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Original Paper

Thiamine Status in Children with Septic Shock from a Developing Country: A Prospective Case–Control Study

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ABSTRACT

Objective: Mitochondrial dysfunction is central to sepsis-induced multi-organ dysfunction. Thiamine deficiency may contribute to mitochondrial dysfunction and thus high mortality. Study was planned to assess thiamine status in children with septic shock in comparison to healthy controls from a developing country and to study the effect of thiamine levels on its outcome.

Methods: A prospective case-control study (April 2017 to May 2018) enrolling consecutive children with septic shock as 'cases' ($n = 76$), their healthy siblings ($n = 51$) and apparently healthy children from immunization clinic ($n = 35$) as 'controls'. Whole blood total thiamine (WBTT) level was measured on days 1, 10 and 1-month post-discharge. Outcome parameters were acute care area free days on days 14 and 28, and mortality.

Results: WBTT [nMol/l; median (interquartile range, IQR)] was significantly lower on day 1 in cases compared with sibling controls [23.1 (21.8–26.3) vs. 36.9 (33.6–40.5); $p < 0.001$]. It fell further on day 10 [20.8 (18.1–21.1); $p < 0.02$]. Levels rose significantly 1-month post-discharge [35.5 (31.2–36.6)] and became comparable to sibling controls ($p = 0.4$). Immunization clinic controls also had lower WBTT [42.3 (40.1–45.9)], but was significantly higher than sibling controls and cases at 1-month post-discharge ($p < 0.001$). Survivors and non-survivors of septic shock were similar. WBTT levels did not correlate with any of the severity indicators of septic shock or its outcomes.

Conclusions: WBTT was significantly low in all children, and fell further during septic shock. Observed severe deficiency might have precluded any further association of thiamine levels with

severity of septic shock and its outcome. Data obtained may inform trials on metabolic resuscitation in paediatric septic shock in developing countries.

LAY SUMMARY

Thiamine deficiency may contribute to high mortality in paediatric septic shock as thiamine is an essential factor for functioning of mitochondria, the powerhouse of the cells. This prospective case–control study was conducted to assess thiamine status in children with septic shock in comparison with healthy controls in a developing country. Consecutive children with fluid-refractory septic shock were enrolled as 'cases'. Their apparently healthy siblings, and apparently healthy children from immunization clinic, were enrolled as 'controls'. The whole blood total thiamine (WBTT) level was measured on days 1, 10 and 1 month after hospital discharge. Seventy-six children were enrolled as cases, 51 children as sibling controls and 35 children as immunization clinic controls. WBTT was significantly lower on day 1 in cases as compared with their sibling controls. It fell further on day 10. The level rose significantly after a month of discharge and became comparable to sibling controls. Immunization clinic controls also had lower WBTT but was significantly higher compared with sibling controls and cases at 1-month post-discharge. Survivors and non-survivors of septic shock had similar WBTT levels. Observed severe deficiency might have precluded any further association of thiamine levels with septic shock outcome.

KEYWORDS: thiamine deficiency, septic shock, metabolic resuscitation, mitochondria, children

INTRODUCTION

Children with septic shock have high mortality in developing countries [1, 2]. Malnutrition is seen in up to one-third of children admitted in the intensive care units of tertiary care hospitals [1, 3], and may be contributing to higher mortality [4]. Current guidelines for resuscitation of septic shock revolve around the macro- and microcirculatory parameters to improve oxygen delivery and global oxygen deficit [5]. However, sepsis-related hypercytokinemia, hypoxia, and ischaemia cause mitochondrial dysfunction at the cellular level and reduce oxygen utilization. This occurs early in sepsis and plays a central role in the development of multi-organ dysfunction syndrome (MODS). Spronk *et al.* [6] coined the unifying term 'microcirculatory and mitochondrial distress syndrome' to describe the pathophysiology of sepsis at the cellular and subcellular levels and to guide the development of targeted interventions. In addition to microcirculation-targeted therapy, mitochondria-targeted therapy may be a reasonable and promising strategy to prevent or mitigate MODS and sepsis-related mortality. Thiamine, being a critical cofactor of mitochondrial enzyme complexes, maybe one of the potential therapeutic agents for the mitochondria-targeted therapy in septic shock [7, 8]. Thiamine deficiency (TD) is noted in critically ill patients even from well-nourished communities [9–13]. Thiamine supplementation [10, 11, 14] may assume more significance in presence of malnutrition and pre-existing TD in children with septic shock, which is likely to be common in developing countries.

