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Research Article

The Effect of Thiamine Administration on Clinical Outcomes in Traumatic Brain Injury Patients Saudi Arabia

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ABSTRACT

Background/ Purpose of the research: The impressive beneficial effects of thiamine in many diseases have recently gained widespread attention. However, this study investigated the impact of administering intravenous thiamine on clinical outcomes in traumatic brain injury (TBI) pa-tients admitted to ICU.

Materials/ Methods: Retrospective cohort observational design from January 2019 to Decem-ber 2020 for TBI patients admitted to ICU; Al-Noor Specialist Hospital, Makkah, was per-formed. The selected sample (221 with TBI) was grouped into a treatment group (received thiamine therapy, 100 mg/day; n=7) and a control group. Matched treatment and control groups were assigned and compared in terms of Glasgow Coma Scale (GCS) and biochemical parame-ters. All parameters were compared between both groups at hospital discharge.

Results: Thiamine administration did not achieve any significant impact between the control and treatment groups on lactate level (1.2 vs. 1.6 mmol/L; P = 0.22) or GCS progression on discharge (2.6 vs. 2.2, P = 0.578). This therapy had an impact on other biochemical outcomes including hemoglobin (78 vs. 97 g/L, P = 0.004) and blood urea nitrogen (4.8 vs. 7.6 mmol/L, P = 0.005), which were significantly higher in the treatment group, while serum sodium level was significantly lower in the treatment group (143 vs. 140 mmol/L, P = 0.013).

Conclusions: The administration of thiamine therapy had no clinical impact on lactate or GCS in patients with TBI at hospital discharge, and a significant impact was observed for hemoglo-bin, blood urea nitrogen, and sodium levels.

INTRODUCTION

The impressive beneficial effects of thiamine in many diseases such as severe sepsis and refeeding syndrome, metabolic acidosis, renal disease, and neurodegenera-tion have recently gained widespread attention from both scientists and researchers (Spoelstra-de Man et al., 2019). Thiamine, also known as vitamin B1, is a water-soluble vitamin that serves as an essential cofactor for four enzymes involved in mitochondrial and cellular functions (Attaluri et al., 2018). Thiamin diphosphate is the active form of vitamin B1. It acts as a fundamental cofactor in the Krebs cycle for pyruvate dehydrogenase to transform pyruvate, which comes from glucose, into acetyl coenzyme A to produce adenosine triphosphate (Dhir et al., 2019). It also plays an essential role in the pentose phosphate pathway as a cofactor for trans-ketolase and α-ketoglutarate. This pathway is important for neurotransmitter, lipid, nucleic acid, glutathione, and amino acid synthesis (Attaluri et al., 2018; Leite et al., 2018). Thiamine is unable to be produced by the hu-man body, and total body stores are restricted to around 30 mg, mostly located in the liver, kidney, and muscles (Spoelstra-de Man et al., 2019). Tissue thia-mine stores can be depleted within 18 days with insuffi-cient intake in healthy adults (Mallat et al., 2016).

Thiamine depletion can be accelerated in cases of sys-temic inflammation, oxidative stress, and hyper-metabolism in critical illness such as trauma, sepsis, after cardiac arrest, and cardiac surgery (Leite et al., 2018). Moreover, the prevalence of thiamine deficiency (TD) is around 20% of all critically ill patients (Attaluri et al., 2018). During intensive care unit (ICU) stay, this percentage might increase to 70%, with a 50% increase in mortality rate (Spoelstra-de Man et al., 2019).

The presentation of TD in hospitalized patients, espe-cially in

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ICU, has been linked to septic shock and sepsis, metabolic acidosis, neurodegeneration, and refeeding syndrome (Collie et al., 2017). TD induces anabolic me-tabolism, caused by converting pyruvate into lactate, then lactic acidosis may develop to accumulate lactic acid (Attaluri et al., 2018). High lactate levels related to acidosis contribute to an increased mortality risk (Hem-ing et al., 2020). Donnino et al. (2010) reported a signifi-cant negative correlation between lactic acidosis and levels of thiamine in a subgroup of a study population without liver dysfunction . Moskowitz et al. showed that patients with diabetic ketoacidosis had a negative corre-lation between thiamine and lactate levels (Moskowitz et al., 2014). Moreover, thiamin supplementation has been shown to correct metabolic acidosis and decrease mortality (Amrein et al., 2011; Attaluri et al., 2018; Col-lie et al., 2017).

The Glasgow Coma Scale (GCS) is one of the common tools used in traumatic brain injury (TBI) patients to determine the severity of disease (Corrigan et al., 2014). According to Rogers and Trickey, the GCS is a physio-logic scale that has shown to be particularly beneficial in the clinical management and prognosis of TBI (Rog-ers & Trickey, 2017). The GCS is based on the three stimuli: eye, verbal, and motor. Each stimulus has a range of values to be collected to classify the patient into three injury severity categories: severe, moderate, and minor impairment of consciousness level (Rath & Ray, 2016). The minimum GCS score is three which is completely unconscious, and the maximum is 15 which is fully alert. A low GCS score has a significant negative correlation with poor prognosis rates and higher mortali-ty (Braine & Cook, 2017).

