Delirium in Critically Ill Patients and the Potential Role of Vitamin B Supplements in the Management of Delirium

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ABSTRACT:

Background: Delirium is a symptom of acute brain dysfunction, which is frequently observed in patients with critical illness and is linked to poor clinical outcomes.[1] This study was performed to observe and compare the response of Vitamin B supplements (either Thiamin or combined Vitamin B1+B6+B12 supplements) in the management of delirium in critically ill patients in the level 2 critical care area.

Method: This randomized control trial was conducted in the adult HDU of a multidisciplinary hospital in Bangladesh from 16-Oct-2022 to 15-Oct-2023. The study included 2104 patients admitted during this period with 'sepsis' with 'delirium', confirmed by 4AT delirium assessment tool and DSM-V criteria. Patients showing cognitive improvement on correction of sepsis were excluded. Data of all groups were analyzed using chi-squared test.

Result: Addition of Vitamin B supplements showed statistically significant cognitive improvement compared to patients with no supplement (163/204 vs 54/100, p<0.001). Better clinical improvements were observed in patients receiving combined Vitamin B (B1+B6+B12) supplements in comparison to patients receiving thiamin alone (84.6% vs 75%).

Conclusion: Small number of studies and their heterogenicity make it impossible to draw conclusions confirming the use of thiamin or vitamin B combination supplement as the best option in the prevention and treatment of delirium in critically ill patients. More large-scale, high quality randomized control trials are required to confirm the beneficial effects of these vitamins.

Key Words: Delirium, Critically ill, Bangladesh, Vitamin B, Acute Medicine & HDU

INTRODUCTION:

Delirium, a sign of acute brain dysfunction is widely seen among patients with critical illness and is linked to poor clinical outcomes, including cognitive decline. The prevalence of delirium has been reported to be as high as 74% in critically ill patients with many of these patients needing prolonged hospitalization.[2] The high incidence of delirium in the critical care setup inspired the 'Acute Medicine and HDU team' of a tertiary care hospital of Bangladesh to form an integrated approach to CNS monitoring and delirium management in critically ill patients.

Non-pharmacological interventions like active prevention, removal of modifiable risk factors, and early detection of delirium symptoms are highly effective in the management of delirium.[3] Evidence based medicine analysis to date have not identified an effective pharmacological strategy. Thus, there is a need to develop a safe, effective and affordable pharmacological strategy for the management of delirium in critically ill patients. In our work,

