Whole blood thiamine, intravenous thiamine supplementation and delirium occurrence in the intensive care unit: retrospective cohort analyses

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Abstract

Background: Thiamine di-phosphate is an essential cofactor in glucose metabolism, glutamate transformation and acetylcholinesterase activity, pathways associated with delirium occurrence. We hypothesised that a deficiency in whole blood thiamine and intravenous thiamine supplementation could impact delirium occurrence.

Aim: To establish whether a deficiency in whole blood thiamine and/or intravenous thiamine supplementation within 72 hours of intensive care admission is associated with delirium occurrence.

Method: The first dataset was secondary analysis of a previous study in an intensive care unit in the Netherlands, reported in 2017. The second dataset contained consecutive intensive care admissions 2 years before (period 1: October 2014 to October 2016) and after (period 2: April 2017 to April 2019) routine thiamine supplementation was introduced within 72 hours of admission. Delirium was defined as a positive Confusion Assessment Method-Intensive Care Unit score(s) in 24 hours.

Results: Analysis of the first dataset (n=57) using logistic regression showed no relationship between delirium and sepsis or whole blood thiamine, but a significant association with age (p=0.014). In the second dataset (n=3074), 15.1% received IV thiamine in period 1 and 62.6% during period 2. Hierarchical regression analysis reported reduction in delirium occurrence in the second period; this did not reach statistical significance, OR =0.81 (95% CI: 0.652 – 1.002); *p*=0.052.

Conclusion: No relationship was detected between whole blood thiamine and delirium occurrence on admission, at 24 and 48 hours. It remains unclear whether routine intravenous thiamine supplementation during intensive care admission impacts delirium occurrence. Further prospective randomised clinical trials are needed.

Keywords

Critical care; Delirium; Intensive care; Retrospective studies; Thiamine.

Impact of findings on practice

- Whole blood thiamine (WBT) may be helpful in assessing thiamine deficiency and could inform thiamine supplementation in critical illness
- Intravenous (IV) thiamine supplementation on intensive care unit (ICU) admission could impact delirium occurrence
- Adherence to an IV thiamine supplementation regime could be enhanced by the presence of an ICU pharmacist
- Future research into IV thiamine supplementation and delirium occurrence is needed; the impact of IV thiamine supplementation on delirium occurrence is yet to be fully established.

Introduction

Delirium is common in critical illness with a reported prevalence of up to 50%, and higher in patients who are mechanically ventilated (1–3). Delirium is associated with poor outcomes including increased length of hospital and intensive care unit (ICU) stay, costs and long-term cognitive impairment after critical illness (4). Clinically, patients with delirium present with a number of symptoms including inattention, confusion, emotional distress and agitation which can be severe. Delirium results from one or more causes including sepsis and septic shock, metabolic disturbances, sedation, respiratory failure with hypoxia, SARS-Co-V2 infection and/or environmental factors (1, 5, 6). In delirium, brain glucose demands increase, and this may not be met in patients presenting or developing thiamine depletion in the central nervous system (7). Thiamine in its active form, thiamine di-phosphate (TDP), is an essential cofactor in glucose metabolism, glutamate accumulation and acetylcholine synthesis, all of which are associated with delirium occurrence (8). It is therefore scientifically plausible that thiamine depletion or supplementation could impact delirium occurrence in ICU.

Deficiency of whole blood thiamine (WBT) has been sporadically reported in ICU patients over the last 15 years (7, 9–12). In 2020, Heming et al. reported erythrocyte levels of total thiamine, free thiamine, thiamine mono-, di- and tri-phosphate (TMP, TDP, and TTP respectively), the erythrocyte transketolase activity (ETKA), and the effect of TDP on ETKA were measured in septic patients and correlated with arterial lactate (n=28)(7). Total thiamine and TDP concentration were significantly higher in ICU survivors than in non-survivors (p=0.03) (7). In 2018, Pourhassan et al. reported lower WBT in patients with delirium (54.2 ng/mL), when compared to those without delirium (66.4 ng/mL) (p=0.002) (13).

In 2021, a systematic review (SR) and meta-analysis in critical illness reported that intravenous (IV) thiamine supplementation resulted in a 42% lower odds of developing ICU delirium (2). The authors did not report adjusting for residual confounding factors such as alcohol dependence or existing

vitamin supplementation. Moslemi et al. reported a reduction in delirium in ICU patients after IV thiamine supplementation (14). Branco et al. reported reduction in encephalopathy in severe COVID-19 patients after IV thiamine supplementation (15).