Because TD may contribute to common medical disor-ders and lead to poor responses to routine medical ther-apy (Attaluri et al., 2018), the dose of intravenous thi-amine recommended by clinical studies of critically ill patients is similar to the dose that is usually used to re-cover any neurological disorders related to TD, which is 100–300 mg per day for non-alcoholic and 500 mg per day for alcoholic patients during the first 3 days of ad-mission (Dhir et al., 2019; Spoelstra-de Man et al., 2019). However, a laboratory test for thiamine level is not required to initiate thiamine therapy in ICU (Rajen-dram et al., 2015).

The literature suggested that critically ill patients with TBI who are exposed to thiamine intravenously would have positive clinical outcomes compared to those not receiving intravenous thiamine. The present study aimed to examine the beneficial effect of administering intravenous thiamine on TBI patients admitted to ICU.

2.MATERIALS AND METHODS

2.1 Study design and population

This was a single-center, retrospective cohort observa-tional study involving patients with TBI admitted to ICU at Al-Noor Specialist Hospital, the largest trauma center in Makkah City, Saudi Arabia, with a 30-bed capacity. Approximately 1,500 ICU patients are admit-ted to this center annually, 20% of them with TBI. The inclusion criteria were male patients aged ≥18 years diagnosed with TBI and admitted to the ICU. Patients who were admitted to a general ward, stayed less than 24 hours in ICU, died in the ICU, were still in the hospi-tal during the study period, or had uncompleted files were excluded from the analysis.

A total of 412 patients were diagnosed with a head inju-ry and admitted to ICU during the study period from January 2019 to December 2020. Of these, 191 were excluded, and the remaining 221 patients were ana-lyzed. Of the eligible patients, just seven (3.2%) patients received thiamine treatment (Figure 1).

The data and records were handled and kept in high confidentiality. Access to the data was only by the main researcher and the supervisor. Electronic records were saved on the main researcher's computer in a secure file.

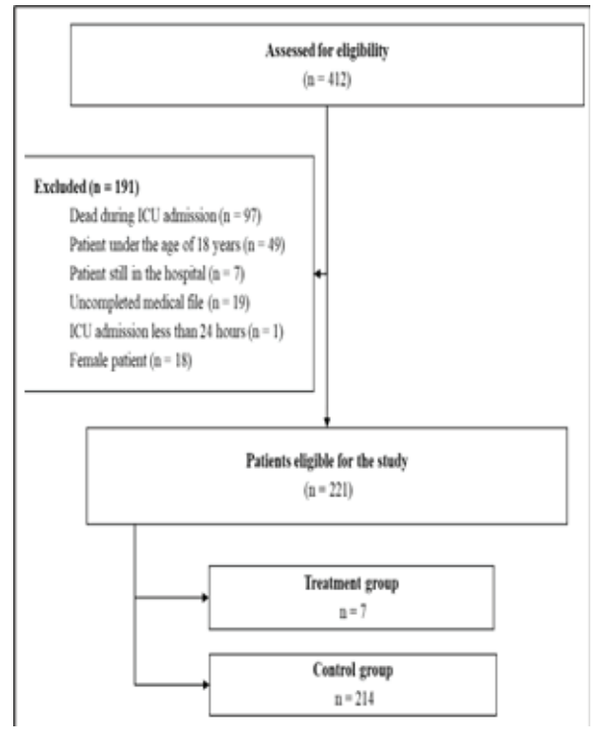


Figure 1. Study flow diagram for participant recruitment

2.2 Data collection

This research retrieved data from recruited participants using the electronic Al-Noor Specialist Hospital system and patient's medical files. The obtained patient data included general data (age, length of stay in ICU, and discharge destination); medical and surgical history; biochemical results; medication data, especially the pattern of thiamine use (dose, duration, and timing of treatment); clinical assessment such as presenting GCS and hemodynamic status; and enteral and parental nutrition data. All data were obtained at admission and discharge from ICU. Additional data were obtained at the end of thiamine administration for treated patients.

The GCS is the total of three measurements score, each with a range of score: eye (1–4), verbal (1–5), and mo-tor (1–6). Based on the GCS score, the TBI patients were grouped into three classifications: severe (3–8), moderate (9–12), and minor (13–15) (Rogers & Trickey, 2017). The selected sample was grouped into patients who received thiamine therapy (treatment group) and patients who did not receive thiamine therapy (control group). The used thiamin dose for all patients was 100 mg/day for 3 days.

2.3 Statistical Analyses

Data analysis was performed using SPSS software ver-sion 20. All categorical variables were summarized using percentages and frequencies, and quantitative variables were shown as mean ± standard deviation or median and interquartile range (IQR) according to data normali-ty. Comparisons of continuous variables between GCS groups were made with the Kruskal–Wallis test, and for non-continuous variables, the Chi-squared test was used. The propensity score matching was performed to adjust the confounders between the control and treat-ment groups according to Park et al., 2020. Between the matched pairs, the differences were compared using the ANCOVA test and Fisher's exact test for continuous and categorical variables, respectively. The significance level was set at $P < 0.05$ and the high significance level was set at $P < 0.001$. The calculation of effect size was performed by partial eta squared from the general linear model univariate analysis. The classifications of effect sizes were <0.1 = none, 0.1–0.4 = small, 0.5–0.7 = medi-um, and >0.8 = large (Sawilowsky, 2009; Park et al., 2020).

