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Thiamine Therapy During Refractory Lactic Acidosis in Critically Ill Children

Kritik Hasta Çocuklarda Dirençli Laktik Asidoz Sırasında Tiamin Tedavisi

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Abstract

Introduction: Thiamin deficiency, which is an overlooked but important cause of lactic acidosis, can lead to several clinical symptoms, including neuropathy, cardiogenic shock, and death, even though it can be easily treated in critically ill children.

Methods: A single-center, retrospective cohort study conducted between March 2020 and March 2022.

Results: Twenty-two patients were included in the study. The mean age was 26.5 (range, 1-214) months. The median thiamin dose was 50 (range, 3-100) milligrams and the mean thiamin treatment duration was 4 (range, 1-16) days. The mean length of PICU when thiamin treatment was started was 8 (range, 2-177) days. Thiamin treatment was administered on the 2nd (1-5) day of lactic acidosis. The mean lactate values after thiamin treatment was 5.5 (range, 5-17) mmol/L at the 6th hour, 4.1 (range, 1.5-17) mmol/L at the 12th hour, 3.1 (1.4-20) mmol/L at the 24th hour, and 2.7 (range, 0.15-17) mmol/L at 48th hour. Eleven (50%) patients' lactate levels decreased below 4 mmol/L at the 12th hour of thiamin treatment. Blood gas values before thiamin treatment, lactate decrease trends, thiamin treatments' duration, and form, and patients' risk factors were not statistically significant in the two groups by 28-day mortality.

Conclusion: We believe that in patients with lactic acidosis not directly related to a circulatory disorder, low clinical suspicion and early thiamin treatment of lactic acidosis is the right approach in the absence of specific diagnostic tests.

Keywords: Thiamin, lactic acidosis, children, pediatric intensive care unit

Öz

Giriş: Laktik asidozun gözden kaçan ancak önemli bir nedeni olan tiamin eksikliği, kritik hasta çocuklarda kolaylıkla tedavi edilebilmesine rağmen nöropati, kardiyojenik şok ve ölüm gibi çok çeşitli klinik spektrumlara yol açabilmektedir.

Yöntemler: Mart 2020 ile Mart 2022 arasında tek merkezli, geriye dönük bir kohort çalışmasıdır.

Bulgular: Yirmi iki hasta çalışmaya dahil edildi. Ortalama yaş 26,5 (1-214) aydı. Ortanca tiamin dozu 50 (3-100) miligram ve ortalama tiamin tedavi süresi 4 (1-16) gündü. Tiamin tedavisine başlandığında hastaların ortalama çocuk yoğun bakım ünite süresi 8 (2-177) gündü. Laktik asidozun 2. (1-5) gününde tiamin tedavisi başlandı. Tiamin tedavisi sonrası ortalama laktat değerleri 6. saatte 5,5 (5-17) mmol/L, 12. saatte 4,1 (1,5-17) mmol/L, 24. saatte 3,1 (1,4-20) mmol/L olarak ve 48. saatte 2,7 (aralık, 0,15-17) mmol/L olarak belirlendi. Tiamin tedavisinin 12. saatinde 11 (%50) hastanın laktat düzeyi 4 mmol/L'nin altına düştü. Tiamin tedavisi öncesi kan gazı değerleri, laktat düşüş eğilimleri, tiamin tedavilerinin süresi, şekli ve hasta risk faktörleri her iki grupta da 28 günlük mortalite açısından istatistiksel olarak anlamlı değildi.

Sonuç: Dolaşım bozukluğu ile doğrudan ilişkili olmayan laktik asidozlu hastalarda, özgül tanı testlerinin yokluğunda düşük klinik şüphe ve laktik asidozun erken tiamin tedavisinin doğru yaklaşım olduğunu düşünüyoruz.