We hypothesised: 1) WBT deficiency is associated with delirium occurrence in ICU, and 2) routine IV thiamine supplementation on ICU admission reduces delirium occurrence during ICU stay.

Aim

To establish whether a WBT deficiency and/or IV thiamine supplementation within 72 hours after ICU admission is associated with delirium occurrence.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Both parts of the study were approved by the local Gelre Hospital ethics committee (LTC 09.24, July 14, 2009) (12).

Method

Patients and Settings

The study took place in the (ICU of Gelre Hospitals, a mixed medical and surgical teaching ICU in Apeldoorn, The Netherlands. Gelre has long-term experience in ICU related delirium research. The study consisted of two parts, based on retrospective cohort analysis of two datasets:

part one: Secondary analysis of data reported by van Snippenburg et al. in 2017 (12)

part two: Exploratory analysis of a 2-year period before and 2 years after introduction of routine IV thiamine supplementation on ICU admission.

Demographics

Patient demographics for Part one and two included: age, gender, ICU length of stay, Richmond Agitation and Sedation Score (RASS) – lowest score at admission day to the ICU, Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, Simplified Acute Physiology Score (SAPS) II score on admission, and hospital mortality.

Delirium presence

Delirium screening for both parts was undertaken twice daily as part of routine practice by trained nursing staff using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU). For the analysis, a day in delirium was defined as one or more positive CAM-ICU scores in a 24-hour period.

Part one: Whole blood thiamine (WBT) and delirium presence

Patients were included in the first analysis if thiamine supplementation was not administered before ICU admission. Blood samples (EDTA and fluoride tubes, Vacutainer; Becton-Dickinson, Franklin Lakes, New Jersey, USA) for measurement of Whole Blood Thiamine (WBT) were collected on admission, at 24- and 48-hours post ICU admission. WBT concentration was determined by ultra-pressure liquid chromatography with fluorescence detection (System/column: Waters, Etten-Leur, the Netherlands; method: Chromsystems, Munich, Germany). The pathology range for WBT deficiency was determined, apriori, at ≤ 100nmol/litre, in line with the normal reference range provided at the local pathology unit at Gerle hospital (12). Data were analysed to explore the relationship between WBT deficiency (at t-0 hrs, t-24 hrs, or t-48 hrs) and delirium occurrence during ICU stay.

Part Two: IV thiamine supplementation and delirium presence

For part two, we evaluated the relationship between routinely prescribed IV thiamine supplementation and delirium occurrence. IV thiamine supplementation was prescribed as 300 mg IV once only, followed by 100 mg IV daily for 5 days as part of the ICU-admission medication order-set in the electronic patient record. This was implemented at Gelre after reporting of low WBT levels in a significant proportion of acutely admitted ICU patients (12). Anonymised patient data was collected continuously for 24 months before and 24 months after introduction of IV thiamine supplementation in September 2016 with a 6-month washout period. Data was collected for the periods: October 2014 to October 2016 (period 1) and April 2017 to April 2019 (period 2). All ICU

patients who had received any dose(s) of routine IV thiamine supplementation within 72 hours of admission were compared against those who did not receive IV thiamine supplementation within their respective periods, but comparisons were also made between the two periods. The rate of adherence to the IV thiamine intervention was additionally assessed.

Analysis

Shapiro-Wilk test was used to determine use of parametric or nonparametric test. For data not conforming to normal distribution, comparisons were made using Mann-Whitney U test. Chi-square test was used to compare groups with nominal variables. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) version 29.0.

For part one, the relationship between WBT and delirium presence was expressed as odds ratio (OR) and 95% confidence interval (CI). Secondary outcomes were explored by analysing confounding factors associated with delirium presence in ICU (5, 16). Data included duration of mechanical ventilation, presence of sepsis and septic shock, sedation depth, age, and severity of illness. Following univariate analysis, logistic regression analysis was performed adjusting for age and sepsis, as only two confounders were eligible for the model due to the small sample size and these are two of the most common risk factors for ICU delirium (17).