Thiamine supplementation is shown to have a protective effect against hypoxic cell death and reperfusion injury [15, 16]. Retrospective clinical studies demonstrated a beneficial role of thiamine therapy in patients with septic shock [17, 18], and severe pneumonia [19]. In a randomized control trial, thiamine supplementation significantly reduced the lactate levels within 24 h in adults with thiamine-deficient, hyperlactatemic (>3 mMol/l), hypotensive septic shock, thus tending towards a survival benefit [11]. On the other hand, the recent VITAMINS trial could not demonstrate the beneficial effect of intravenous vitamin C, hydrocortisone, and thiamine in adult septic shock patients compared with intravenous hydrocortisone alone [20]. With the available evidence and its quality, thiamine is not recommended in the management of paediatric septic shock [5]. However, a knowledge gap in the subject is appreciated and further studies to delineate its role are recommended [5].

Looking at the potential role of thiamine supplementation in sepsis-induced mitochondrial dysfunction

and the beneficial trend seen with thiamine therapy in TD patients, we conducted a prospective, case–control study in children with septic shock to (i) assess the longitudinal behaviour of thiamine during septic shock and convalescence, (ii) to compare the thiamine levels with apparently healthy siblings from the same family-setting (may be reflective of the baseline thiamine status of children with septic shock), (iii) to compare the thiamine levels with apparently healthy controls enrolled from immunization clinic (reflective of the thiamine status in children from the local community) and (iv) to study the effect of TD on the outcome of children with septic shock.

MATERIALS AND METHODS

Patients and controls

This study was a single-center, prospective case–control study conducted over a period of 14 months (April 2017 to May 2018) in the paediatric emergency and intensive care units of the Department of Paediatrics at a tertiary care center from a developing country. The Institutional Ethics Committee approved the study protocol, and the Departmental Review Board approved the article. Consecutive children (age, 6 months to 12 years) presented to the Paediatric Emergency Room with a fluid-refractory shock and clinically suspected to have infection were enrolled as 'cases' within the first 24 h of documentation of septic shock. Fluid-refractory shock was defined as the persistence of hypotension (systolic blood pressure <5th centile for age), or the need for vasoactive drugs despite >40 ml/kg of isotonic fluid boluses in the first hour [21]. One apparently healthy sibling (age, 6 months to 12 years) of each case coming from the same family background and sharing the same kitchen was planned to be enrolled as 'sibling controls'. Apparently healthy children (age, 6 months to 12 years) visiting the immunization clinic of the same hospital were enrolled as 'immunization clinic controls'. Written and informed consent, and assent wherever applicable, was obtained from the parents or legal guardians of all children. The exclusion criteria were (i) lack of informed consent to participate in the study, (ii) receipt of multivitamin supplementation during the past 3 months, (iii) presence of competing causes of elevated lactate level such as known or suspected inborn error of metabolism, liver dysfunction, seizures (and/or acute meningoencephalitis) and (iv) cardiac arrest/cardiopulmonary resuscitation prior to enrolment.

Data collection and clinical care of patients

All demographic, clinical and laboratory data [including serial arterial lactate levels, pH, anion gap till 36 h, serum transaminases, procalcitonin and C-reactive protein (CRP) till day 10] was recorded on a pre-structured questionnaire. Nutritional status [22], fluid resuscitation details, vasoactive inotrope score (VIS) [23], paediatric sequential organ failure assessment (pSOFA) [24] and paediatric logistic organ dysfunction (PeLOD) [25] scores were assessed for all cases. The baseline thiamine level was drawn within 24 h of septic shock identification. Cases were resuscitated as per the standard unit protocol. Repeat thiamine samples were obtained at D10 of hospitalization. Outcome parameters were 'acute care area free days' on day 14 ($ACAFD_{14}$), day 28 ($ACAFD_{28}$) [1] and mortality. Cases were followed until death or until 1 month after hospital discharge, whichever was earlier. The third thiamine sample was obtained at the time of clinically apparent recovery from sepsis (at 1 month after discharge from the hospital) while they were not receiving any vitamin supplements. Thiamine samples from siblings and immunization clinic controls were taken once.