Anahtar Kelimeler: Tiamin, laktik asidoz, çocuklar, çocuk yoğun bakım ünitesi

Introduction

High or increasing lactate levels in the blood usually mean inadequate oxygen delivery or cellular hypoxia in pediatric intensive care units (PICUs). Generally, mortality risk increases when blood lactate levels are the highest or lactate normalization times are increased.[1] Hyperlactatemia refers to lactate levels above 2 mmol/L, and lactic acidosis refers

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to serum lactate concentration above 4 mmol/L. Arterial pH levels decrease when lactic acidosis emerges as an acid-base disorder. At the same time, other coexisting disorders may increase pH levels to the normal range or higher levels. Lactic acidosis occurs when lactic acid production exceeds lactic acid clearance.[2] Children with thiamin deficiency who are incapable of oral feeding and receive total parenteral nutrition (TPN) need age-appropriate thiamin support.[3]

It has been shown in the medical literature that thiamin deficiency contributes to mortality in critically ill children who have shock and lactic acidosis. Thiamin is mostly absorbed in the duodenum and ileum. Oral and intravenous thiamin treatments have similar effects on recovering lactic acidosis.[1] Irreversible neurological deficits can occur in untreated thiamin deficiency.[4] In this study, we aimed to investigate the relationship between thiamin and the related status of patients with lactic acidosis who received thiamin treatment. Also, to investigate patients' demographic data, the outcomes of those who were diagnosed as having thiamin deficiency during diagnosis and treatment, and thiamin's effects on mortality.

Materials and Methods

Setting

This study was conducted in the PICU of a university hospital. In our PICU, intensive care services are provided to patients in non-surgical and surgical departments, and approximately 700 patients are followed up annually. Our PICU is a combined unit offering both pediatric and cardiac critical care. Written permission was obtained from the Local Ethics Committee of Ankara University Hospital for this study (ethics committee number: İ09-566-22). Our study was conducted in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association.

Study Population and Protocol

This study was conducted retrospectively by scanning patients between 2020 and 2022 who had refractory (>24 hours) lactate rise (<2 mmol/L) and lactic acidosis (>4 mmol/L) and received thiamin treatment. Thiamin was given 3-100 mg orally, intravenously (IV), or intramuscularly (IM). Treatment was continued for 5 days if there was a positive treatment response or for 10 days if thiamin levels were monitored and a low level was detected. We mostly prefer the IM form of thiamin even though the available form of thiamin in our hospital pharmacy affects our choice. The inclusion criteria were lactate rise or lactic acidosis lasting 24 h or more and no recently developed hemodynamic problems or an oxygenation problem that explained lactic acidosis. The exclusion criteria were acute hepatic failure, mitochondrial diseases, or cardiac arrest.

Follow-up

The data of 22 patients who met the inclusion criteria including age, weight, thiamin dosage, thiamin form, thiamin treatment duration, thiamin levels if possible, respiratory distress, inotrope usage, anemia existence, abnormal liver function tests, abnormal renal function tests, history of metabolic diseases, history of abdominal surgery, accompanying malignancy, the existence of oral or enteral feeding when lactic acidosis was identified, TPN treatment, imaging in suspected thiamin deficient patients, ICU length of stay, and 28-day mortality were recorded. Blood gas (pH, pCO_2, HCO_3, lactate) before thiamin treatment and lactate levels at 6, 12, 24, 48, and 72 h after thiamin treatments were recorded.

Definitions

Lactate rise and lactic acidosis: A lactate rise above 4 mmol/L regardless of whether the pH level is low, normal, or high.[2] Refractory lactate rise: A lactate rise persisting for 24 h or more and cannot be explained by any other reason. VIS: Vasoactive inotrope score.[5]

Statistical Analysis

The data were analyzed using SPSS version 26.0 software (IBM Corp, Armonk, NY). The mean, standard deviation, median, frequency distribution, and percentage values were determined as descriptive statistics of the variables. Mean values were used in parametric tests and median values in non-parametric tests. Pearson's chi-square test and Fisher's Exact test were used to analyze categorical variables. The data were tested for normal distribution using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). The independent samples t-test was used to analyze differences in normally distributed variables between the two independent groups. The Mann-Whitney U test was used to analyze the differences between the median values of non-normally distributed variables. P-values of <0.05 were considered statistically significant.