3. RESULTS

The baseline demographic data and laboratory values of patients and comparisons between GCS groups at admission and discharge are shown in Table 1. Overall, the mean age was 36.5 ± 17 years, and the youngest age was observed in the severe GCS at admission group (33.7 ± 13.2 years). A significant age difference existed between the GCS groups at admission. The commonest cause of injury was traffic accidents (77.4%), followed by falls (16.7%). The majority of the patients were ad-mitted to the hospital with a severe GCS caused by traffic accidents (81.4%). At discharge, the minor and mod-erate GCS groups from traffic accidents were higher than the severe group. These differences were statistical-ly significant ($P < 0.05$) for both groups. The overall length of stay in ICU and in the hospital were 7.4 ± 6.7 and 28 ± 26.6 days, respectively, with highly significant differences ($P < 0.001$) between GCS groups at both ICU admission and discharge.

Of all patients, 84.6% were free of medical illnesses, and 81.9% of patients had fewer than three chronic illnesses. On other hand, 67.9% of patients had a surgical history. These parameters showed no significant differences between GCS groups. The majority of patients were hemodynamically stable (79.2%). Highly significant differences in hemodynamic status ($P < 0.001$) existed between GCS groups at both ICU admission and dis-charge. In total, 72.4% of patients needed mechanical ventilators and started sedation. The average lengths of intubation and sedation were 5.2 ± 5.5 and 5.6 ± 5.7 days, respectively, with highly significant differences ($P < 0.001$) between GCS groups. Based on body mass index, 42.1% of patients were normal weight, 33.5% were overweight, 18.1% were obese, and 6.3% were un-derweight, with no statistically significant difference between groups. Of the study patients, 33.5% received nutrition support either orally (8.6%) or enterally (24.9%). Two thirds (66.55%) did not start any nutrition support at admission. Highly significant differences ($P < 0.001$) existed between GCS groups. The nutrition sup-port was started within 48 hours of ICU admission for 65.2% of patients in the study population, and after 48 hours of ICU admission for 34.8% of patients.

In the study population, the mean PO2 was 153 ± 117 mmHg. At admission, PO2 was higher than normal (>108 mmHg) in moderate and severe GCS (193.5 ± 109 and 167.2 ± 121 mmHg, respectively) compared to minor GCS (104 ± 92.4 mmHg; $P<0.001$). However, at discharge, PO2 was higher (>108 mmHg) in the severe GCS group (111.2 ± 41.9 mmHg) compared to minor and moderate GCS groups (93.4 ± 51.1 and 103.4 ± 49.5 mmHg, respectively; $P = 0.01$). No significant dif-ferences were observed between GCS groups in pH, PCO2, lactate, bicarbonate, or hemoglobin. Overall, the average blood glucose, serum creatinine, and serum sodium levels were 11.7 ± 22.2 mmol/L, 96.6 ± 58.9 µmol/L, and140.9 ± 11.6 mmol/L, respectively. These parameters were statistically significant ($P < 0.05$) in the GCS groups at admission but showed no significant improvement at discharge. The levels of white blood cells, platelets, and serum creatine phosphokinase were statistically significant ($P < 0.05$) in the GCS groups at discharge and not statistically significant at admission. The mean levels of blood urea nitrogen (BUN) and magnesium were 12.5 ± 56.9 and 0.74 ± 0.22 mmol/L, respectively, and were statistically significant ($P < 0.05$) for each GCS group.

The reported measures of arterial blood gas parameters of the patients who received thiamine during admission (baseline), on the end dose of thiamine, and at dis-charge from the ICU were compared using Friedman's test (Figure 2), showing no statistical significance ($P>0.05$) for any parameters. However, the pH level improved after thiamine administration then slightly increased at discharge (median = 7.33, 7.45, and 7.5, respectively). The serum lactate at baseline showed the highest level (median = 1.95 mmol/L), then decreased after thiamine therapy to normal level (median = 1.42 mmol/L), and at discharge increased beyond the upper level of normal (median = 1.63 mmol/L). The progres-sion of PO2 and PCO2 (baseline median = 144 and 42.3 mmHg, respectively) decreased to normal levels (medi-an = 95.3 and 38 mmHg, respectively) at the end dose of thiamine therapy and further decreased until dis-charge from ICU (median = 68.4 and 33 mmHg, respectively).

Table 1. Baseline characteristics of patients and GCS association with all variables (n = 221)