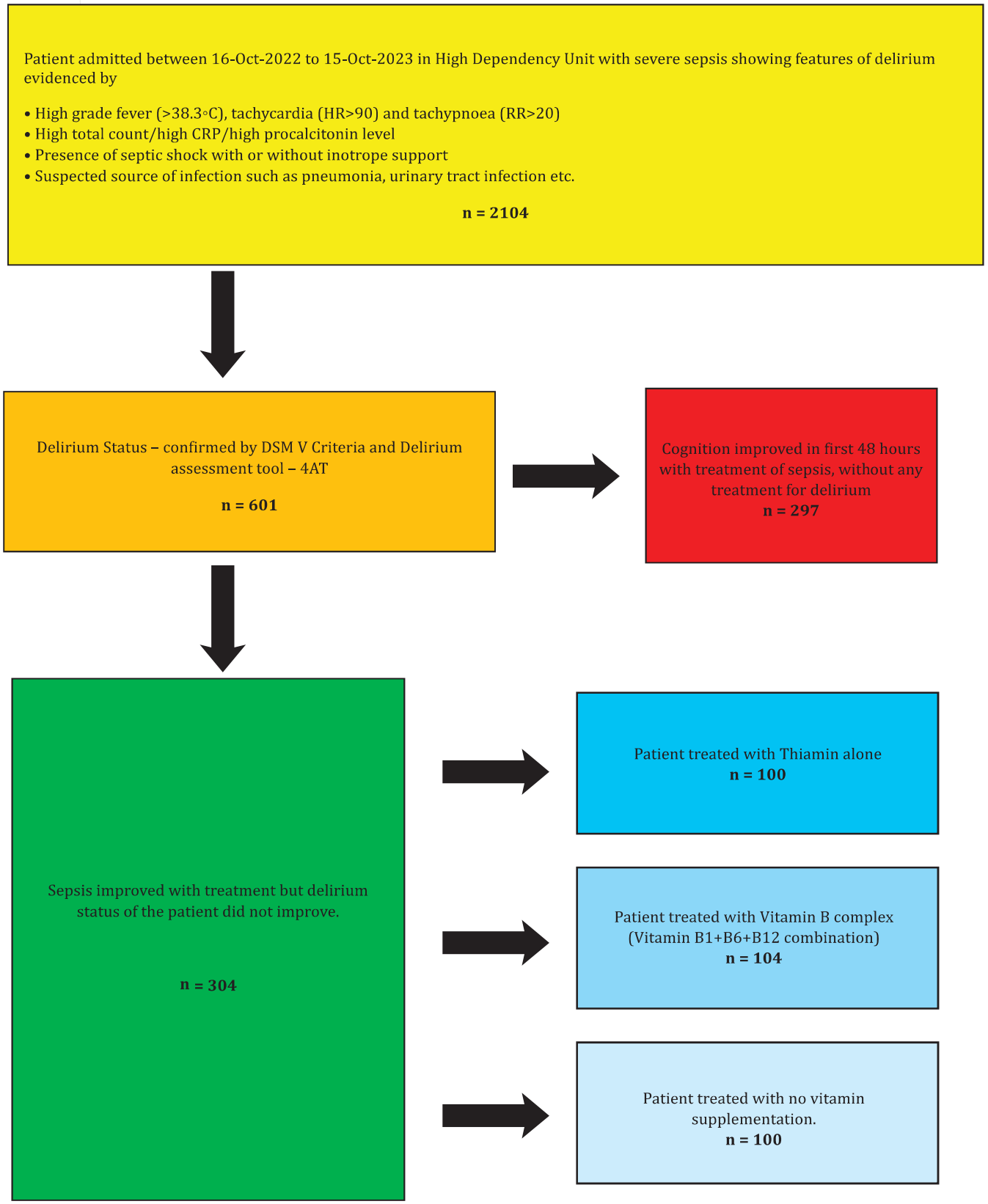

Fig-1: Flow chart of the study of Role of Vitamin B supplements in the management of delirium

Study on Delirium Assessment and Role of Vitamin B in management of delirium

Name	**Diagnosis**
Age	
Sex	
HN	

Presenting complaints	**History of malnutrition**	Yes	No
	History of vomiting	Yes	No
	Any recent starvation	Yes	No
	Recent diet control	Yes	No
	Vegetarian	Yes	No
	H/O alcoholism	Yes	No

Delirium Assessment tool - 4AT = 12 (Score 4 or more = Delirium; Score 1-3 = cognitive impairment)

1. Alertness – This includes patient who are markedly drowsy (difficult to rouse and/or obviously sleepy); ask the patient to state their name and address to assist rating.

	Normal	Mild sleepiness for <10 seconds after waking	Clearly abnormal
D1	0	0	4
D5	0	0	4

2. AMT4 (Abbreviated Mental State)– Age, Date of Birth, place (name of hospital), current year

	Normal	1 mistake	2 or more mistakes/untestable
D1	0	1	2
D5	0	1	2

3. Attention – Ask the patient "Please tell the month of the year backwards, starting at December"

	Achieves 7 or more months	Starts but scores <7 months/ refuses	Untestable (very unwell/ drowsy)
D1	0	1	2
D5	0	1	2

4. Acute change or Fluctuations course – evidence of significant change or fluctuation in alertness, cognition, other mental function (e.g. – paranoia, hallucinations) arising over last 2 weeks and still evident in last 24 hours

D1	No	0	Yes	4
D5	No	0	Yes	4

Fig-2: Assessment chart of Delirium using 'Delirium assessment tool – 4AT'

DSM-V Criteria for Delirium		
Criteria A	A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).	
Criteria B	The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.	
Criteria C	An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).	
Criteria D	The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.	
Criteria E	There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.	

Fig-3: Assessment of Delirium using 'DSM-V criteria'

Management

- Trailed Thiamin
- Trailed B1+B6+B12 combination
- Vitamin B not given.