Results

We enrolled 22 patients who had refractory lactate rise or lactic acidosis and received thiamin treatment. These 22 patients met the inclusion criteria, had refractory lactate rise or lactic acidosis, and received thiamin treatment in the 2-year study period.

Patient Demographic Data (22 Patients)

Twenty-two patients were included in the study. The mean age was 26.5 (range, 1-214) months. The median thiamin dose

was 50 (3-100) milligrams and the median thiamin treatment duration was 4 (range, 1-16) days. The patients' mean length of PICU stay when thiamin treatment was initiated was 8 (range, 2-177) days. Thiamin treatment was administered on the 2nd (range, 1-5) day of lactic acidosis. Thiamin treatment was administered IV to two (9%), IM to 15 (68%) patients, and orally to five (23%) patients. Thiamin levels were obtained in 2 of 22 (9%) patients. Six patients had malignancies [ganglioneuroblastoma, T-cell acute lymphoblastic leukemia (T-ALL), hemophagocytic lymphohistiocytosis (HLH), B-cell acute lymphoblastic leukemia (B-ALL), acute myeloid leukemia, craniopharyngioma). Two (9.2%) patients had metabolic disease [fatty acid oxidation defect, methylmalonic acidemia (MMA)], five patients had respiratory distress and respiratory failure (viral pneumonia n=4, Coronavirus disease-2019 pneumonia n=1), five had cardiac disease (Fallot tetralogy; cardiac arrest due to food aspiration in a patient who was post-op for pulmonary artery binding surgery and had heart failure secondary to anemia), and four (18.2%) patients had other etiologies (convulsion n=3, arteriovenous malformation n=1) and were followed up in our PICU.

Post-thiamin Treatment Lactate Trend

Seventeen of the 22 patients had a significant lactate decrease after thiamin treatment. The mean lactate values after thiamin treatment were 5.5 (5-17) mmol/L at the 6th hour, 4.1 (1.5-17) mmol/L at the 12th hour, 3.1 (1.4-20) mmol/L at the 24th hour, and 2.7 (0.15-17) mmol/L at the 48th hour. Eleven patients (50%), lactate levels decreased below 4 mmol/L at the 12th hour of thiamin treatment (Figure 1). Patient characteristics and thiamin treatment outcomes are shown in Figure 2. Patient characteristics and incidence of 28-day mortality

When patients were analyzed in two groups by 28-day mortality (survivor and non-survivor); age, weight, and length of stay in the PICU were statistically significant (p=0.04, p=0.02, and p=0.01, respectively). Thiamin treatment start days were found to be statistically significant between the living and deceased groups (p=0.02). Blood gas values before thiamin treatment, lactate decrease trends, thiamin treatments' duration, and form, and patients' risk factors were not statistically significant in either group (Table 1, Figure 3).