For part two, the relationship between IV thiamine supplementation and delirium presence was investigated. The analyses are reported as odds ratio (OR) and 95% confidence interval (CI) to determine significance of association between presence or absence of IV thiamine supplementation on admission and delirium occurrence at any time during ICU admission. As the intention of the change in practice was an attempt to ensure all ICU admissions received IV thiamine, the positivity condition was present. However, the decision to actually prescribe was left to the attending physician. As such, not all patients received the suggested thiamine infusion. Nevertheless, there

was a greater than zero chance that patients in the second phase of the study would receive thiamine compared to those in the first phase of the study when thiamine prescription was not part of a routine protocol in the hospital's digital system.

Hierarchical logistic regression analysis was performed to evaluate impact of IV thiamine supplementation on delirium presence, and known risk factors of delirium: sepsis, age, duration of ventilation, severity of illness (APACHE II) and length of stay in ICU (5, 16, 18, 19). This is a variant of the multiple regression procedure that introduces variables in a stepwise manner to identify the most influential variables within the model and allow better understanding of the relationship between these factors and delirium occurrence.

Results

Part One: Whole blood thiamine (WBT) and delirium occurrence

There were 66 patients that met the inclusion criteria for WBT analysis collected between August 2009 and February 2010, and previously reported in 2017 (12). Eight patients receiving IV thiamine supplementation before ICU admission were excluded, with a further loss of one patient due to insufficient data, resulting in 57 patients available for analysis (Table 1). WBT levels within thiamine deficient patients were observed from admission to 48 hours of ICU admission (Supplemental Table S1).

Delirium was detected, at any time, during ICU stay in 36.4% patients with normal WBT on admission, and 38.1% patients at 48 hours (Table 2). In those that were WBT deficient, delirium was detected in 45.8% patients on admission and 46.7% patients at 48 hours. Exploratory analysis reported delirium presence during ICU stay in those with normal WBT (> 100 nmol/litre) compared to those that were WBT deficient (≤ 100 nmol/litre) at t-0, t-24h, and t-48h, (OR: 0.68 [95% confidence interval (CI): 0.23-1.97]), (OR: 0.63 [95% CI: 0.20-2.00]) and (OR: 0.70 [95% CI: 0.21-2.31]) respectively.

Using age and sepsis as confounding variables alongside WBT in a binary logistic regression model, a significant relationship was observed between aging and delirium (OR= 1.075; 95% CI: 1.015-1.140; *P* = 0.014) (Supplemental Table S2). No significant relationship was observed between delirium and sepsis or WBT on admission.

Part Two: Routine prescription of IV thiamine supplementation and delirium occurrence

For part two, 3074 ICU admissions were evaluated, 1508 in period one and 1566 in period two (Table 3).

During period one, 228 of 1508 (15.1%) patients received IV thiamine supplementation in the first 72 hours. In period two, adherence to any dose of IV thiamine was observed in 980 of 1566 (62.6%) patients; 37.4% of ICU admitted patients did not receive IV thiamine (Table 3).

IV thiamine supplementation, delirium, and outcome

In both periods, patients receiving IV thiamine had higher APACHE II score and SAPS II scores on ICU admission (Table 3). In period one (pre-October 2016), those not receiving IV thiamine had a lower mean APACHE II of 15.9 (± 6.93), compared to those who did, with 19.9 (± 7.64)**,** p <0.001; Mann-Whitney U test (Table 3). In period two (after April 2017), the same correlation was observed. SAPS II scores also supported this finding (Table 3).

The median length of stay (LOS) in ICU was greater for the group receiving IV thiamine during period one, 4 (IQR= 2-9), compared to those not receiving thiamine, 2 (IQR=2-4), *p*<0.001; Mann-Whitney U test. The same correlation was true for period two.

An overall reduction in delirium occurrence during period two (0.16) was found in an unadjusted analysis, compared to period one (0.20); OR: 0.78 [95% CI: 0.65- 0.94; *P*=0.009; Chi-square test] (Table 3). Hierarchical logistic regression analysis was carried out for delirium occurrence using known risk factors for delirium: hours of mechanical ventilation, age, sepsis on ICU admission, APACHE II on admission, ICU LOS and period of study; a reduction in delirium occurrence was

identified in the second period, although this did not reach statistical significance, OR =0.81 (95% CI: 0.652 – 1.002); *p*=0.052 (Supplemental Table S3).

