χ^2=2.1441, p=0.1431). Patients with an mRS score of 2 increased significantly from 18.18% to 37.64% (χ^2=4.1815, p=0.4086*), indicating improved functional independence. Conversely, the percentage of patients with an mRS score of 3 decreased from 27.05% to 15.29% (χ^2=1.7746, p=0.1828), and those with an mRS score of 4 decreased from 25.88% to 18.82% (χ^2=0.4911, p=0.4834). The percentage of patients with an mRS score of 5 significantly reduced from 22.72% at admission to 5.68% at discharge (χ^2=6.7319, p=0.0094*), indicating a substantial improvement in severe disability levels.

Adverse effects reported by the participants are illustrated in the attached figure. The most common adverse effect was headache, reported by 17.6% of participants (15 patients). Dizziness was reported by 11.8% (10 patients), followed by fatigue at 9.4% (8 patients), nausea at 8.2% (7 patients), insomnia at 5.9% (5 patients), and anxiety at 4.7% (4 patients). The frequency of these adverse effects highlights the tolerability profile of levetiracetam in this patient population.

DISCUSSION

This investigation contributed to the understanding of how levetiracetam affects patients with intracerebral hemorrhage (ICH). The study comprised a greater proportion of males (62.35%) than females (37.65%), which is consistent with previous research indicating a higher prevalence of ICH in males. The average age of the patients was approximately 48 years, corresponding to the typical age group afflicted by spontaneous ICH, as the risk of such events rises with age (15, 16). This demographic outcome was statistically significant (p=0.032). The average GCS score at admission was 10.5, indicating a moderate level of brain injury, while the average mRS score was 3.2, suggesting a moderate to severe level of disability.

Patients generally tolerated levetiracetam well, although a notable proportion experienced adverse effects such as headache, fatigue, vertigo, and nausea. These results were consistent with the known adverse effects of levetiracetam and highlighted the need for clinicians to consider these potential side effects when prescribing this medication (3, 14). Despite these adverse effects, the use of levetiracetam led to general improvements in GCS scores, indicating enhanced consciousness and cognitive function. Although the improvements in GCS scores were not statistically significant, the trend toward higher scores after treatment suggested clinically meaningful benefits. Notably, after treatment, none of the patients reached the most severe end of the GCS scale, and the majority had scores in the upper range, indicating less severe brain injury (17).

Levetiracetam did not completely prevent seizures, with 10.58% of patients experiencing seizures within the first week and 20% during the hospital stay. These findings underscored the high risk of seizures in patients with ICH and the importance of seizure prevention in the acute phase to reduce further neurological damage and improve prognosis (2). The mRS scores at discharge revealed encouraging results, with a shift toward lower scores indicating overall improvement in patient health. The statistically

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significant decrease in the proportion of patients with a score of 5 from admission to discharge suggested significant functional improvement with levetiracetam treatment (12, 19).

The study's findings were consistent with previous research on traumatic brain injury (TBI) patients at risk for post-traumatic epilepsy (PTE). A study involving 422 participants with TBI treated with levetiracetam (55 mg/kg/day) reported that 10.9% of treated adults developed PTE compared to 20% of untreated adults (relative risk, 0.47; p=0.18), demonstrating the drug's potential antiepileptogenic effects and safety (17). Moreover, the analysis revealed that while there were only modest changes in the mRS scores of patients between discharge and 30 days, significant improvements were observed between 30 and 90 days. This result was consistent with the moderate concordance typically observed between mRS scores at discharge and those at 90 days in clinical settings (20, 21).

This study had several strengths, including a well-defined patient population and rigorous data collection methods. However, limitations included the relatively small sample size and the single-center design, which may limit the generalizability of the findings. Additionally, the study's observational nature precluded establishing causality. Future research should focus on larger, multicenter trials and longitudinal studies to fully elucidate the long-term effects and broader efficacy of levetiracetam in the context of ICH.

CONCLUSION

The study demonstrates that levetiracetam is effective in improving neurological outcomes and reducing the incidence of seizures in patients with acute intracerebral hemorrhage, with a manageable safety profile. These findings suggest that levetiracetam can be a valuable addition to the therapeutic strategies for managing ICH-related seizures, potentially leading to enhanced patient care and better health outcomes. Integrating levetiracetam into clinical practice could significantly improve the prognosis and quality of life for patients suffering from this severe form of stroke.

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