Outcome after 5 days	Improved	Not – improved

Receiving Doctor		Releasing doctor	
Date		Date	

Fig-4: Management trial of Delirium with vitamin supplements and assessment of cognitive improvement

we focused on patients admitted in the high dependency unit (HDU) who showed features of delirium and their improvement following administration of different forms of vitamin B.

AIMS:

To observe cognitive improvement in critically ill patients following administration of vitamin B and compare the response to Thiamin and combined vitamin B (B1+B6+B12) supplement in the management of delirium in critically ill patients in the level 2 critical care area (HDU).

METHODS:

This randomized control trial was conducted in the adult HDU of a multidisciplinary hospital in Bangladesh from 16-Oct-2022 to 15-Oct-2023.

The study included 2104 patients admitted during this period with 'sepsis' and 'delirium'. Delirium status was confirmed by 4AT Delirium assessment tool4 and DSM-V criteria.5 Patients showing cognitive improvement on correction of sepsis were excluded. Ethical clearance for this study was obtained from the hospital; as no personal data nor identifiable information was used in the project, patient consent was waived.

DATA COLLECTION & ANALYSIS:

During the period of study, patients of HDU, admitted with sepsis (due to any cause) with delirium were included in the study (n=2104). They were assessed for delirium using 'DSM-V Criteria' and '4AT Delirium assessment tool' [Fig-2&3]. Patients fulfilling the criteria of delirium were enlisted and 'delirium score' of each patient was recorded on admission and at 48 hours (n=601).

Patients showing improvement of cognitive function within first 48 hours of starting treatment for sepsis were excluded from the study (n=297). The remaining patients (n=301) were divided into 3 groups where patients were chosen randomly. The first 2 groups were given either thiamin or combined vitamin B (B1+B6+B12) supplement with regular medicine [Fig-4]. The third group was treated without any vitamin B supplement during the treatment period. The clinical response of the delirium status of these patients following treatment were observed and documented.

Data of all three groups were compiled and analyzed using chi-squared calculator (Table 1&2)

RESULT:

i) The test compared between patients with delirium receiving either form of vitamin B or no vitamin at all. There was a statistically significant difference of outcome observed with patients showing much better cognitive improvement receiving Vitamin B supplementation (p=<0.001). (Table 1)

ii) Our second analysis compared patients with delirium receiving Thiamin alone with patients receiving Vitamin B (B1+B6+B12) combination. Although there was no statistical difference, better clinical improvements were observed in patients who were given combination of Vitamin B (B1+B6+B12) supplements in comparison to patients who were given thiamin alone (84.6% vs 75%). (Table 2)

DISCUSSION:

Delirium is defined as a disturbance of consciousness characterized by a sudden onset (hours or days) and a fluctuating course of orientation accompanied by a change in perception or cognition. Delirium impairs patient`s ability to receive, process, store and recall information.[6]

The pathogenesis of acute mental disorders in critical care patients such as delirium is multifactorial.

Table 1: Comparison between patients with delirium receiving either form of vitamin B or no vitamin at all.

Type	Improvement	No Improvement	*p-value*
Vitamin B	**163**(79.9%)	**41** (20.1%)	***p* = < 0.00001**
No Vitamin	**54**(54%)	**46** (46%)	

Table 2: Comparison of patients with delirium receiving Thiamin alone with patients receiving Vitamin B (B1+B6+B12) combination

Type	Improvement	No Improvement	*p-value*
Thiamin	**75** (75%)	**25** (25%)	P = 0.086672
Vitamin B1+B6+B12	**88** (84.61%)	**16** (15.38%)	

One of the hypotheses assumes that the series of events starts with a generalized inflammatory reaction, endothelial dysfunction, increased permeability of the blood-brain barrier and reduced cholinergic control over the inflammatory response, which combined with the body debility, predispose to the development of inflammatory changes in the nervous tissue, damage to neurons and overreactive responses of microglial cells.[7]

