Thiamine Administration and the Prevalence of Delirium in the Intensive Care Unit: A Retrospective Before and After Interventional Study

Sara Dichtwald MD[1,2], Nedi Varbarbut MD[1,2], Elad Dana MD[1,2], Edna Zohar MD[1,2], Nisim Ifrach MD[1,2], and Brian Fredman MD[1,2]

[1]Department of Anesthesiology, Meir Medical Center, Kfar Saba, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Thiamine is an essential co-factor for aerobic intracellular respiration, nerve conduction, and muscle contraction. Thiamine deficiency is common in the intensive care unit (ICU). Delirium is a frequent unwanted symptom among critical ill patients. Although the exact cause of ICU-associated delirium is unknown, abnormal nutrition and thiamine deficiency may contribute to the etiology.

Objectives: To compare the prevalence of delirium among ICU patients who received thiamine with those who did not and to compare morbidity and mortality.

Methods: A retrospective study was conducted among ICU patients admitted 2014–2018. Routine thiamine administration began in 2016. Collected data included patient demographics, medical history, indication for ICU admission, hospital admission times, ventilation days, inotropic therapy, hemodialysis, tracheostomy, 28-day mortality, and need for anti-psychotic therapy. Group A received thiamine, group B did not. All data were statistically analyzed according to type.

Results: The study included 930 patients: 465 patients in group A and 465 in group B. At admission and throughout the hospitalization severity of disease parameters was worse in group A compared to group B, including acute physiology and chronic health evaluation (APACHE) score, admission lactate level, ventilation days, inotropic support, renal replacement therapy, tracheostomy, and ICU hospitalization. Group A had fewer delirium events without difference of maximal delirium score. No difference in mortality rate was observed.

Conclusions: Thiamine administration was associated with lower delirium prevalence despite longer ICU admission times and higher disease severity parameters at admission and during ICU stay.

IMAJ 2023; 25: 200–204

KEY WORDS: beri-beri, delirium, intensive care unit (OCU), intensive care unit outcomes, thiamine, Wernicke-Korsakoff

Thiamine pyrophosphate (vitamin B1) absorption occurs in the jejunum. This vitamin is an essential co-factor for glycolysis and oxidative decarboxylation and therefore for cellular energy production [1]. Depending on intraluminal concentrations thiamine absorption is either passive along a concentration gradient or by an active transport mechanism. Since thiamine is poorly stored, in conditions of thiamine nutritional deficiency, clinical signs of thiamine deficiency will rapidly develop. In the ICU setting, thiamine deficiency is accelerated by metabolic stress. If not treated red blood cell transketolase activity and cellular energy production is impaired, with a consequent increase in blood pyruvate and lactate. In addition to these adverse effects of acute thiamine deficiency, thiamine deficiency can also lead to the development of peripheral neuropathy, cranial nerve dysfunction, ataxia, delirium, and cognitive decline (Wernicke or Wernicke-Korsakoff syndrome), severe heart failure (wet beri-beri), and lactic acidosis. Various disease states, as well as medications, may cause a partial or complete thiamine deficiency.

Recent studies have demonstrated up to 50% increase in mortality among intensive care patients who presented with partial or complete thiamine deficiency when compared to patients with normal thiamine levels [2].

Thiamine deficiency should be suspected in various clinical conditions such as severe sepsis, extensive burns, congestive heart failure of unknown origin [3], lactic acidosis [4,5], certain neurological deficiencies in patients with a history of alcohol use [6], malnutrition, long-term use of parenteral nutrition, hyperemesis gravidarum, and following bariatric surgery. Among ICU patients treated for sepsis or septic shock, the incidence of thiamine deficiency is estimated to be 30–70%.

Thiamine administration is not associated with dangerous side effects. To date, thiamine toxicity has not been reported, even in end-stage renal disease patients treated with hemodialysis.

To the best of our knowledge, there is no uniform policy of routinely administering thiamine supplements to patients hospitalized in the ICU. Historically, we administered adjuvant thiamine to high-risk patients (chronic alcohol usage, malnutrition) and to those who developed symptoms suspicious of thiamine

deficiency. However, as of 2016 adjuvant thiamine is administered to all our ICU patients.