Thiamine estimation method

Blood samples were collected in Ethylenediaminetetraacetic acid (EDTA) vials and frozen immediately [26]. Thawed hemolysates, calibrators and controls were deproteinized using trichloroacetic acid. Thiamine and its phosphate esters were derivatized with potassium ferricyanide and were measured by using ultra-high-performance liquid chromatography method. Chromatographic separation was achieved by Zorbax eclipse C18 reversed-phase column (2.1 mm × 50 mm × 1.8 μm) using a gradient elution of dibasic sodium phosphate (25 mmol, pH 7.0): methanol (90:10, v/v) and dibasic sodium phosphate (25 mmol, pH 7.0): methanol (30:70, v/v). Free thiamine, thiamine

monophosphate (TMP) and thiamine pyrophosphate (TPP) were detected by fluorescence detector using an excitation wavelength of 375 nm and an emission wavelength of 435 nm. The WBTT level was obtained by taking the sum of free thiamine, TMP and TPP. As there is lack of Indian data on thiamine levels, we obtained non-fasting blood samples from four healthy volunteer resident doctors from our hospital after due consent during the study period. They were not on any vitamin supplement.

Statistical analysis

Data were analyzed using R statistical software version 3.6.1 [27] and SPSS version 22 (IBM®). Continuous and categorical variables were analyzed using the Mann–Whitney U test and chi-square test, respectively. The standardized residual was used for *posthoc* comparison of the chi-square test of independence with more than 2 × 2 groups. Thiamine levels obtained at a one-time point from patients, sibling controls and immunization clinic controls were analyzed with the Kruskal–Wallis test, followed by Dunn's tests for *post hoc* intergroup comparisons. Thiamine levels obtained at days 1, 10 and 1-month post-discharge from patients were analyzed with Friedman test, followed by *post hoc* multiple pairwise comparisons. Correlations between admission thiamine and septic shock severity indicators were analyzed with Spearman's correlation.

RESULTS

Seventy-six children with fluid-refractory septic shock were enrolled as cases, 51 children were enrolled as sibling controls, and 36 children were enrolled as immunization clinic controls. Cases were symptomatic for a median duration of 6 days [interquartile range (IQR), 4–10] prior to the admission. The demographic, nutritional, and thiamine status of the cases and controls are shown in Table 1 and Fig. 1A. One-third of the cases and sibling controls were malnourished. Cases and sibling controls were significantly more malnourished compared with immunization clinic controls, both in terms of incidence ($p = 0.01$, standardized residuals = 2.99) as well as severity (<0.001). All cases and controls were thiamine-deficient compared with the reference range documented from healthy North American adults [24]. The clinical details of the cases are shown in Table 2. A comparative analysis of thiamine levels among cases on days 1, 10 and 1 month after discharge are shown in Fig. 1B and Table 3. WBTT levels among the four healthy volunteer doctors were 70, 71, 80 and 91 nMol/l respectively, which was comparable to the lower reference levels found in healthy North American and Japanese adults [24, 25].

WBTT on day 1 was similar amongst the survivors and non-survivors [median (IQR); 23.1 (21.4–25.4) vs. 23.1 (22.3–25.6); $p = 0.5$]. Amongst the survivors, the WBTT on day 1 was similar in children who took ≥72 h for shock reversal ($n = 22$), compared with those who took <72 h ($n = 19$) [23.64 (20.22–25.66) vs. 22.80 (21.41–26.75); $p = 0.98$], as was the case for patients who needed maximum VIS of >20 ($n = 49$) vs. those who needed VIS of ≤ 20 ($n = 27$) [23.76 (22.20–26.66) vs. 22.54 (19.62–24.30); $p = 0.16$]. Similarly, presence or absence of hyperlactatemia (lactate >2 mMol/l) did not show any difference in WBTT [lactate >2 ($n = 40$) vs. ≤2 ($n = 36$); 23.33 (21.89–27.10) vs. 22.64 (21.66–24.99); $p = 0.36$]. Figure 2 presents relationship between day 1 WBTT levels and admission lactate levels among survivors (rho = 0.08, $p = 0.63$) and non-survivors (rho = 0.06, $p = 0.73$). Various other severity indicators (e.g. metabolic acidosis, PRISM III score, worst pSOFA and PeLOD scores, maximum VIS, duration of inotropic support and time taken for shock reversal) and biomarkers (CRP and procalcitonin) did not show any correlation with WBTT on day 1 (data not shown). WBTT cut-off level of 20.48 nmol/l revealed a specificity of 0.24 and sensitivity of 0.91 in predicting mortality (receiver operating characteristic) ROC (area under curve) AUC, 0.54; Delong 95% CI 0.41–0.67).

