Original Article

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Linezolid-associated Hyponatremia in Guillain-Barré Syndrome Patients in Intensive Care Unit: A Retrospective Analysis

Internal Medicine Section

SHWETA SURESH NAIK[1], MATHANGI KRISHNAKUMAR[2], S MOULEESWARAN[3], VJ RAMESH[4]

ABSTRACT

Introduction: Guillain-Barré Syndrome (GBS) is a neurological disorder associated with ascending paralysis due to damage to the peripheral nerves by the immune system. Hyponatremia is the most common electrolyte disorder encountered in patients with GBS admitted to the Neurointensive Care Unit (NICU). Hyponatremia is associated with a poor outcome, prolonged hospital stay, and increased hospital cost. Linezolid is an oxazolidinone antibiotic used against gram-positive bacteria. The main adverse effect limiting its use is the development of myelo suppression; however, it can also cause hyponatremia.

Aim: To investigate the incidence of hyponatremia in GBS patients treated with linezolid.

Materials and Methods: This was a retrospective study conducted in a 14-bedded NICU at the National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India, over a period from January 2017 to January 2018. All patients with GBS who received linezolid therapy were included in the study. Out of 46 admitted patients, 16 received linezolid therapy. Final data were available for 12 patients. Hyponatremia was defined as sodium <134 mmol/L, and severe hyponatremia was defined as sodium <128 mmol/L. Descriptive statistics were used to characterise the data. The Wilcoxon signed-rank test was used to compare sodium levels before and after linezolid therapy. A p-value <0.05 was considered significant.

Results: The incidence of hyponatremia was 9 out of 12 (75%). Five out of 12 patients had severe hyponatremia. There was a significant decrease of 11 (7-12) mmol/L in sodium level before and after linezolid therapy (p<0.001). The median days to develop hyponatremia were 3 (2-4) days after initiation of therapy. No mortality was observed in the study population.

Conclusion: The incidence of hyponatremia is high in GBS patients treated with linezolid in the NICU. It is imperative to monitor sodium levels at frequent intervals in patients treated with linezolid to recognise and treat hyponatremia.

Keywords: Antibiotic, Neurological disorder, Oxazolidinone

INTRODUCTION

Hyponatraemia is the most common electrolyte disturbance seen in a hospital setting, significantly influencing patient outcomes in terms of morbidity and mortality. Hyponatraemia is defined as sodium <134 mmol/L, and severe hyponatraemia is defined as sodium <128 mmol/L [1,2]. The common causes include fluid shifts, renal and cardiac failure, drug-induced, and infections. It contributes to higher hospital costs, longer duration of hospital stay, and increased re-admission rates. The incidence of hyponatraemia in hospitalised patients ranges from 3-35% [1]. The incidence in neurologically ill patients is reported to be as high as 50% [2,3].

The etiology of hyponatraemia is multifactorial; Syndrome Of Inappropriate Antidiuretic Hormone secretion (SIADH) and Cerebral Salt-Wasting Syndrome (CSWS) are the most common causes in patients with neurological problems [3]. SIADH is characterised by hypervolemia or normovolemia due to the inappropriate secretion of ADH, resulting in dilutional hyponatraemia. On the other hand, CSW is associated with the loss of sodium and water in the urine, resulting in hypovolemia and hyponatraemia [3].

GBS is an inflammatory polyradiculopathy characterised by acute flaccid paralysis with or without sensory/autonomic nerve dysfunction. Approximately, 30% of patients with GBS require mechanical ventilation or management in the ICU [4]. The incidence of hyponatraemia in patients with GBS is as high as 48%, and it is associated with severe disability and a worse prognosis [5]. The most common cause of hyponatraemia in GBS is SIADH, and risk factors such as age, co-morbidities, sodium levels, and the use of Intravenous Immunoglobulin (IVIG) further increase the risk [5]. The pathophysiology of SIADH in GBS is not clearly understood. It has been attributed to enhanced renal tubular sensitivity to vasopressin and abnormalities in peripheral autonomic afferent fibers [5]. Hyponatraemia occurring in the setting of GBS is usually associated with severe clinical states. It can present with mild clinical symptoms to life-threatening adverse effects. It is important to eliminate potential modifiable risk factors for hyponatraemia to improve clinical outcomes. Patients with GBS are also at an increased risk of infection requiring antibiotics, as most of the patients admitted to the ICU require mechanical ventilation [6].