Variable	Total (n = 221)		Glasgow Coma Scale Score (Admission)				Glasgow Coma Scale Score (Discharge)			
	n	%	Minor (n = 51)	Moderate (n = 9)	Severe (n = 161)	P-value	Minor (n = 156)	Moderate (n = 36)	Severe (n = 29)	P-value
Age (mean ± SD)	36.5 ± 17		45.2 ± 21.8	40.6 ± 22.7	33.7 ± 13.2	<0.001**	37.2 ± 18	30.8 ± 12.2	35.2 ± 13.3	0.13
Mechanism of Injury						0.04*				0.02*
Traffic accident	171	77.4	33 (64.7)	7 (77.8)	131 (81.4)		123 (78.8)	29 (80.6)	19 (65.5)	
Fall	37	16.7	16 (31.4)	1 (11.1)	20 (12.4)		27 (17.3)	5 (13.9)	5 (17.2)	
Hit by object	9	4.1	1 (2)	1 (11.1)	7 (4.3)		5 (3.2)	2 (5.6)	2 (6.9)	
Other	4	1.8	1 (2)	0	3 (1.9)		1 (0.6)	0	3 (10.3)	
Length of stay in ICU (mean ± SD)	7.4 ± 6.7		3.3 ± 2.2	2.9 ± 1.8	8.9 ± 7.2	<0.001**	7.6 ± 7.2	10.3 ± 7.5	10.9 ± 6.5	<0.001**
Length of stay in the hospital (mean ± SD)	28 ± 26.6		16.8 ± 14.7	12.8 ± 5	32.5 ± 28.9	<0.001**	25 ± 22	40 ± 34	46.3 ± 35.1	<0.001**
Medical history						0.07				0.84
Yes	34	15.4	19 (15.8)	2 (12.5)	13 (7.5)		17 (12)	2 (5.7)	0	
No	187	84.6	32 (84.2)	7 (87.5)	148 (92.5)		125 (88)	33 (94.3)	29 (100	
Chronic illnesses						0.56				0.38
<3	181	81.9	39 (76.5)	8 (88.9)	134 (83.2)		127 (81.4)	32 (88.9)	22 (75.9)	
≥3	40	18.1	12 (23.5)	1 (11.1)	27 (16.8)		29 (18.6)	4 (11.1)	7 (24.1)	
Surgical history						0.29				0.72
Yes	150	67.9	37 (72.5)	1 (11.1)	105 (65.2)		108 (69.2)	24 (66.7)	18 (62.1)	
No	71	32.1	14 (27.5)	8 (88.9)	56 (34.8)		48 (30.8)	12 (33.3)	11 (37.9)	
Hemodynamic status						<0.001**				<0.001**
Stable	175	79.2	51 (100)	9 (100)	115 (71.4)		156 (100)	32 (88.9)	29 (100)	
Unstable	46	20.8	0	0	46 (28.6)		0	4 (11.1)	0	
Sedation						<0.001**				<0.001**
Yes	160	72.4	5 (9.8)	6 (66.7)	149 (92.5)		11 (7.1)	8 (22.2)	9 (31)	
No	61	27.6	46 (90.2)	3 (33.3)	12 (7.5)		145 (92.9)	28 (77.8)	20 (69)	
Intubation (days)	5.2 ± 5.5		2.3 ± 3.7	1.7 ± 1	5.5 ± 5.7	<0.001**	4.1 ± 4.9	7.1 ± 6	7.3 ± 6.5	<0.001**
Sedation (days)	5.6 ± 5.7		2.9 ± 3.3	1.7 ± 1	6.2 ± 6	<0.001**	4.8 ± 5.2	7.4 ± 6.1	8.1 ± 7.1	<0.001**
Body mass index (kg/m^2)						0.44				0.39
Underweight	14	6.3	2 (3.9)	0	12 (7.5)		8 (5.1)	6 (16.7)	1 (3.4)	
Normal	93	42.1	23 (45.1)	6 (66.7)	64 (39.8)		68 (43.6)	14 (38.9)	10 (34.5)	
Overweight	74	33.5	20 (39.2)	1 (11.1)	53 (32.9)		52 (33.3)	10 (27.8)	12 (41.4)	
Obese	40	18.1	6 (11.8)	2 (22.2)	32 (19.9)		28 (17.9)	6 (16.7)	6 (20.7)	
Nutrition support						<0.001**				<0.001**
Orally	19	8.6	16 (31.4)	1 (11.1)	2 (1.2)		133 (85.3)	13 (36.1)	1 (3.4)	
Enteral nutrition	55	24.9	0	0	55 (34.2)		16 (10.3)	18 (50)	25 (86.2)	
NPO	147	66.5	35 (68.6)	8 (88.9)	104 (64.6)		7 (4.5)	5 (13.9)	3 (10.3)	
Early administration of nutrition support						0.169				0.895
Yes	144	65.2	13 (25.5)	2 (22.2)	62 (38.5)		55 (35.5)		55 (35.5)	
No	77	34.8	38 (74.5)	7 (77.8)	99 (61.5)		101 (64.7)	23 (63.9)	20 (69)	
PH	7.3 ± 0.1		7.4 ± 0.09	7.4 ± 0.10	7.3 ± 0.11	0.53	7.4 ± 0.04	7.4 ± 0.05	7.4 ± 0.05	0.08
PCO2 (mmHg)	40.4 ±8.8		38.2 ± 9.6	41.9 ± 9.3	41.1 ± 8.4	0.12	36 ± 7.1	36.3 ± 4.8	34.6 ± 3.9	0.78
PO2 (mmHg)	153 ± 117		104 ± 92.4	193.5 ± 109	167.2 ± 121	<0.001**	93.4 ± 51.1	103.4 ± 49.5	111.2 ± 41.9	0.01*
Lactate (mmol/L)	2.2 ± 1.7		2.2 ± 1.8	1.4 ± 0.4	2.3 ± 1.7	0.25	1.3 ± 0.7	1.5 ± 0.6	1.3 ± 0.7	0.16
Bicarbonate (mmol/L)	21.9 ± 3.3		21.9 ± 3.2	22.5 ± 2.7	21.9 ± 3.4	0.84	24.4 ± 3.5	24.2 ± 2.7	25 ± 3.4	0.07
Hemoglobin (g/L)	116.4 ± 30.9		117.3 ±36.9	110.4 ±16.4	116.6 ± 29.5	0.28	96.8 ± 22.7	99.9 ± 23.8	96.2 ± 15.6	0.46
White blood cell (10^9/L)	14.8 ± 13.8		18.1 ± 25.3	15 ± 9.2	13.9 ± 7.4	0.98	10.9 ± 7.4	10.9 ± 3.2	14.1 ± 5.8	0.00**
Platelet (Fl)	206.1 ± 106.6		214.3 ± 117.4	231.2 ± 57.5	202.2 ± 105.3	0.19	266 ± 177	372 ± 229	376 ± 165	0.00**
Blood glucose (mmol/L)	11.7 ± 22.2		9.3 ± 5.1	30.9 ± 63.9	11.4 ± 21.1	0.04*	8.1 ± 12.3	6.7 ± 1.3	6.8 ± 1.7	0.98
Blood urea nitrogen (mmol/L)	12.5 ± 56.9		8.5 ± 9	6.5 ± 2.9	14.1 ± 66.5	<0.001**	5.5 ± 2.9	6.2 ± 4.8	7.1 ± 2.8	0.02*
Creatinine (µmol /L)	96.6 ± 58.9		108.8 ±57.2	82.6 ± 28.2	93.5 ± 60.4	0.03*	62.1 ± 19.9	70.5 ± 36.2	62.4 ± 19.5	0.38
Phosphorus (mmol/L)	2.1 ± 10.3		1.3 ± 0.7	1.2 ±0.4	2.4 ±12.1	0.08	0.91 ± 0.25	0.94 ± 0.27	0.95 ± 0.22	0.67
Sodium (mmol/L)	140.9 ± 11.6		137.5 ± 9.9	139.3 ± 2.4	142.2 ± 12.2	<0.001**	141.9 ± 3.9	142.5 ± 5.6	142.8 ± 5.3 ±	0.09
Magnesium (mmol/L)	0.74 ± 0.22		0.79 ± 0.22	0.63 ± 0.12	0.73 ± 0.23	<0.001**	0.82 ± 0.17	0.80 ± 0.13	0.96 ± 0.29	<0.001**
Potassium (mmol/L)	4.2 ± 2.9		4.1 ± 0.7	4.5 ± 0.9	4.3 ± 3.6	0.24	3.6 ± 0.4	3.6 ± 0.6	4.9 ± 6.2	0.40
Creatine phosphokinase (U/L)	2303 ± 3257		2075 ± 2882	2374 ± 4340	2368 ± 3380	0.17	2526 ± 2683	2079 ± 4729	1340 ± 1395	0.01*