Delirium is a common and severe problem among ICU patients (prevalence is estimated at 30–40% of all patients) [7]. It is well known that thiamine deficiency is associated with delirium and/or dementia as part of Wernicke-Korsakoff and delirium tremens syndromes [8]. It is possible that ICU-associated delirium is an early presentation of these well-known neurological conditions. However, the clinical characteristics of these syndromes are hard to estimate in sedated and ventilated patients.

Due to the high prevalence of thiamine deficiency among intensive care patients and the possibility that thiamine deficiency may contribute to ICU-induced delirium, we postulated that routine thiamine supplementation would decrease the incidence of ICU-related delirium. Therefore, we performed a retrospective before-after intervention study to determine whether adjuvant thiamine administration decreases the incidence of ICU-associated delirium.

PATIENTS AND METHODS

Following institutional board approval, we conducted a retrospective before-after interventional study. The data of all adult patients (> 18 years of age) who were admitted to the intensive care unit at the Meir Medical Center, Kfar Saba, Israel, 2014–2018 (two years before and after the beginning of the therapeutic intervention) were analyzed. Data were collected from hospital electronic computer systems (Chameleon® and iMDsoft® software).

Following data entry, the database was sorted such that patients were subdivided into those who received thiamine supplement (Group A) and those who did not (Group B).

The following variables were collected: Age, sex, history of chronic disease and medications, reason for ICU admission, lactate level on admission, acute physiology and chronic health evaluation (APACHE) 2 score, number of ventilation days, tracheostomy placement, vasopressor administration, incidence of delirium and antipsychotic treatment, and need for dialysis or other renal replacement therapies. Furthermore, the administration of medical therapies that may increase the risk of delirium (steroids, anti-cholinergic, benzodiazepines) was recorded. Last, the length of ICU stay and hospital admission as well as mortality within 28 days was recorded.

Statistical analysis was performed by an independent professional statistician. Demographic data, clinical variables, and the incidence of delirium between the two groups were compared and analyzed using chi-square test for the discrete variables and Mann-Whitney test for the continuous variables.

RESULTS

Data were collected from a total of 930 patients: 465 in group A and 465 in group B. Demographic data were comparable between the groups (chi-square test and Mann-Whitney test for the discrete and continuous parameters, respectively) [Table 1].

ICU admission after surgery was more common in group A compared to group B (38.7% vs. 30.8%, respectively; chi-square 6.49, $P = 0.01$). All other admission etiologies were similar between the groups [Table 1].

The incidence of chronic hypertension was higher in group B compared to group A (43.2% vs. 34.6%, respectively; chi-square 7.24, $P < 0.01$). Similarly, the incidences of chronic congestive heart failure (CCF) and chronic renal failure (CRF) were higher in group B compared to group A (CCF: 9.9% vs. 6.0%, respectively; chi-square 4.76, $P = 0.03$; CRF: 11.2% vs. 7.1%, respectively; chi-square 4.76, $P = 0.03$) [Table 1].

The frequency of diuretics and angiotensin II receptor blockers (ARBS) usage was higher among patients in group B (diuretics: with thiamine 11.8%, without thiamine 17.0%; chi-square 5.02, $P = 0.02$; ARBS with thiamine 5.4% without thiamine 9.2%, chi-square 5.14, $P = 0.02$) [Table 1].

The frequency of addictive or prohibited substance usage was higher among the group of patients treated with thiamine. Among the group of patients treated with thiamine, there was a higher incidence of chronic use of alcohol (group A 3.4% vs. group B 1.3%; chi-square 4.66, $P = 0.03$). Similar results were found among patients with a known history of drug abuse (group A 4.5% vs. group B 2.2%, chi-square 4.04, $P = 0.02$) [Table 1].

Among patients receiving thiamine there was a higher prevalence of chronic treatment with antipsychotic drugs (Etumin and Olanzapine) (group A 10.3% vs. group B 6%, chi-square 5.73, $P = 0.02$) [Table 1].