Linezolid is an oxazolidinone antibiotic used in the treatment of infections caused by gram-positive cocci. It is effective against Vancomycin-Resistant Enterococci (VRE), Methicillin-Resistant *Staphylococcus aureus* (MRSA), and highly penicillin-resistant *S.pneumoniae*. However, its usage is limited due to adverse events such as myelosuppression [7]. Linezolid has been shown to cause vomiting, nausea, lactic acidosis in select patients, and hyponatraemia has been reported in a few cases [8]. The mechanism of hyponatraemia caused by linezolid is unknown and has been attributed to SIADH [9]. The development of linezolid-induced hyponatraemia is influenced by several risk factors. Linezolid exposure, as the most direct factor, can increase the likelihood of hyponatraemia, especially with extended or high-dosage use. Age plays a role, with older individuals, particularly those over 65, being at a higher risk. Baseline sodium levels in the patient's blood are important, as individuals with low levels are more predisposed. High C-reactive protein levels, indicative of inflammation, can also elevate the risk of developing hyponatraemia when initiating linezolid treatment [10,11]. In patients with GBS, linezolid is initiated in the NICU for the treatment of infections, especially MRSA. This study aimed to investigate the incidence of hyponatraemia in GBS patients treated with linezolid in the Neuro Intensive Care Unit (NICU).

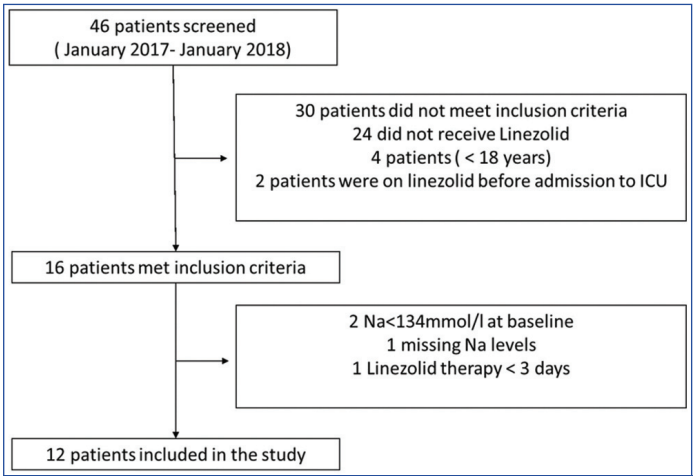
MATERIALS AND METHODS

This was a retrospective cohort study conducted in a 14-bed tertiary NICU at the National Institute of Mental Health and Neurosciences, Bengaluru Karnataka, India. The study population comprised all patients diagnosed with GBS who were admitted to the NICU between January 2017 and January 2018 and were treated with 1200 mg of linezolid for at least three days. GBS was diagnosed using lumbar puncture and nerve conduction studies according to the institutional protocol. The study was granted an institutional ethical clearance waiver due to its retrospective nature.

Inclusion criteria: Those patients with availability of serum sodium (Na) values at least three days prior to the initiation of linezolid therapy or those with more than one serum sodium value available after the initiation of linezolid therapy until completion or those undergoing linezolid therapy in the NICU were included in the study.

Exclusion criteria: Patients under the age of 18 years, pregnant patients; and 3) patients whose Na levels were less than 134 mmol/L before the initial administration of linezolid.

During the study period, 46 patients with a diagnosis of GBS were admitted to the NICU. Sixteen patients received linezolid, and those patients were included in the study. Two patients were excluded: one had Na levels below 134 mmol/L prior to linezolid treatment, one received linezolid for less than three days, and one patient did not have a recorded Na level during linezolid therapy [Table/Fig-1].



[Table/Fig-1]: CONSORT Flow diagram.