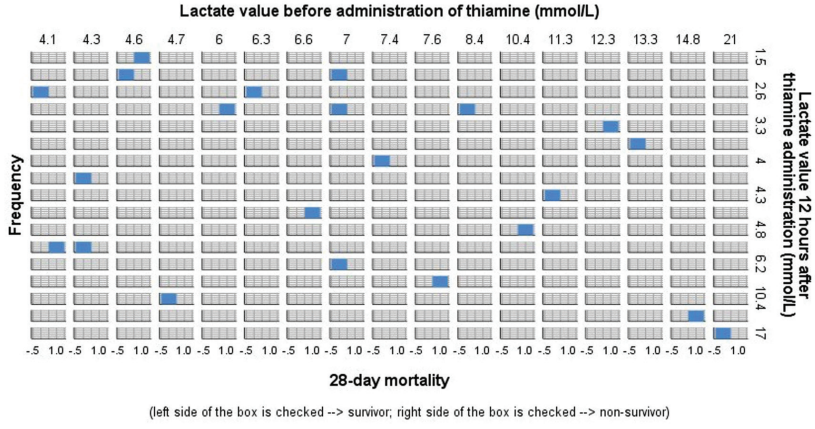

Figure 1. Post-thiamin treatment lactate trend

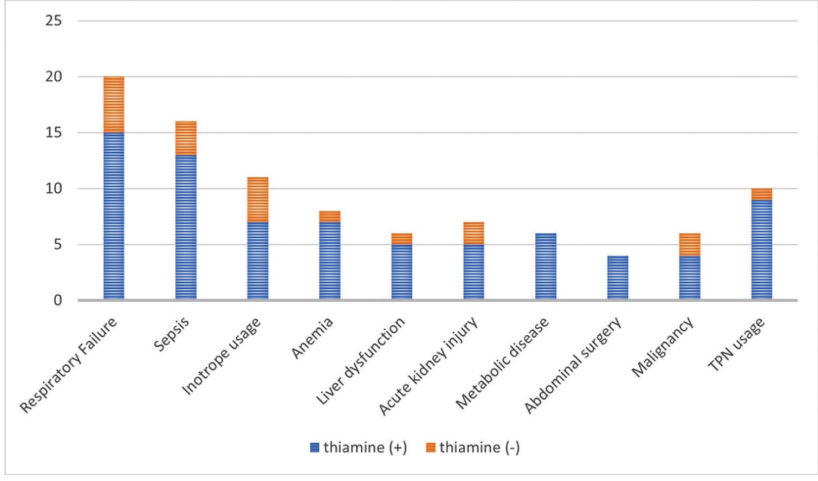

Figure 2. Patients' characteristics and thiamin treatment outcomes

Table 1. The patient characteristics and outcomes according to the 28-day mortality

Parameters	All patients (n=22)	28-day mortality, survivor (n=14)	28-day mortality, non-survivor (n=8)	p-value
Age (months)	26.5 (1-214)	57.0 (2-191)	5.7 (1-214)	**0.04***
Weight (kg)	14 (2.7-50)	23.0 (4.6-50)	5.3 (2.7-40)	**0.02***
Thiamine dose (mg)	50 (3-100)	50.0 (3-100)	50.0 (13-100)	0.71*
Thiamine, days	4 (1-16)	5.0 (1-16)	2.0 (1-9)	0.57*
Enteral nutrion, no, days (until LA)	4 (0-45)	3.5 (0-45)	5.5 (0-11)	0.97*
PRISM III score	9±5.6	7.9±5.6	10.8±5.3	0.24**
PELOD 2 score	15.6±9.4	14.9±9.5	17±9.8	0.63**
VIS score	2.5 (0-92)	0 (0-35)	12.5 (0-92)	0.18*
CRRT, yes	5 (100%)	3 (21%)	2 (25%)	0.84***
PEX, yes	6 (100%)	4 (28%)	2 (25%)	0.85***
ECMO, yes	3 (100%)	1 (7%)	2 (25%)	0.24***
Duration of lactic acidosis (until treatment)	2 (1-5)	2 (1-4)	2 (1-5)	0.97*
Thiamine treatment day	8 (2-177)	4 (2-83)	14.5 (4-177)	**0.02***
Pre-thiamine treatment laboratory values				
pH	7.39±0.05	7.39±0.04	7.39±0.07	0.96**
pCO_2	37.5 (17-58)	37.2 (17-43.5)	40.2 (27-58)	0.19*
HCO_3	23.0±5.7	21.7±4.0	25.4±7.6	0.15**
Lactate (mmol/L)	7 (4-21)	7.0 (4-21)	7.1 (4.1-14.8)	0.70*
Post-thiamine treatment lactate values				
6^{th} hours lactate (mmol/L)	5.5 (5-17)	5.4 (1-17)	5.3 (0.5-13.2)	0.83*
12^{th} hours lactate (mmol/L)	4.1 (1.5-17)	3.7 (2-17)	4.6 (1.5-13.2)	0.47*
24^{th} hours lactate (mmol/L)	3.1 (1.4-20)	2.9 (1.4-20)	3.9 (2.6-14.3)	0.11*
48^{th} hours lactate (mmol/L)	2.7 (0.5-17)	2.3 (0.5-17)	2.9 (1.2-17)	0.63*
Post-thiamine treatment lactate trends				
Lactate <4 mmol/L (12^{th} hours), yes	11 (100%)	8 (57.1%)	3 (37.5%)	0.37***
Lactate <4 mmol/L (48^{th} hours), yes	17 (100%)	11 (78.5%)	6 (75.0%)	0.84***
Thiamine administration (iv, oral, im)				
Intravenous	2 (100%)	1 (87.5%)	1 (12.5%)	
Intramuscular	15 (100%)	9 (64.2%)	6 (75.0%)	0.66***
Oral	5 (100%)	4 (28.5%)	1 (12.5%)	
Patients characteristics				
Respiratory failure, yes	19 (100%)	11 (78.5%)	8 (100%)	0.15***
Sepsis, yes	16 (100%)	10 (71.4%)	6 (75%)	0.85***
Inotrope usage, yes	11 (100%)	6 (42.8%)	5 (62.5%)	0.37***
Anemia, yes	8 (100%)	6 (42.8%)	2 (25.0%)	0.40***
Liver dysfunction, yes	6 (100%)	2 (14.2%)	4 (50%)	0.07***
Acute kidney injury, yes	7 (100%)	5 (35.7%)	2 (25.0%)	0.60***
Abdominal surgery, yes	4 (100%)	3 (21.4%)	1 (12.5%)	0.60***
Malignancy, yes	6 (100%)	5 (35.7%)	1 (12.5%)	0.24***
TPN usage, yes	10 (100%)	7 (50.0%)	3 (37.5%)	0.57***
PICU length of stay, days	17 (3-242)	10.5 (3-116)	35.0 (15-242)	**0.01***