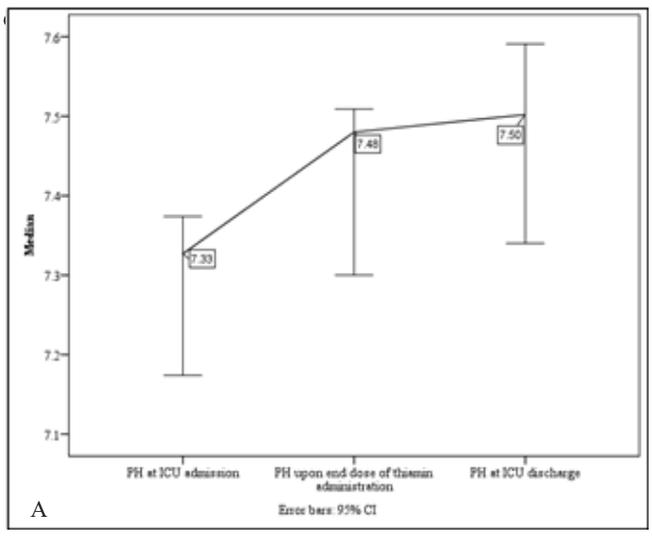
NPO: nothing by mouth; PCO_2: Partial pressure of carbon dioxide; PO_2: Partial pressure of oxygen.
*P<0.05, **P<0.001

Table 2. Effect of thiamine supplementation on biochemical results and GCS groups after matching (n = 7 for each group)

Parameter	Control: Median [IQR] Mean ± SD Frequency (%)	Treatment: Median [IQR] Mean ± SD Frequency (%)	P-value	Effect size
pH	7.41 [0.06]	7.5 [0.20]	0.554	0.033
PCO_2 (mmHg)	36.3 [8]	33 [9.6]	0.440	0.055
PO_2 (mmHg)	113 [47.1]	68.4 [46.8]	0.454	0.052
Lactate (mmol/L)	1.2 [1.5]	1.6 [1.1]	0.22	0.133
Bicarbonate (mmol/L)	24.7 [5.1]	26 [2.3]	0.922	0.001
Hemoglobin (g/L)	78 [44]	97 [30]	0.004*	0.538
White blood cells (10^9/L)	9.1 [5]	12.1 [2.7]	0.639	0.021
Platelets (Fl)	227 [177]	354 [447]	0.515	0.039
Blood glucose (mmol/L)	6.7 [1.8]	6.3 [2.4]	0.317	0.091
Blood urea nitrogen (mmol/L)	4.8 [4.6]	7.6 [8.5]	0.005*	0.53
Creatinine (µmol/L)	60 [17]	53 [60]	0.343	0.082
Phosphorus (mmol/L)	1.1 [0.5]	1 [0.2]	0.915	0.001
Sodium (mmol/L)	143 [5]	140 [8]	0.013*	0.441
Magnesium (mmol/L)	0.9 [0.2]	0.8 [0.1]	0.365	0.075
Potassium (mmol/L)	3.7 [0.4]	4.4 [0.8]	0.105	0.22
Creatine phosphokinase (U/L)	1586 [1294]	713 [1033]	0.379	0.071
Glasgow Coma Scale Severe Moderate Minor	2.6 ± 0.8 1 (14.3%) 1 (14.3%) 5 (71.4%)	2.2 ± 0.7 1 (14.3%) 4 (57.1%) 2 (28.6%)	0.578 0.388^	0.083