The patients' medical records of 12 patients who received Linezolid therapy were retrospectively reviewed. The following clinical data recorded before linezolid treatment were extracted: gender, age, blood investigations including haemoglobin, total leukocyte count, platelets, serum albumin, alanine aminotransferase, alkaline phosphatase, total bilirubin, serum creatinine, Blood Urea Nitrogen (BUN), serum potassium, serum chloride, and serum sodium.

The levels of serum sodium recorded during the duration and termination of linezolid therapy were also documented. Treatment details such as plasmapheresis, cumulative fluid balance, drug therapies received, and time to first abnormal sodium (Na <134 mmol/L) during linezolid therapy were also noted. Concomitant drugs that may influence sodium levels, such as antibiotics, diuretics, steroids, antiplatelets, anticoagulants, and antihypertensive therapy, as defined by previous reports, were also recorded. The STROBE cross-sectional reporting guidelines were used [12].

Outcome Measure

Hyponatremia is defined as Na <134 mmol/L, and severe hyponatremia is defined as Na <128 mmol/L after the initiation of linezolid therapy.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software, version 21.0 (IBM, Armonk, NY, USA). Quantitative data were expressed as mean±SD or median (IQR), and qualitative data were expressed as a number or percentage. Baseline characteristics were analysed using descriptive statistics. Pair sample differences were compared using the Wilcoxon signed-rank test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The baseline demographic characteristics of the population are described in [Table/Fig-2]. The patients were predominantly males with a mean age of 39.6±15.9 years. All patients received the injectable form of linezolid. The concomitant drugs used during linezolid therapy are listed in [Table/Fig-3]. The most commonly used drug was carbapenems. The concomitant drug use did not increase the occurrence of hyponatremia. All patients received plasmapheresis as treatment for GBS. The most common condition for linezolid therapy was pneumonia (41.6%), urinary tract infection (33.3%), and bloodstream infection (25%).

Characteristic	Values (Mean+SD)
Demographic data	
Age (Years)	39.6±15.9
Sex (Male/Female)	9/3
Baseline laboratory investigations	
Baseline Sodium (mmol/L)	139.3±3
Haemoglobin (g/dL)	11.6±1.8
White blood cell count (cells/mm^3)	11.7±4.7
Platelet (/MicroL)	309.8±110
Albumin (g/dL)	3.3±0.7
Alaninetransaminase (U/L)	42.6±43
Aspartate transaminase (U/L)	30±24
Bilirubin (mg/dL)	0.6±0.3
Creatinine (mg/dL)	0.5±0.3
Blood urea nitrogen (mg/dL)	20.5±15.8
Potassium (mmol/L)	4.0±0.5

[Table/Fig-2]: Demographic and baseline laboratory investigations.

Drugs	n
Carbapenems	8
Fluoroquinolones	2
Trimethoprim-sulfamethoxazole	2
Antifungal agents	2
Loop diuretics	1
Potassium-sparing diuretics	1
β-Blockers	1
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers	1
Calcium blockers	1
Steroid	0
Nonsteroidal anti-inflammatory agents	5
Diabetes drugs	1
Proton pump inhibitors	12
Aspirin	1
Warfarin	2
Heparin	10
Antihistamines	1
Albumin	3

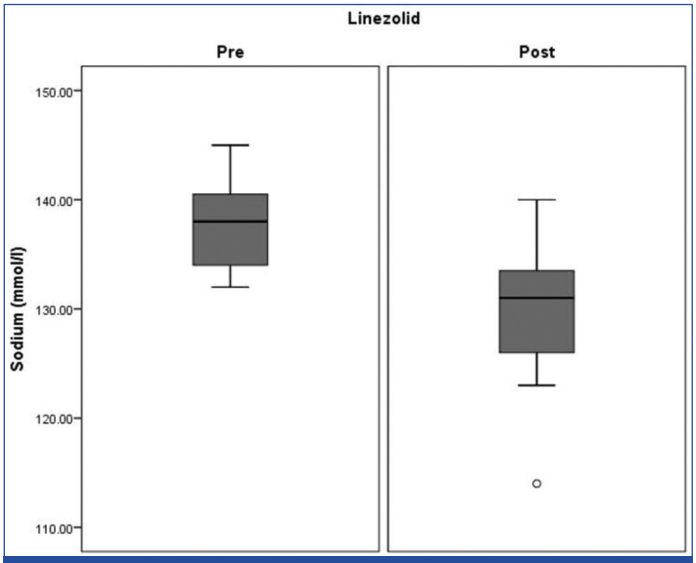
[Table/Fig-3]: Concomitant drugs used with Linezolid.