ECMO: Extracorporeal membrane oxygenation, VIS: Vasoactive inotropic score, PRISM III: Pediatric Risk of mortality, PELOD 2: Pediatric logistic organ dysfunction, CRRT: Continuous renal replacement therapy, PEX: Plasma exchange, TPN: Total parenteral nutrition, PICU: Pediatric intensive care unit, LA: Lactic acidosis, *: Mann-Whitney U test, ** Independent samples t-test, ***: chi-square test

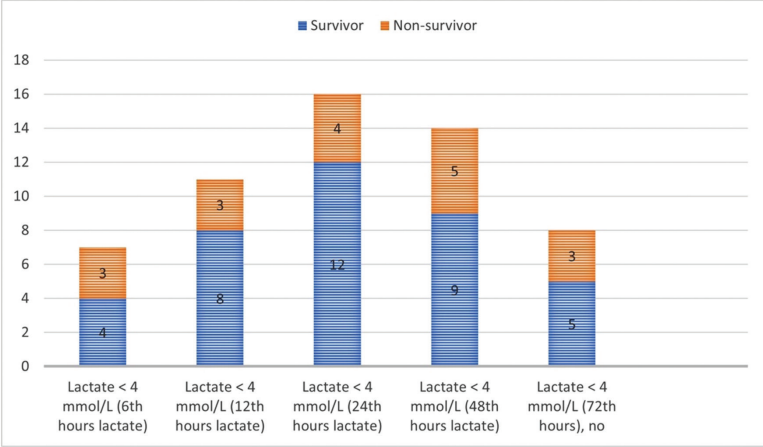

Figure 3. Lactate trends and 28-day mortality outcomes

Patient Characteristics and 24th-hour Lactate Levels

When patients were analyzed in two groups by whether lactate levels at the 24th hour were below 4 mmol/L, bicarbonate values were found to be statistically significant (p=0.01). Lactate levels at the 24th hour of thiamin treatment were found to be statistically significant in both groups (p=0.02). Blood gas levels except for bicarbonate level, lactate decrease trend, thiamin treatments' duration, and form, and patients' risk factors except for acute kidney injury were not statistically significant in either group (Table 2).