In the first 24 hours after admission to the ICU, patients in group A had a higher APACHE 2 score compared to group B (mean 9.09 ± 5.16 vs. mean 8.31 ± 4.90, $P = 0.01$). Similarly, lactate level on admission was higher in group A (mean 2.09 ± 1.98 mg/dl) compared to group B (mean 1.77 ± 1.68 mg/dl, $P < 0.01$) [Table 1].

ICU admission time was longer in group A (mean 10.64 ± 11.77 days) compared to group B (mean 7.97 ± 9.94 days, $P < 0.01$). Similarly, hospital admission time was longer in group A compared to group B (mean 23.54 ± 21.60 days vs. mean 20.33 ± 21.23 days, $P < 0.01$, respectively. Patients in the thiamine group were ventilated more days (for patients with thiamine, mean 8.12 ± 10.79 days; for patients without thiamine, mean 5.67 ± 9.30 days, $P < 0.01$) and underwent tracheostomy more frequently than the group of patients who were not treated with thiamine (patients with thiamine 23.9%, without thiamine 14.4%, chi-square 13.45, $P < 0.01$) [Table 1].

During ICU hospitalization, the thiamine group required more pressor support (48.4% vs. 30.3%, chi-square 31.79, $P < 0.01$) and renal replacement therapy, including hemodialysis and continuous renal replacement therapy (9.0% vs. 3.0%, (chi-square 14.90, $P < 0.01$) [Table 1]. There was no significant difference in mortality rate within 28 days between the groups [Table 1].

Table 1. Patient demographic and co-morbidities and clinical characteristics in intensive care unit

	Group A (with thiamine)	Group B (without thiamine)	*P*-value
Number (n)	465	465	
Age (year)	51 ± 18	52 ± 19	NS
Sex (female/male)	180 / 285	173 / 292	NS
Co-morbidities, n (%)			
Hypertension	161 (34.6)	201 (43.2)	< 0.01
Chronic renal failure	33 (7.1)	52 (11.2)	0.03
Congestive heart failure	28 (6.0)	46 (9.9)	0.03
Drug abuse	21 (4.5)	10 (2.2)	0.04
Ethanol abuse	16 (3.4)	6 (1.3)	0.03
Chronic medication, n (%)			
Diuretics	55 (11.8)	79 (17.0)	0.02
Angiotensin receptor blockers	25 (5.4)	43 (9.2)	0.02
Anti-psychotic	48 (10.3)	28 (6.0)	0.02
Calcium channels blockers	59 (12.7)	80 (17.2)	0.05
Clinical characteristics			
APACHE 2	9.09 ± 5.16	8.31 ± 4.90	0.01
Lactate level during ICU admission	2.09 ± 1.98	1.77 ± 1.68	< 0.01
Cause of admission, n (%)			
Postoperative	180 (38.7)	143 (30.8)	0.01
Sepsis	72 (15.5)	88 (18.9)	NS
Acute respiratory failure	61 (13.1)	75 (16.1)	NS
Trauma	41 (8.8)	54 (11.6)	NS
Neurologic	34 (7.3)	37 (8.0)	NS
Intoxication	26 (5.6)	21 (4.5)	NS
Congestive heart failure	10 (2.2)	5 (1.1)	NS
Other causes**	41 (8.8)	42 (9.0)	NS
Other treatment modalities			
Noradrenaline	225 (48.4)	141 (30.3)	< 0.01
Mechanical ventilation (days)	8 ± 11	6 ± 9	< 0.01
Tracheostomy, n (%)	111(23.9)	67(14.4)	< 0.01
Renal replacement therapy, n (%)	42 (9.0)	14 (3.0)	< 0.01
Admission milestones			
ICU admission (days)	11 ± 12	8 ± 10	< 0.01
Hospital admission (days)	24 ± 22	20 ± 21	< 0.01
28-day mortality, n (%)	58 (12.5)	71 (15.3)	0.22