The average duration of linezolid therapy was 6 (5-7) days.

The incidence of hyponatremia and severe hyponatremia was 75% and 41.6%, respectively. The clinical characteristics of patients who developed hyponatremia are shown in [Table/Fig-4]. The average time to develop hyponatremia was 3 (2-4) days after the initiation of linezolid therapy. There was a significant difference in sodium levels pre and post linezolid treatment (p-value- 0.0001) [Table/Fig-5]. The median pre-sodium levels were 140 mmol/L (136-141), and post-sodium levels were 128 mmol/L (124-130). There was no mortality observed in the NICU among the study population.

Patient No.	Baseline (mmol/L)	Lowest value during linezolid treatment (mmol/L)	% change	Duration of linezolid therapy (days)	Time to hyponatremia after linezolid (days)	Therapy received
1	143	133	6.9	7	3	Saline therapy, Fludrocortisone
2	141	130	7.8	6	3	Fluid restriction
3	138	132	4.3	7	2	Nil
4	136	128	5.8	5	2	Saline therapy
5	140	128	8.5	7	3	Saline therapy
6	140	133	5	14	4	Nil
7	136	124	8.8	3	2	Saline therapy
8	135	114	15.5	4	2	Saline therapy, tolvaptan
9	141	123	12.7	5	3	Saline therapy, tolvaptan

[Table/Fig-4]: Clinical details of patients with hyponatremia.



[Table/Fig-5]: Effect of linezolid therapy on sodium.
p=0.0001

DISCUSSION

Hyponatremia is an important electrolyte disorder in the NICU [2]. It can have devastating complications if not recognised and treated. It is not a disease entity per se but rather a complication arising from disturbed salt-water homeostasis during a disease process. The common causes of hyponatremia include SIADH, CSWS, drug-induced, adrenal insufficiency, cardiac failure, and liver cirrhosis [13,14]. In neurological patients, it is challenging to identify the cause of hyponatremia. Therefore, understanding other mechanisms and factors that increase the occurrence of hyponatremia is important. In this retrospective analysis, the present aim was to study the incidence of hyponatremia in GBS patients treated with linezolid.

In the present study, the authors found the incidence of hyponatremia in GBS patients treated with linezolid to be 75% (9/12), with 41.6% (5/12) experiencing severe hyponatremia. Previous studies have reported the incidence of hyponatremia in GBS ranging from 11.8% to 48% [15,16]. In a study analysing risk factors for poor outcomes in GBS, hyponatremia was independently associated with adverse discharge disposition, increased hospital cost, mortality, and prolonged hospital stay [16,17]. The study also identified increased age, alcohol intake, anaemia, hypertension, and immunoglobulin therapy as other risk factors associated with hyponatremia [17].

SIADH is diagnosed in approximately 5% of GBS patients, and studies have shown a temporal relationship between the occurrence of hyponatremia and flaccid paralysis [18]. The mechanism of hyponatremia in GBS is predominantly attributed to SIADH, although other causes such as CSWS, autonomic dysfunction, and pseudo hyponatremia due to immunoglobulin therapy have also been reported [4,13,19]. In the present study population, all patients received plasmapheresis and were euvolemic, eliminating the possibility of pseudohyponatremia or CSW as potential causes for hyponatremia. These findings are consistent with studies that have shown SIADH as the most common cause in the ICU [20].