DISCUSSION

Our study highlights the longitudinal behaviour of thiamine levels during septic shock in children from a developing country. Thiamine levels did not vary between the cases (at 1-month post-discharge) and their siblings but were below the normal range in both. This suggested a pre-existing TD in children, and the levels further reduced during septic shock.

Table 1. Demographic characteristics, nutritional status and thiamine levels among cases, sibling controls and immunization clinic controls

Variables	Cases ($n = 76$)	Sibling controls ($n = 51$)	Immunization clinic controls ($n = 36$)	p value[a]	p value[b]
Age in months, median (IQR)	74 months (33, 110.2)	98 months (69, 118.5)	64 months (35, 113.5)	$p = 0.02$	$p1 = 0.005$ $p2 = 0.4$ $p3 = 0.01$
Sex ratio (M:F)	40:36	29:22	23:13	$p = 0.5$	–
Nutritional status					
Weight for age z-score, median (IQR)	−1.0 (−2.2, −0.1)	−1.3 (−2.1, −0.9)	−0.3 (−0.9, 0.2)	$p < 0.001$	$p1 = 0.05$ $p2 < 0.001$ $p3 = 0.05$
Normal weight (WAZ >2 z-score), n (%)	53 (70%)	36 (71%)	34 (94%)	$p = 0.01$[c]	Standardized residuals of immunization clinic controls is 2.99
Underweight (WAZ <2 z-score), n (%)	23 (30%)	15 (29%)	2 (5.6%)		
Height for age z-score, median (IQR)	−1.3 (−1.8, −0.6)	−1.2 (−1.8, −0.7)	0.1 (−1.1, 0.5)	$p < 0.001$	$p1 = 0.4$ $p2 < 0.001$ $p3 < 0.001$
Not stunted (HAZ >2 z-score), n (%)	59 (78%)	41 (80%)	32 (89 %)	$p = 0.07$[c]	–
Stunted (HAZ <2 z-score), n (%)	17 (22%)	10 (20%)	4 (11%)		
Free thiamine (nMol/l)	1.54 (1.26, 1.76)	2.37 (30.1, 35.9)	4.10 (3.89, 4.28)	$p < 0.001$	$p1 < 0.001$ $p2 < 0.001$ $p3 < 0.001$
TMP (nMol/l)	1.00 (0.81, 1.10)	1.78 (1.54, 2.01)	2.01 (1.80, 2.27)	$p < 0.001$	$p1 < 0.001$ $p2 < 0.001$ $p3 = 0.070$
TPP (nMol/l)	20.4 (19.2, 23.8)	32.80 (30.1, 35.9)	36.19 (33.12, 40.02)	$p < 0.001$	$p1 < 0.001$ $p2 < 0.001$ $p3 = 0.015$
Total thiamine (nMol/l)	23.08 (21.83, 26.26)	36.94 (33.63, 40.47)	42.33 (40.07, 45.90)	$p < 0.001$	$p1 < 0.001$ $p2 < 0.001$ $p3 = 0.002$

Notes: All values are in median (IQR) unless specified otherwise. IQR, interquartile range; WAZ, weight for age z-score [22]; HAZ: Height for Age z-score [22]; TMP, thiamine monophosphate; TPP, thiamine pyrophosphate (thiamine diphosphate).

[a]Comparative analysis was done with Kruskal–Wallis test unless specified otherwise.