Characteristics of Patients Unresponsive to Thiamin Therapy (n=8)

Four of eight patients (50%) for whom thiamin treatment was unsuccessful died in the PICU. The patients' diagnoses were HLH (n=1, 12.5%), MMA (n=1, 12.5%), T-ALL (n=1, 12.5%), EBV-related lymphoma (n=1, 12.5%), pneumonia (n=2, 12.5%), arteriovenous malformation (n=1, 12.5%), and postoperative pulmonary binding surgery (n=1, 12.5%).

Discussion

Thiamin deficiency is an important cause of lactic acidosis, and a wide clinical spectrum, including neuropathy and cardiogenic shock, is observed. Thiamin deficiency may be fatal for critically ill children in the PICU. We aimed to assess the relationship between thiamin and the related status of patients with lactic acidosis who received thiamin treatment. In our study, we investigated patient characteristics and the effects of thiamin treatment on patients.

Fourteen (63.6%) patients' lactate levels who were given thiamin treatment decreased below 4 mmol/L after 24 h of treatment. Thiamin dosage, treatment form, blood gas levels before treatment, patients' risk factors, and lactate decrease trend were not found to be statistically significant between the two groups that were responsive to thiamin treatment. When patients were evaluated by 28-day mortality, there was no statistical significance between lactate levels before thiamin treatment and mortality.

There is a strong relationship between mortality, morbidity, tissue hypoxia, hypoperfusion, and lactate levels in both shock models and clinical studies.[6] The higher the lactate levels, the longer the time of normalization, and the greater the risk of death. Vincent et al.'s[7] study, which evaluated lactate clearance in 96 patients from different disease groups, showed a correlation between steady lactate decrease and lower mortality rate in all disease groups. Abbas et al.'s[8] single-variable retrospective study on 202 patients showed a correlation between lactate rise, multiple organ dysfunction syndrome (MODS) development, and mortality. Lactate rise and MODS development were correlated with mortality in multivariate logistic regression analysis, and hyperlactatemia was correlated with poor prognosis in PICU stay.[8] Hatherill et al.'s[9] study, which evaluated 24-h lactate trends after PICU admission, found a correlation between hyperlactatemia and high mortality in children. Sachdev et al.'s[10] logistic regression analysis study on 172 patients admitted to a PICU for dengue fever stated that 24th-hour mortality was an important indicator. Thiamin deficiency was not associated with mortality in our study. Due to the design of our study, we believe that the diagnosis of thiamin deficiency depending on whether the treatment works or not. We concluded that there was no association between thiamin deficiency and 28-day mortality, primarily because we did not consider thiamin deficiency in clinically unstable patients.

Vincent et al.'s[7] study on patients' lactate clearance in different disease groups (sepsis, septic shock, cardiogenic shock, and respiratory failure in the general surgery ICU, general ICU, and cardiac ICU) detected similar results in lactate clearance and kinetics of different patient groups. Most

studies found a significant difference in the lactate trend at 6, 12, and 24-h or shorter intervals.[7] Teagarden et al.[11] showed lactate normalization in 30 h of a newborn who received extracorporeal membrane oxygenation (ECMO) support for respiratory failure, and Ramsi et al.[12] reported a 16-year-old patient's notable decrease in lactate levels and recovery of metabolic acidosis after one dose of thiamin treatment whose lactate levels increased up to 35 mmol/L after inotrope support for MODS.[11,12] Lerner et al.[13] found that after thiamin treatment in two patients aged 4 and 10 years with refractory

Table 2. The patient characteristics and outcomes according to the 24th-hour lactate level