The much higher incidence observed in the present study could be attributed to the presence of an additional risk factor, namely linezolid therapy. Previous studies have shown the incidence of linezolid-associated hyponatremia to be up to 18% [11]. The occurrence of severe hyponatremia is very rare, reported to be less than 2% in a few studies [9]. However, in the present study, the incidence of severe hyponatremia was 41.6%. Previous studies have used a cut-off of Na <123 to define severe hyponatremia, while in the present study, the authors used a cutoff of Na <128 mmol/L [5,14,17].

Another possibility is the additive effect of linezolid and GBS in the pathogenesis of hyponatremia.

The mechanism of linezolid-induced hyponatremia remains unknown. Previous case reports of patients who developed hyponatremia during linezolid therapy suggest inflammation, SIADH, and renal salt wasting as the main mechanisms [7,21,22]. Linezolid may exacerbate the development of hyponatremia by interacting with serotonin receptors, directly stimulating ADH release, or affecting natriuretic peptide levels. The precise mechanism is still unclear, and the dominant pathogenesis may depend on the patient's clinical condition, volume status, and other concomitant drugs [21,22].

Important risk factors for linezolid-induced hyponatremia, based on previous studies, include high C-reactive protein levels, elderly patients, lower body weight, low baseline sodium levels, and co-administration of potassium-sparing diuretics [9-11]. In the present study, the patients were young, had minimal use of diuretics, and had normal baseline sodium levels. The incidence of gram-positive infections has been rapidly increasing, and with emerging drug resistance, treatment options are becoming limited [23]. These organisms cause various infections, such as pneumonia, urinary tract infections, and bloodstream infections, particularly in patients admitted to the NICU [6]. With the rising incidence of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and VRE, the use of linezolid is expected to increase in the future.

The findings of the present study, along with the existing literature, suggest that in patients with GBS, where the incidence of hyponatremia is already high, additional contributing factors like linezolid can further increase the burden of hyponatremia.

Hyponatremia in GBS is associated with worse outcomes. Therefore, it is crucial to monitor sodium levels more frequently in patients receiving linezolid therapy. It is also important to identify the exact etiology of hyponatremia so that appropriate treatment, such as vasopressin receptor antagonists for SIADH, mineralocorticoids for cerebral salt wasting, or saline therapy for renal losses, can be implemented. This approach will help reduce the disease burden and improve clinical outcomes in GBS patients treated with linezolid.

Limitation(s)

The study had several limitations. Firstly, the diagnosis of hyponatremia was based solely on the absolute value of sodium, and the clinical severity of hyponatremia was not recorded. Secondly, due to the retrospective nature of the study, the available sodium levels for analysis were not uniform, and it was not possible to determine the specific cause of hyponatremia, such as SIADH, CSW, or other aetiologies. Thirdly, the study did not assess the outcomes of the patients, and there was no comparative group for comparison. Lastly, due to the limited sample size, not all potential risk factors for hyponatremia could be studied.

CONCLUSION(S)

The incidence of hyponatremia is high in GBS patients treated with linezolid in the NICU. Hyponatremia is a multifactorial condition and significantly influences outcomes. While the risk factors for hyponatremia in GBS are predominantly non-modifiable, such as age, disease severity, and associated co-morbidities, this study has identified a potentially modifiable risk factor: linezolid therapy. It is imperative to monitor sodium levels frequently in patients treated with linezolid to recognise and treat hyponatremia. Hyponatremia is the most common electrolyte imbalance observed in the NICU, with a higher incidence in GBS. Linezolid-associated hyponatremia has been reported sparsely in the literature. However, this study is the first to highlight the importance of recognising linezolid as a contributing factor to hyponatremia in patients with GBS. In this subset of patients, monitoring and treating hyponatremia is crucial, as it serves as a prognostic indicator.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India.
2. Assistant Professor, Department of Anaesthesia, St. John's Medical College Hospital, Bengaluru, Karnataka, India.
3. Assistant Professor, Department of Anaesthesiology, Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai, Maharashtra, India.
4. Professor, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Mathangi Krishnakumar,
Surgical Intensive Care Unit, Department of Anaesthesia, 2nd Floor, St. Johns Medical College Hospital, Bengaluru-560034, Karnataka, India.
E-mail: mathz89@gmail.com

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