A second hierarchical logistic regression analysis was performed where all patients receiving IV thiamine were compared against all patients not receiving IV thiamine, irrespective of the period. With inclusion of the same confounders in the model, more delirium occurrence was observed in those receiving IV thiamine compared to those not receiving IV thiamine (OR = 1.40 [1.12-1.73]; p= 0.003) (Supplemental Table S4).

Discussion

Statement of key findings

In this analysis of two distinct datasets, we describe that WBT levels at ICU admission are not related to delirium occurrence during ICU admission, and it was unclear whether routinely prescribing IV thiamine on ICU admissions resulted in an overall reduction in delirium occurrence during ICU stay.

Strengths and weaknesses

There are a number of limitations: In both parts, sample size calculations were not performed due to the retrospective and pre-determined nature of the studies; however, all available data were utilised for analysis.

Part one was an observational single center analysis with a small sample size. Further, the WBT samples were collected between 2009 and 2010; however, we decided to include these results because: whole blood samples are more challenging to store for subsequent analysis, plasma or serum is more stable and can be frozen for clinical or research purposes. Therefore there is paucity of WBT evidence in ICU literature, and WBT is the gold standard for thiamine detection (20). Despite the data's age, we believe the findings are important, as there is still an absence of proven pharmacotherapies for delirium prevention and management. Part two is a large observational dataset obtained during routine ICU care and thus subject to observational bias. Of note, a 62.6%

adherence to the IV thiamine supplementation is low, although those not receiving IV thiamine during this period had a lower severity of illness and ICU length of stay. The poor adherence could additionally be attributed to difficulties in changing clinical behaviour in ICU (21). Our focus was to compare two different periods following the decision to routinely introduce IV thiamine supplementation. Over the 4.5-year study duration, while delirium occurrence was higher overall among IV thiamine recipients, we attribute this to their higher illness severity and poor adherence to IV thiamine regime on admission. To improve compliance, implementation strategies could explore the inclusion of a dedicated ICU pharmacist to support prescribing adherence; this was not standard practice in the Netherlands during the study period (22–24). This is relevant as pharmacists have been reported to be underutilised in prevention and management of delirium, especially as 50% of pharmacists' recommendations have been reported to be frequently or always accepted by delirium treating teams (25). In part two, we were unable to detect thiamine deficiency because of challenges in storing whole blood. This is unfortunate, because the greatest benefit in IV thiamine supplementation could be in those who are thiamine deficient.

In Gelre ICU, the overall delirium occurrence was low (18%); in UK ICUs, where a higher delirium prevalence is reported, our results may have been very different (26). Higher disease severity in UK patients with higher APACHE-II scores may in part account for the difference. This could additionally be attributed to patient selection, where a shortage of ICU beds in the UK compared to other countries including the Netherlands could result in a more severely unwell patient cohort. Further work is required to establish whether the differences are related to local practices for delirium management or patient population.

CAM-ICU remains the most commonly used screening tool for delirium detection, despite its limitations (27, 28). Scores were collected following routine documentation by trained nursing staff in the ICU, potentially reducing the variation in inter-rater reliability that is observed with this tool among untrained users (29).

Thiamine (vitamin B1) is a water-soluble vitamin, with a short elimination half-life (30) and in refeeding and alcohol dependence, the recommended dose of IV thiamine is up to 750 mg three times a day for 5 days followed by oral supplementation (31, 32). Studies that report a reduction in encephalopathy or delirium after thiamine supplementation consistently prescribed a regimen at higher doses and for longer duration than those observed in these datasets (33).

Interpretation

A retrospective study (n=233) on older patients with delirium reported a significantly lower mean WBT compared to those without delirium (13). However, the setting was a geriatric acute care ward with substantial malnutrition risk (47%). Similar to our study, high performance liquid chromatography (HPLC) was used to measure WBT. Another single-centre retrospective study of 71 cancer patients reported serum-thiamine deficiency in 45.1% of delirium cases (34). Not all patients underwent thiamine level assessments, suggesting potential selection bias favoring those with severe delirium symptoms. WBT levels were investigated for delirium prevention in 61 patients post-allogenic hematopoietic stem cell transplantation (35). IV thiamine was administered at 200 mg three times daily for seven days and compared to placebo. Although the thiamine group exhibited significantly higher WBT levels, Delirium Rating Scale scores showed no significant differences. While using comparable chromatography, deficiency threshold was lower (70 nmol/L) compared to our study (100 nmol/L). The sample size was small, similar to our study, and the population very different from ICU.