Parameters	All (n=22)	Lactate <4 mmol/L (24th hours), yes (n=14)	Lactate <4 mmol/L (24th hours), no (n=8)	p-value
Age (months)	26.5 (1-214)	18 (2-214)	37 (1-191)	0.73*
Weight (kg)	14 (2.7-50)	12 (2.7-50)	15 (3.5-41)	0.94*
Thiamine dose (mg)	50 (3-100)	50 (3-100)	50 (10-100)	0.35*
Thiamine, days	4 (1-16)	3 (1-16)	6 (1-9)	0.36*
Enteral nutrion, no, days (until LA)	4 (0-45)	3.5 (0-20)	5 (0-45)	0.58*
PRISM III score	9±5.6	12.6±4.2	6.9±5.2	0.13**
PELOD 2 score	15.6±9.4	17.1±11.1	14.8±8.6	0.59**
VIS score	2.5 (0-92)	20 (0-92)	0 (0-35)	0.17*
CRRT, yes	5 (100%)	3 (21%)	2 (25%)	0.84***
PEX, yes	6 (100%)	3 (21%)	3 (37.5%)	0.41***
ECMO, yes	3 (100%)	1 (7%)	2 (25%)	0.24***
Duration of lactic acidosis (until treatment)	2 (1-5)	2 (1-5)	2 (1-4)	0.97*
Thiamine treatment day	8 (2-177)	12.5 (2-177)	6 (2-83)	**0.02***
Pre-thiamine treatment laboratory values				
pH	7.39±0.05	7.40±0.05	7.37±0.05	0.18**
pCO_2	36.9±9.8	38.4±10.7	34.3±7.8	0.31**
HCO_3	23.0±5.7	25.1±5.8	19.4±3.7	**0.01****
Lactate (mmol/L)	8.0±4.3	7.31±2.7	9.2±6.2	0.42**
Post-thiamine treatment lactate values				
6th hours lactate (mmol/L)	6.0±3.9	5.26±2.7	7.3±5.3	0.34**
12th hours lactate (mmol/L)	4.1 (1.5-17)	3.2 (1.5-10.4)	4.7 (2.6-17)	0.12*
48th hours lactate (mmol/L)	2.7 (0.5-17)	2.3 (0.5-6)	4.8 (1.2-17)	0.14*
Patients characteristics				
Respiratory failure, yes	19 (100%)	12 (85.7%)	7 (87.5%)	0.90***
Sepsis, yes	16 (100%)	10 (71.5%)	6 (75%)	0.85***
Inotrope usage, yes	11 (100%)	5 (35.7%)	6 (75%)	0.07***
Anemia, yes	8 (100%)	6 (42.8%)	2 (25%)	0.4***
Liver dysfunction, yes	6 (100%)	4 (28.5%)	2 (25%)	0.85***
Acute kidney injury, yes	7 (100%)	4 (28.5%)	3 (37.5%)	0.66***
Metabolic disease, yes	2 (100%)	2 (14.2%)	0 (0%)	0.26***
Abdominal surgery, yes	4 (100%)	3 (21.4%)	1 (12.5%)	0.6***
Malignancy, yes	6 (100%)	4 (28.5%)	2 (25%)	0.85***
TPN usage, yes	10 (100%)	7 (50%)	3 (37.5%)	0.57***
PICU length of stay, days	17 (3-242)	15.5 (3-116)	20.5 (6-242)	0.49*
28-day mortality	8 (100%)	4 (28.5%)	4 (50%)	0.31***

ECMO: Extracorporeal membrane oxygenation, VIS: Vasoactive inotropic score, PRISM III: Pediatric Risk of mortality, PELOD 2: Pediatric logistic organ dysfunction, CRRT: Continuous renal replacement therapy, PEX: Plasma exchange, TPN: Total parenteral nutrition, PICU: Pediatric intensive care unit, LA: Lactic acidosis, *: Mann-Whitney U test, **: Independent samples t-test, ***: chi-square test