In SPSS, minor GCS was entered as 3, moderate GCS was entered as 2, and severe GCS was entered as 1.
^ P-value was determined by Fisher's exact test. Other P-values in the table were determined by ANCOVA test. *P<0.05
Effect size values were determined by partial eta squared from the general linear model *univariate analysis.*

Finally, the bicarbonate serum level was lower than the normal range during baseline (median = 19.2 mmol/L), then increased to normal after thiamine therapy and maintained until



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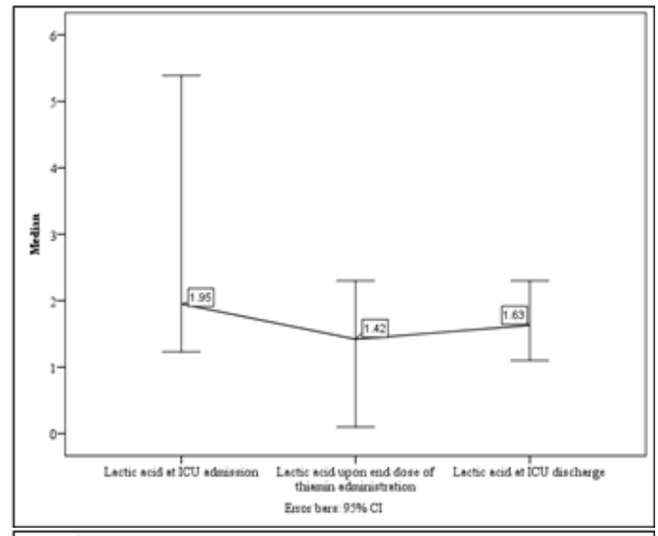

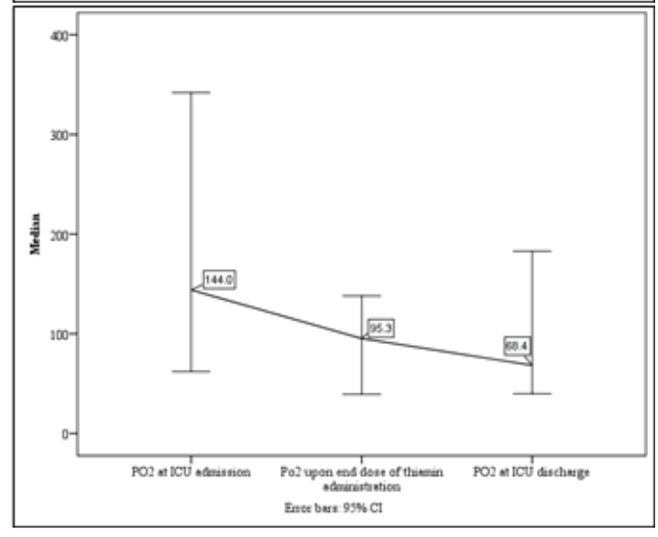

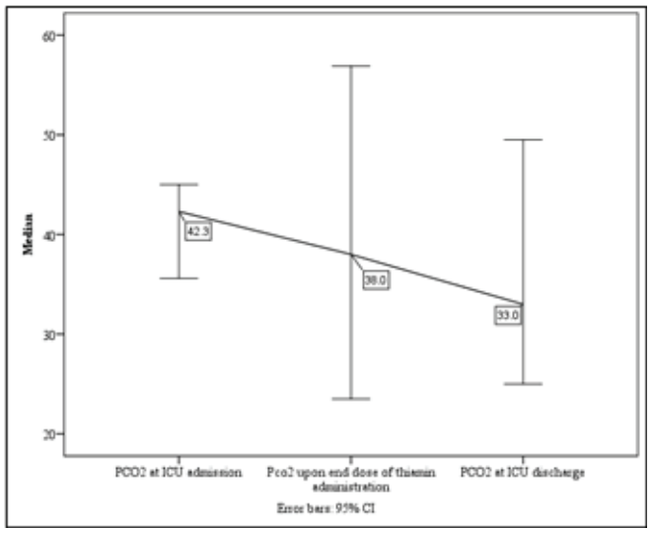

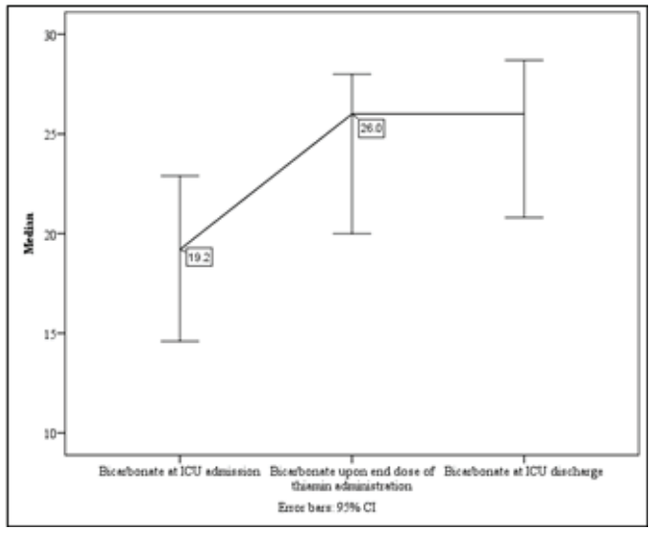

Figure 2. The progression of arterial blood gas (ABG) parameters of the patients received thiamine during admis-sion (baseline), upon end dose of thiamine, and at dis-charge from the ICU.