A recent meta-analysis of IV thiamine supplementation in ICU, encompassing three RCTs, demonstrated lower incidence of delirium with thiamine (2). Two RCTs were underpowered and had narrow patient focuses (gastrointestinal and cardiac surgery), potentially affecting the generalisability of findings to wider critical care patients (14, 36). All patients who received IV thiamine supplementation in our second dataset had significantly higher severity of illness and longer stays in ICU, suggesting selection bias. This could potentially have influenced the clinical

decision by the attending intensivist to prescribe IV thiamine supplementation introducing performance bias. Unfortunately, we do not have data to test this hypothesis. It is worth noting in critical care trials greater effects may be observed in patients with higher severity of illness (37, 38); although we are aware that the opposite can also be true (39).

Further research

More investigation is needed to explore the impact of IV thiamine on delirium in the ICU, preferably in a randomised controlled clinical trial. Finally, thiamine is concentrated in the brain and in the heart, and a higher dose may be required to replenish thiamine stores in the brain and impact delirium (40). Therefore, it could well be that a higher dose administered more than once a day for 5 to 7 days, may have achieved a very different outcome. Data with regards to renal replacement therapy was not available for this study, which could have contributed further to the dosing discussion. Future work should also focus on the pharmacokinetics and pharmacodynamics of IV thiamine in critical illness and its impact on delirium.

Conclusion

In these two retrospective observational analyses, we could not establish whether either WBT depletion or IV thiamine supplementation had an impact on delirium occurrence. Prospective multicenter randomised controlled studies, taking appropriate dosing regimen of IV thiamine and associated whole blood thiamine levels into account, are needed to assess the impact of IV thiamine supplementation on delirium occurrence and duration in ICU.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Tables

Table 1: Patient demographics: Whole blood thiamine dataset

	All Patients	***Thiamine Deficient on admission (≤100 nmol/L)***	***Not thiamine deficient on admission (>100 nmol/L)***
n (%)	57	24 (42.1%)	33 (57.9%)
Age, years, median (IQR)	73 (62-79)	76 (65-81)	72 (61-77)
>60 years, n (%)	44 (77.2%)	19 (79.2%)	25 (75.8%)
Male, n (%)	36 (63.2%)	14 (58.3%)	22 (66.7%)
ICU stay, days, median (IQR)	9 (4-19)	9 (5-18)	7 (4-19)
Hospital stay>7 days before ICU admission, n (%)	12 (21.1 %)	7 (29.2%)	5 (15.2%)
Surgery within 1 week before ICU admission, n (%)	31 (54.4%)	19 (79.2%)	12(36.4%)
Sepsis on ICU admission, n (%)	13 (22.8%)	8 (33.3%)	5 (15.2%)
APACHE- II Score on ICU admission, median (IQR)	19 (12-25)	18 (12-21)	20 (16-26)
SAPS-II Score on ICU admission, median (IQR)	45 (34-54)	44 (34-53)	47 (34-54)
Hospital Mortality, n (%)	7 (12.3%)	2 (8.3%)	5 (15.2%)

Abbreviations: WBT, Whole Blood Thiamine, APACHE, Acute Physiology, Age and Chronic Health Evaluation; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score, IQR= interquartile range.

[a] Results are shown as median with interquartile range or as absolute number with percentage of group

Table 2: Part one- relationship between WBT and delirium occurrence ICU admission (t-0), 24 hours (t-24h) and 48 hours (t-48h).

	On admission		24 hours		48 hours	
	Delirium	*Not delirium*	*Delirium*	*Not delirium*	*Delirium*	*Not delirium*
Normal WBT (>100 nmol/L)	12	21	14	25	16	26
WBT Deficient (≤100 nmol/L)	11	13	8	9	7	8
Odds ratio (95% CI)	0.68 (0.23 - 1.97)		0.63 (0.20 – 2.00)		0.70 (0.21 - 2.31)	

Abbreviations: WBT = whole blood thiamine. ICU = Intensive Care Unit. CI = Confidence Interval

Table 3: Relationship between intravenous thiamine and delirium, ventilation, sepsis, disease severity, ICU length of stay and mortality