Values are mean ± standard deviation or numbers, *P*-value > 0.05

*Cerebral vascular accident, chronic obstructive pulmonary disease, cirrhosis, dementia, diabetes mellitus, ischemic heart disease, peripheral vascular disease

**Angiotensin converting enzyme inhibitors, anti-cholinergic drugs, anti-depressant drugs, anti-platelet aggregation drugs, anti-coagulation drugs, benzodiazepines, beta blockers, insulin, opioids, oral hypoglycemic drugs, steroids

Apache = acute physiology and chronic health evaluation, ICU = intensive care unit

The mean time to first adjuvant thiamine administration in group A was 22.76 ± 63.93 hours. The total amount of thiamine administered to these patients was 630.69 ± 1024.09 mg. Last, the duration of thiamine administration was 3.22 ± 2.27 days.

Delirium variables between the groups are shown in Table 2. Patients receiving thiamine had a significantly lower number of delirium events (mean 0.92 ± 2.82, median 0.00), as evidenced by a lower number of Richmond Agitation-Sedation Scale (RASS) > 0 compared with thiamine-free patients (mean 1.72 ± 5.60, median 0.00, $P < 0.01$). However, there was no significant difference in the maximal RASS score recorded between the groups.

We conducted a linear multivariate regression to control the potential cofounders of drug abuse, ethanol abuse, and diuretics. After adjusting for these variables, patients who did not received thiamine had more RASS episodes compared with patients who received thiamine ($\beta = 0.08$, $P = 0.01$) [Table 3].

Table 2. Richmond agitation and sedation scale (RASS)

	Group A (with thiamine)	Group B (without thiamine)	*P*-value
Number of episodes RASS > 0	0.92 ± 2.82	1.72 ± 5.6	0.02
Maximal RASS	-0.02 ± 1.72	-0.06 ± 1.49	0.41

Values are mean ± standard deviation or numbers (%)

Table 3. Multivariate model for predicting RASS > 0

	B	S.E. B	Beta	*P*-value
Drug abuse	-1.47	0.84	-0.06	0.08
Ethanol abuse	4.27	0.99	0.15	< 0.001
Diuretics	0.03	0.41	0.00	0.93
Thiamine (vs. non-thiamine)	0.74	0.29	0.08	0.01

RASS = Richmond agitation and sedation scale

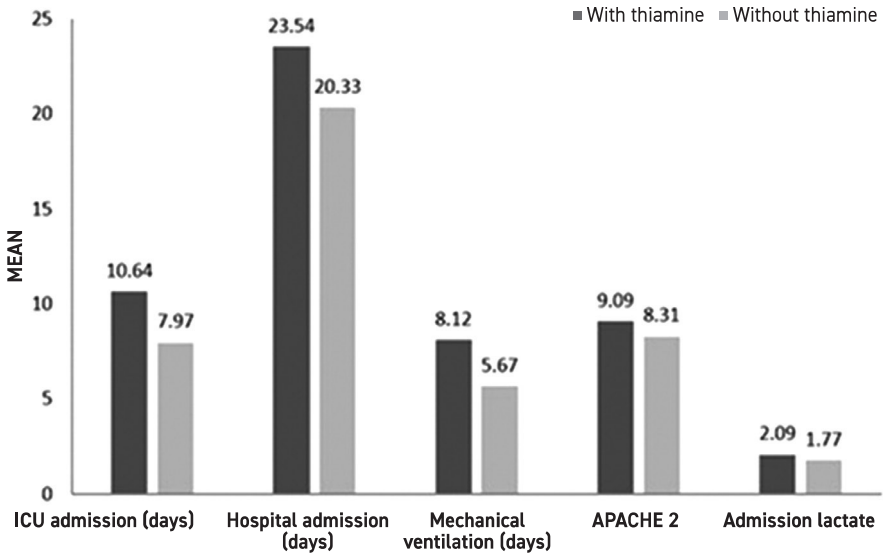
DISCUSSION

Delirium is a common condition among patients in the intensive care unit. Furthermore, delirium lengthens hospital admission time, and has been associated with significant morbidity and subsequent cognitive decline [9]. To date, the exact etiology of intensive care-induced delirium is unknown and there is no effective prophylactic drug treatment for this phenomenon [10].