A: The progression of PH parameter.

B: The progression of lactate parameter.

C: The progression of PO2 (partial pressure of oxygen) parameter.

D: The progression of PCO2 (partial pressure of carbon dioxide) parameter.

E: The progression of bicarbonate parameter.

Finally, the bicarbonate serum level was lower than the normal range during baseline (median = 19.2 mmol/L), then increased to normal after thiamine therapy and maintained until discharge from ICU (median = 26 mmol/L).

then increased to normal after thiamine therapy and maintained until discharge from ICU (median = 26 mmol/L).

Of the 221 patients, seven propensity score–matched pairs for the treatment and control groups were ob-tained and compared in terms of GCS and biochemical parameters (Table 2). Hemoglobin (78 [44] vs. 97 [30], P = 0.004) and BUN (4.8 [4.6] vs. 7.6 [8.5], P = 0.005) were significantly higher in the treatment group and had a moderate effect size. Additionally, a statistical differ-ence existed between the treatment and control groups in serum sodium level (143 [5] vs. 140 [8], P = 0.013), with a small effect size of 0.44. The average and percentages of GCS were not significantly different be-tween the two groups.

4. DISCUSSION

This retrospective cohort study aimed to examine the effect of thiamine administration on TBI patients in ICU, Al-Noor Hospital, Makkah. The main result was that thiamine administration achieved no significant impact on lactate level or GCS progression. However, thiamine administration was associated with a signifi-cant increase in hemoglobin and BUN and a significant decrease in the level of sodium on discharge.

Lactate levels after thiamine administration fell to the normal level, then slightly increased at hospital dis-charge. Additionally, no statistical difference in lactate between the treatment and control groups was ob-served.

Unexplained lactic acidosis is one of the ICU complica-tions caused by lactate accumulation, which is mainly attributed to TD. Furthermore, various cases have re-ported the correlation between thiamine supplementa-tion and metabolic acidosis. Amrein et al. (2011) report-ed that lactic acid diminished into the normal range within 24 hours of intravenous thiamine administration (300 mg/day) in a case of a 56-year-old man, an alco-holic patient admitted to ICU due to decreased level of consciousness (GCS = 6). Moreover, Donnino et al. (2010) reported an inverse correlation between thiamine and lactic acidosis in sepsis patients without liver dys-function.

The severity of brain injury was not improved signifi-cantly in the treatment group compared to the control group, as reflected by the GCS score on hospital dis-charge (Table 2). This result is in line with the study of Berger et al. (2008), who conducted a randomized, double-blind, placebo-controlled study to assess the impact of an intervention of selenium (270 μg), zinc (30 mg), vitamin C (1.1 g), and vitamin B1 (100 mg) micro-nutrient supplements for 5 days in ICU patients. They found that TBI patients in ICU had significantly more severe GCS scores on discharge compared to the place-bo group. The probable explanation for the previous result might be related to improper supplement admin-istration or interactions that could occur after the ad-ministration of multivitamins and minerals.

Several possible justifications may explain why thia-mine administration did not attenuate lactate and GCS significantly in this study. Firstly, the small number of patients enrolled in the treatment group (n = 7) is not considered a representative sample because thiamine administration is not used routinely in the standard ICU protocol in the study hospital. Secondly, the dose and duration of thiamine administration might be insuffi-cient. Based on the study database, the used thiamin treatments might be insufficient for such patients. A similar result was observed in a prior study by Ferguson et al. (1997). Even though the hospital protocol for thi-amine administration was based on previous studies on critically ill patients,

the optimal dose and duration for patients with TBI have not been established. Thirdly, based on many studies, initiating thiamine administra-tion is recommended within 3 days of ICU admission (Attaluri et al., 2018; Collie et al., 2017; Dhir et al., 2019). Early initiating thiamine administration is crucial as it may help prevent the progression of thiamine defi-ciency, reduce oxidative stress, and mitigate secondary brain injury processes (Spoelstra-de Man et al., 2019). In this cohort, thiamine supplementation was initiated within 3 days for only two patients, within 1 week for three patients, and within 3 weeks for two patients ac-cording to the hospital database. Accordingly, delayed thiamine administration occurred for 71.4% of the treated patients.

The study results found that thiamine administration significantly ($P<0.05$) improved hemoglobin levels in TBI patients. Thiamine plays an important role in sev-eral metabolic reactions in the human body, mainly in assisting and regulating protein, carbohydrate, and fat metabolism, which are fundamental for energy genera-tion, and contribute to red blood cell production and hemoglobin synthesis (Chaitanya et al., 2012). A previ-ous study reported that TD might affect hematopoiesis and various body organ systems (Chineke et al., 2006). Sharma & Bist (2018) conducted an experimental study to investigate the impact of TD on the complete blood count of Swiss albino mice. They found a significant reduction in hemoglobin and erythrocytes in the TD group. These results indicated that thiamine could influ-ence hematopoiesis and hemoglobin levels. The decline in hemoglobin and erythrocytes reported by Falahatkar et al. (2014) may be due to hematopoiesis alteration. This directly affects the blood-forming organs, resulting in extreme impairment of red blood cell synthesis (Badraoui et al., 2011). Therefore, thiamine therapy may maintain the hematological parameters, and fur-ther studies are needed to better explain this result in healthy subjects.