	Overall	*Period 1*	*Period 2*	*p-value*	*Period 1 (thiamine)*	*Period 1 (no thiamine)*	*p-value*	*Period 2 (thiamine)*	*Period 2 (no thiamine)*	*p-value*
Patient No, n (%)	3074	1508 (49.1%)	1566 (50.9%)	-	228 (15.1%)	1280 (84.9%)	-	980 (62.6%)	586 (37.4%)	-
Age (IQR)	67 (55-75)	67 (57-76)	66 (54-75)	-	66 (57-72)	68 (57-76)	-	68 (58-75)	61 (45-72)	-
Delirium, n (%)	545 (17.7%)	295 (19.6%)	250 (16.0%)	-	87 (38.2%)	208 (16.3%)	-	201 (20.5%)	49 (8.4%)	-
Delirium occurrence	0.18	0.20	0.16	0.009	0.38	0.16	-	0.21	0.08	-
Sepsis, n (%)*	485 (15.8%)	218 (14.5%)	267 (17.1%)	-	52 (22.8%)	166 (13.0%)	-	211 (21.5%)	56 (9.6%)	-
APACHE II, mean ± SD*	16.4 ± 7.09	16.5 ± 7.18	16.4 ± 6.99	-	19.9 ± 7.64	15.9 ± 6.93	<0.001	17.9 ± 6.63	13.8 ± 6.84	<0.001
SAPS II, mean ± SD*	35.8 ± 15.97	36.4 ± 15.91	35.24 ± 16.02	-	43.8 ± 16.94	35.0 ± 15.34	<0.001	38.7 ± 15.51	29.4 ± 15.18	<0.001
ICU LOS, median (IQR)	3 (2-5)	3 (2-5)	3 (2-5)	-	4 (2-9)	2 (2-4)	<0.001	3 (2-6)	2 (2-3)	<0.001
Mortality, n (%)	430 (14.0%)	198 (13.1%)	232 (14.8%)	-	42 (18.4%)	156 (12.2%)		165 (16.8%)	67 (11.4%)	-

Abbreviations: APACHE, Acute Physiology, Age and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score, LOS, length of stay; IQR= interquartile range.
*on ICU admission

Supplementary materials

Supplemental Table S1: Part one- Whole blood thiamine levels on admission, at 24 hours and 48 hours

	All patients (n=57)	***Thiamine deficient (≤100 nmol/L) (n=24)***	***Not thiamine deficient (>100 nmol/L) (n=33)***
WBT on ICU admission, nmol/L, median (IQR)	109 (90-152)	87 (71-92)	147 (126-157)
WBT at 24h post ICU admission, nmol/L, median (IQR)	127 (96-159)	91 (83-118)	157 (132-190)
WBT at 48h post ICU admission, nmol/L, median (IQR)	129 (99-159)	99 (84-124)	150 (125-178)

Abbreviations: IQR= Interquartile range. ICU = Intensive Care Unit

Supplemental Table S2: Part one- regression analysis: factors impacting delirium on admission

	OR (CI)	P-value
WBT	1.011 (0.307-3.325)	0.986
Age	1.075 (1.015-1.140)	0.014
Sepsis	3.745 (0.833-16.841)	0.085

Supplemental Table S3: Part two- hierarchical logistic regression analysis of delirium with *thiamine period*, APACHE II, ventilation hours, length of stay in ICU, age and sepsis

	OR (CI)	p-value
Ventilator hours	1.004 (1.003-1.006)	<0.001
Age	1.031 (1.022-1.041	<0.001
Sepsis	1.372(1.052-1.790)	0.02
APACHE II	1.056 (1.038-1.073)	<0.001
LOS ICU	1.094 (1.066-1.122)	<0.001
Thiamine Period	0.81 (0.652-1.002)	0.052

Supplemental Table S4: Part two- hierarchical logistic regression analysis of delirium with *thiamine*, APACHEII, ventilation hours, length of stay in ICU, age and sepsis.

	OR (95 % C.I.)	P-value
Thiamine	1.40 (1.12 – 1.73)	0.003
APACHEII	1.04 (1.03- 1.06)	<0.001
Ventilation hours	1.88 (1.49 – 2.37)	<0.001
Length of stay in ICU	1.12 (1.10 – 1.15)	<0.001
Age	1.03 (1.03-1.04)	<0.001
Sepsis	1.38 (1.06-1.80)	0.016