Thiamine (vitamin B1) is a water-soluble vitamin that is essential for aerobic function of the Krebs cycle as well as for proper nerve conduction [11]. Thiamine deficiency-induced delirium has been described in alcohol abuse associated Wernicke-Korsakoff syndrome and in other conditions that cause

Figure 1. Differences between patients with thiamine and patients without thiamine in continuous clinical variables
APACHE = acute physiology and chronic health evaluation, ICU = intensive care unit

All variables in Figure 1 are statistically significant



thiamine deficiency. Among patients in the ICU there are many conditions sepsis, malnutrition, burns, oncological diseases, dialysis, alcohol abuse, and the chronic use of diuretic medications can cause acute or chronic thiamine deficiency [3,6,12,13].

Because many patients in the ICU are at risk of developing or exacerbating an existing thiamine deficiency, which may cause delirium, we investigated whether routine thiamine treatment for all patients reduced the rate of delirium among our ICU patients.

We described our routine practice and time dependent changes in clinical approaches. As a result, the dosage of thiamine administered changed with time. In 2016 the dosage of thiamine administered was 100 mg/day for 3 days. In 2017, we adjusted the dose of thiamine administered according to the findings of Marik et al. [14], which recommended that patients with sepsis or septic shock receive 200 mg twice a day for 5 days. Based on those results, we reviewed our practice and administered 200–500 mg/day for 3–5 days. Since 2016, the average dose of thiamine administered for 3 days was 200 mg/day. The mean dose reflected the change in dose over the years.

The control group included patients admitted to the ICU from 2014 to 2016, in which thiamine was not given routinely to all patients. The treatment group included patients admitted to the unit in the years 2016–2018, in which all patients in the unit were treated with thiamine.

In our study, thiamine-treated patients presented with more severe acute disease, both on admission and during ICU hospitalization. When compared to non-thiamine treated patients, these patients had a poorer APACHE 2 score on ICU admission and were ventilated and pressor dependent for a longer time. More patients required hemodialysis. However, while there is a direct correlation between baseline severity of disease and ICU-associated delirium [7], a significantly lower incidence of ICU-associated delirium was noted among patients in the thiamine treatment group.

The lower incidence of delirium events in group A is even more pronounced because among these patients there was a higher incidence of chronic alcohol and drug use and a need for chronic antipsychotic treatment relative to group B. Furthermore, these patients had a poorer APACHE 2 score on ICU admission and were ventilated and pressor dependent for a longer time. More patients required hemodialysis. Among these patients the incidence of delirium was even lower relative to the second healthier group, which reinforces the hypothesis that thiamine administration may have contributed to the decrease in delirium levels in these patients.

Sedation may affect the incidence of delirium in the ICU setting [7]. Therefore, it is important to note that our sedation protocols did not change during the study period. These protocols included administration of remifentanil with adjuvant propofol in stable patients and midazolam in unstable patients. However, there was no difference in the frequency and dosage of these drugs between the two groups.

A limitation of this study is its retrospective design and pre- and post-intervention analysis. However, our routine clinical experience with 930 critically ill patients was described. Furthermore, the optimal thiamine dosage was not examined. Last, there may

be additional variables that influence delirium that were not in the scope of this study. Therefore, further studies should be performed to better define the etiology as well as to determine the optimal thiamine dosage required to prevent ICU associated delirium.

CONCLUSIONS

Thiamine administration to intensive care patients may be associated with a lower incidence of delirium despite more risk factors for ICU delirium (APACHE 2 score on ICU admission, days of ventilation and pressor dependency, frequency of hemodialysis).