In this cohort study, the sodium level was within the normal range in both treatment and controls group at ICU admission, then significantly different on dis-charge. A previous study showed that thiamine has a potential therapeutic effect on serum sodium. Khalifa et al. (2016) studied the role of thiamine in the regulation of the renal response to metabolic acidosis in rats. This study showed that thiamine supplementation modulat-ed serum sodium and bicarbonate levels, which were reduced in metabolic acidosis rats compared with other experimental groups that received a high-dose thiamine supplement. However, they concluded that a high-thiamine diet (600 mg/kg/day) enhanced kidney func-tion and the response to metabolic acidosis induced by chloride ammonium in adult male rats (Khalifa et al., 2016).

BUN levels depend on the complex balance of urea production, metabolism, and excretion (Beier et al., 2011). Several renal and non-renal factors modulate the BUN level, such as glomerular filtration, dietary protein intake, catabolism of endogenous proteins, and aging (Higgins, 2016). In the current study, serum BUN was significantly slightly higher than the normal range in the treatment group compared with the control group. However, the median level of creatinine was within the normal range for both study groups (60 [17] vs. 53 [60] μmol/L, respectively, for the control and treatment groups). The interpretation of BUN level elevation in association with normal renal function may include multiple factors. Firstly, hypercatabolic status related to critical illness and trauma is associated with tissue dam-age that increases protein catabolism and consequently, increased urea synthesis (Beier et al., 2011; Higgins, 2016). Secondly, metabolic acidosis increases amino acid utilization to increase ureagenesis, which increases protein breakdown and decreases protein synthesis (Beier et al., 2011). Thirdly, increased urea excretion is associated with increased protein intake, according to ICU study center guidelines that consider high protein for critically ill TBI patients (1.3 to 2.5 g/kg/day) (Hig-gins, 2016; Langley et al., 2017). Fourthly, certain med-ications that induce a catabolic state cause increased urea production (Beier et al., 2011). Finally, states of low blood circulation such as heart failure, dehydration, and hypovolemic shock (Aronson et al., 2004; Mehta, 2008) could affect serum BUN results. No clear explanation was found in the literature regarding vitamin B1 and BUN, a matter that needs further investigation.

Nutritional support in the hospital was initiated accord-ing to the guidelines of the European Society for Clinical Nutrition and Metabolism for ICU. This protocol rec-ommends early administration of nutrition support, initiated within 48 hours of ICU admission (Singer et al., 2019). In the study population, early administration of nutrition support was observed for 65.6% of patients, while 34.8% received nutrition support after 48 hours of admission. The delay in nutrition administration might have been related to polytrauma patients, 67.9% of whom required surgical intervention. Delayed nutrition initiation might also accelerate thiamine store depletion and develop TD in those patients due to inadequate thiamine intake (Attaluri et al., 2018).

This study has some limitations. Firstly, it is fundamen-tally limited by its retrospective cohort observational design. Thiamine treatment was not randomized, and thiamine treatment was only ordered by and at the dis-cretion of the ICU physician. The study was conducted in a single center, limiting the generalization of the re-sults. Finally, the administration of thiamine to TBI patients was not a standard protocol for administration at the beginning of the patient's treatment.

5. CONCLUSION AND RECOMMENDATION

The study results concluded that the administration of thiamine therapy had no clinical impact on lactate or GCS on discharge in patients with TBI. This therapy had an impact on other biochemical outcomes includ-ing hemoglobin, BUN, and sodium. However, a larger, multi-center cohort would indeed provide more robust data and improve the precision of our findings. Addi-tionally, such an expansion would allow for the inclu-sion of diverse patient populations, which could help us better evaluate the effect of thiamine administration on mitigating the adverse effects of TBI. It is also recommended to administering higher doses of thiamine ther-apy and increasing the treatment length for critically ill TBI patients and perform further prospective cohort trials to better determine the clinical roles of thiamine therapy in critically ill TBI patients. Finally, initiate early nutritional support combined with thiamine administra-tion within 48 hours for all ICU patients, enhance ICU physicians' awareness of thiamine

deficiency and the importance of routine thiamine therapy in TBI man-agement, and conduct further prospective cohort trials to better elucidate the clinical role of thiamine therapy in critically ill TBI patients.

AUTHORS CONTRIBUTION

FA and AG conceived and designed the study; AG and RB conducted research; AG and RB provided research materials and collected the data; FA and HA analyzed and interpreted data; FA and AG wrote the initial draft, and FA and AG finalized the manuscript. All authors have critically reviewed and approved the final manu-script and are responsible for its content.

DISCLAIMER

ETHICAL CONSIDERATION

Ethical approval for this study was obtained from the General Administration for Research and Studies, Min-istry of Health, and Al-Noor Specialist Hospital by ap-plication using the research request form, bilingual data-sharing agreement, and non-disclosure agreement forms (Approval number: H-02-k-076-0820-328).

Participants Consent

Not Applicable.

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CONFLICT OF INTEREST

All authors have given final approval of this manuscript to be published. In addition, they have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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