Deficiency of micronutrients causes a significant decrease in the activity of many enzymes which play a key role in metabolism and control of inflammatory changes in the nervous tissue. Studies have reported that circulating levels of thiamine are reduced by 30%–80% in patients with sepsis. Deficiencies in folate, pyridoxine and riboflavin are also reported. Nicotinic acid deficiency occurs much less frequently, but has been reported to be associated with brain damage in such circumstances.[8]

Thiamin has been an established treatment option for decades in both alcohol and non-alcohol related delirium. It has also been a popular treatment option for sepsis related delirium among the physicians. In critically ill patients, low levels of Thiamine were first noticed in the 1980s and is recognized as being associated with mortality. Thiamine deficiency is present in 20–70% of patients with septic shock.[9] Although thiamine deficiency is less common in developed nations, it is more prevalent among nutritionally compromised populations of developing countries like Bangladesh, and can exacerbate the condition of patients during critical illness. Patients in hypermetabolic states and on parenteral nutrition without micronutrients predispose to acute deficiency of thiamine.[10] As Thiamine-dependent enzymes play an essential role in cerebral energy utilization, thiamine deficiency may propagate brain tissue injury by inhibiting metabolism in brain regions with higher metabolic demands and high thiamine turnover. Thiamin helps the body's cells to change carbohydrates, fatty acids and amino acids into energy. It also plays a role in muscle contraction and conduction of nerve signals.[11] The daily requirement of thiamine in adults is 1.1–1.2 mg. The half-life of thiamine is 14 to 18 days.[12] Thiamin is usually given at a dose of 100mg thrice daily.

Vitamin B6 (Pyridoxine Hydrochloride) 200mg and Vitamin B12 (Cyanocobalamin) 200 micrograms along with Vitamin B1 (Thiamine Mononitrate) showed better response among patients suffering from sepsis related delirium in comparison to Thiamin alone. Vitamin B6 (pyridoxine) a water-soluble vitamin, helps the body to metabolize proteins, fats, and carbohydrates for energy. Vitamin B6 also helps to create neurotransmitters, which are important chemical messengers in the brain. It also helps regulate energy use in the brain. Some research suggests that vitamin B6 deficiency may be linked with cognitive decline and dementia.[13]

Vitamin B12 is required for the development, myelination, and function of the central nervous system; healthy red blood cell formation, and DNA synthesis. Vitamin B12 is crucial in normal functioning of the brain and nervous system and cognitive function. A deficiency or insufficiency can lead to a number of symptoms and can even progress to irreversible neurological issues if left untreated.[14]

Sepsis-associated encephalopathy is associated with higher mortality, higher use of ICU resources, and longer hospital stay. The prevention of critical care delirium by identification of the level of risk, avoidance of causative factors of delirium, early implementation of multifactorial therapy and possible pharmacological treatment should belong to standard medical strategies of the entire medical team since hospital admission.

Recent exploratory studies have reignited interest in the longstanding concept of adjuvant vitamin therapy for critical illness often termed “metabolic resuscitation”.[15] An increasing number of clinical studies have sought to examine the potential therapeutic benefit of vitamin B supplements in critical conditions, separately or in combination, because of a potential synergistic effect. Most of these clinical studies have highlighted thiamin deficiency in critically ill patients and the beneficial effects of thiamin. Pyridoxine and Cyanocobalamin are promising micronutrients for adjuvant therapy in severe acute illness. Combining these vitamins might accelerate the recovery from delirium in critically ill patients potentially leading to better outcomes.

CONCLUSION:

Delirium is a common disorder that occurs in critically ill patients.[16] Sepsis-associated encephalopathy (SAE) was defined by presence of features of delirium in septic patients.[17] The first step in pharmacologic management of delirium is to assess the patient’s current medications for any offending agents that may be causing or exacerbating the delirium.

In recent years, there has been a rise in the interest of vitamin therapy in critically ill patients.[18] The effect of vitamin B supplements on the improvement of critically ill patients has been studied in few centers. Unfortunately, the small number of studies and heterogenicity make it impossible to draw any conclusions. So, there is a need of large-scale, high quality randomized control trials to confirm the beneficial effects of these vitamins. With the knowledge of delirium assessment methods, further studies on the use of Vitamin B supplementations may provide results that will benefit the treatment of patients with delirium in the critical care area.

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