Correspondence

Dr. S. Dichtwald
Dept. of Anesthesiology, Meir Medical Center, Kfar Saba 4428164, Israel
Phone: 972-9-7472133
Email: saradicht@gmail.com

References

1. Depeint F, Bruce WR, Shangari N, Mehta R, Obrien PJ. Mitochondrial function and toxicity: Role of the B vitamin family on mitochondrial energy metabolism. *Chem Biol Interac* 2006; 163: 94-112.
2. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. *Curr Opin Clin Nutr Metab Care* 2011; 14 (6): 610-7.
3. Kitamura K, Yamaguchi T, Tanaka H, Hashimoto S, Yang M. TPN-induced fulminant beriberi: a report on our experience and review of the literature. *Surg Today* 1996; 26 (10): 769-76.
4. Amrein K, Ribitsch W, Otto R, Worm HC, Stauber RE. Severe lactic acidosis reversed by thiamine within 24 hours. *Crit Care* 2011; 15 (6): 457.
5. Oriot D, Wood C, Gottesman R, Huault G. Severe lactic acidosis related to acute thiamine deficiency. *JHPEN J Parenter Enteral Nutr* 1991; 15: 105-9.
6. Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. *N Engl J Med* 1985; 312 (16): 1035-9.
7. Krewulak KD, Stelfox HT, Leigh JP, Ely EW, Fiest KM. Incidence and Prevalence of Delirium Subtypes in an Adult ICU: A Systematic Review and Meta-Analysis. *Crit Care Med* 2018; 46 (12): 2029-35.
8. Sanford AM, Flaherty JH. Do nutrients play a role in delirium? *Curr Opin Clin Metab Care* 2014; 17: 45-50.
9. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, Petersen RC. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol* 2014; 10 (11): 634-42.
10. Burry LD, Cheng W, Williamson DR, Adhikari NK, Egerod I, Kanji S, Martin CM, Hutton B, Rose L. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. *Intensive Care Med* 2021; 47 (9): 943-60.
11. Woolum JA, Abner EL, Kelly A, Thompson Bastin ML, Morris PE, Flannery AH. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. *Crit Care Med* 2018; 46 (11): 1747-52.
12. Onishi H, Sato I, Uchida N, Takahashi T, Furuya D, Ebihara Y, Yoshioka A, Ito H, Ishida M. High proportion of thiamine deficiency in referred cancer patients with delirium: a retrospective descriptive study. *Eur J Clin Nutr* 2021; 75 (10): 1499-505.
13. Truong t, Hetzel F, Stiff KM, Husnain MG. Case of hypoactive delirium precipitated by thiamine deficiency. *BMJ Case Rep* 2021; 17 (14): 3:e239886.
14. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock. *Chest* 2017; 151: 1229-38

Jokes of the proper kind, properly told, can do more to enlighten questions of politics, philosophy, and literature than any number of dull arguments.

Isaac Asimov (1920–1992), American writer and professor of biochemistry at Boston University, known for his works of science fiction and popular science

Capsule

Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer

Tintelnot and co-authors, using shotgun metagenomic sequencing and metabolomic screening, showed that the microbiota-derived tryptophan metabolite indole-3-acetic acid (3-IAA) is enriched in patients who respond to chemotherapy treatment in pancreatic cancer. Faecal microbiota transplantation, short-term dietary manipulation of tryptophan, and oral 3-IAA administration increase the efficacy of chemotherapy in humanized gnotobiotic mouse models of PDAC. Using a combination of loss- and gain-of-function experiments, the authors showed that the efficacy of 3-IAA and chemotherapy is licensed by neutrophil-derived myeloperoxidase. Myeloperoxidase oxidizes 3-IAA, which in combination with chemotherapy induces a downregulation of the reactive oxygen species (ROS)-degrading enzymes glutathione peroxidase 3 and glutathione peroxidase 7. All of this results in the accumulation of ROS and the downregulation of autophagy in cancer cells, which compromises their metabolic fitness and, ultimately, their proliferation. In humans, we observed a significant correlation between the levels of 3-IAA and the efficacy of therapy in two independent PDAC cohorts. They identify a microbiota-derived metabolite that has clinical implications in the treatment of PDAC, and provide a motivation for considering nutritional interventions during the treatment of patients with cancer.

Nature 2023; 615: 168

Eitan Israeli