lactic acidosis and hematologic malignancy, the lactate value decreased to the normal range within 2 h in the 4-year-old patient and approximately 6 h in the 10-year-old patient. Similar to studies in the literature, we evaluated 6-12-24 and the 48-hour lactate trends in our clinical study. Twelve (50%) patients' lactate levels decreased below 4 mmol/L at the 12th hour, and 14 (63.6%) patients' lactate levels decreased below 4 mmol/L at the 24th hour. Only three (12.5%) patients' thiamin levels were obtained and found to be low. The greatest obstacle to obtaining thiamin levels for the patients was the availability of the necessary kit in our clinical center and the obligation to transport blood in optimal conditions to a private laboratory. Thiamin treatment decision times were the greatest obstacles to obtaining necessary blood samples and transportation to the available laboratory because 11 (45.8%) were on weekdays after working hours and 6 (25%) were on weekends. Given the results of other related studies, If a patient had not shown a response to thiamin treatment after 24 h, we did not consider a diagnosis of thiamin deficiency in the patient. Akkuzu et al.'s[14] prospective study researched thiamin deficiency prevalence and duration in 476 pediatric patients in three PICUs, including our clinical center and detected the thiamin deficiency prevalence as 11.1%. Thiamin deficiency risk is increased in patients undergoing solid organ transplantation, gastrointestinal surgery, malignancy, systemic diseases in PICUs, and TPN.

Thiamin is a water-soluble vitamin that has a significant role in energy metabolism; therefore, a wide spectrum of metabolic, neurologic, cardiovascular, respiratory, gastrointestinal, and musculoskeletal problems are observed in its deficiency.[15] Our clinical center participated in Akkuzu et al.'s[14] study, which included 24 patients whose treatment was over 2 years. During that period, we predicted that 155 patients with thiamin deficiency were admitted to our clinical center; 700 patients were admitted during the same period. Because the inclusion and exclusion criteria were applied similarly to patients with refractory lactic acidosis and lactate rise in the last 2 years, thiamin deficiency was not considered in some symptomatic patients whose thiamin deficiency contributed to clinical worsening or in patients on TPN who received thiamin supplements unknowingly because TPN includes a thiamin supplement. We concluded that patients' features that could create a risk factor for thiamin deficiency did not affect 28-day mortality.

In summary, there is no proven treatment regime for thiamin deficiency specific to infants and children, and every clinical center empirically decides its dosage and form of treatment. The lowest thiamin dose in our study was 3 mg, and it was administered to a patient who had undergone a solid organ transplant whose lactate levels increased up to 11.9 mmol/L on the 21st follow-up day of cardiac arrest after the glucose infusion rate was increased from 3 mg/kg/minutes to 7 mg/kg/minutes. Oral thiamin (2.5 mg) was administered to the patient because they had intestinal perforation and were on TPN without thiamin supplements. Lactic acidosis quickly resolved after thiamin treatment. Lactate levels decreased to 0.9 mmol/L in 24 h. We have seen a dramatic response to thiamin treatment even at low doses.

Study Limitations

The greatest limitations of this study were that it was a retrospective study, the study was conducted in a relatively small patient group, and thiamin levels could not be obtained from most of the patients. In our study, thiamin deficiency was not associated with mortality. In our study, we believe that one of the reasons for the no relationship detected between thiamin deficiency and 28th-day mortality was not diagnosed thiamin deficiency in clinically unstable patients.

Conclusion

Thiamin is not an uncommon cause of lactic acidosis and lactate rise in patients in PICUs. It can contribute to current comorbidities because of its relationship with energy metabolism. When patients were analyzed in two groups by whether lactate levels were below 4 mmol/L at the 24th hour and if there was 28-day mortality, blood gas values before thiamin treatment, lactate decrease trends, thiamin treatments' duration, and form, and patients' risk factors were not statistically significant. We believe that in patients with lactic acidosis not directly related to a circulatory disorder, low clinical suspicion, and in the absence of specific diagnostic tests, early thiamin treatment of lactic acidosis is the right approach.

Ethics

Ethics Committee Approval: Written permission was obtained from the Local Ethics Committee of Ankara University Hospital for this study (ethics committee number: İ09-566-22). Our study was conducted in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association.

Informed Consent: Written informed consent was obtained from all patients' relatives or legal authorities when necessary.

Authorship Contributions

Concept: F.K., İ.F., Design: F.K., H.Ö., M.H., Data Collection or Processing: M.K.C., H.U., A.G., B.B., Analysis or Interpretation: F.K., T.K., Literature Search: F.K., Writing: F.K., T.K.

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