[b]$p1$ (cases vs. sibling controls), $p2$ (cases vs. immunization clinic controls) and $p3$ (sibling controls vs. immunization clinic controls) represent *post hoc* intergroup comparisons by Dunn's test.

[c]Chi-square test with standardized residuals for *post hoc* intergroup comparisons.

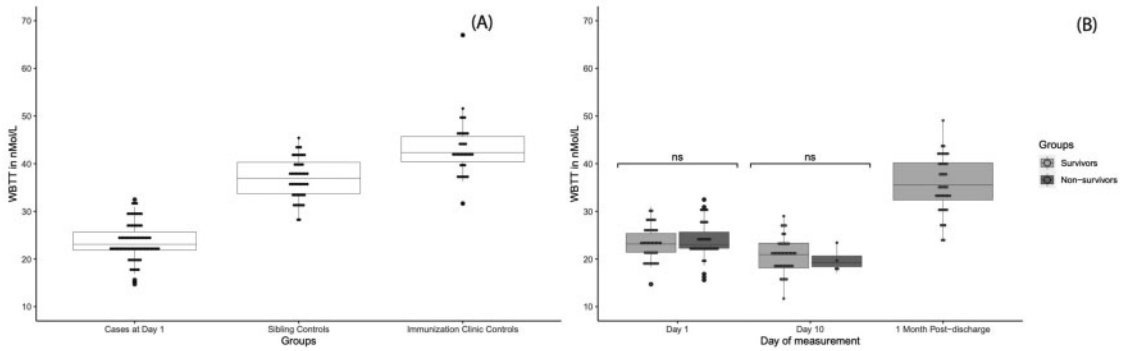

Fig. 1. Boxplot (with dots) comparing distribution of WBTT levels between (**A**) septic shock cases (on day 1), sibling controls and immunization clinic controls; (**B**) days 1, 10 and 1-month post-discharge levels among surviors and non-survivors of septic shock cases (refer to Tables 1 and 3, respectively for statistical comparison).

The thiamine levels did not affect the severity of illness and survival outcomes among children with fluid-refractory septic shock.

Thiamine is a water-soluble vitamin that has limited body stores due to a rapid turnover time ($t^1/_2$ below 10 days) [28]. Even a short period of critical illness affects body stores and predisposes them to a TD state. This is due to the higher metabolic demand, reduced intake, and reduced intestinal absorption during periods of stress [28]. The situation is likely to be worse with a pre-existing TD. The prevalence of TD at admission is reported to be 10–70% of adult patients with septic shock and critical illnesses [9, 11, 12, 29]. Donnino *et al.* [12] demonstrated TD in 10% of adults with septic shock, while an additional 10% developed it during the 72 h of hospitalization. A paediatric study from Brazil reported the incidence of TD to be 30% among children admitted in intensive care unit [13, 14]. Our study showed that even the apparently healthy children attending the routine immunization clinics have low thiamine levels—nearly 50% of the lower reference level reported from healthy North American and Japanese adults [28, 30] and the level found in four healthy volunteer doctors from our hospital. The levels reduced further by about one-third during the septic shock. Ethnicity, dietary patterns, socioeconomic status, access to quality and quantity of food may contribute to the TD in our cohort as it was noted in all children (cases and controls).

Observed high incidence of adverse outcomes (46%) in the studied cohort is similar to studies from our hospital [1, 31], and other tertiary care teaching hospitals of India [2, 32]. It is attributable to suboptimal acute care facilities, late referral and poor implementation of time-tested and clinically proven resuscitative bundles [33]. The effect of TD on septic shock mortality in malnourished children is debatable [10, 14]. In our study, thiamine levels did not correlate with the severity indicators of septic shock, critical care needs and mortality. However, this may also be due to the fact that all cases already had pre-existing severe TD, and any further changes in the thiamine levels did not reflect adequately on the severity indicators and outcomes of septic shock. It remains conjectural whether TD predisposed them to such severe sepsis. Despite the biological plausibility and trends toward beneficial effects of thiamine supplementation in septic shock [7, 34, 35], a recent, randomized control trial did not observe a clinically significant effect of the combined treatment with intravenous vitamin C, hydrocortisone and thiamine on the duration of resolution of septic shock in adult patients, compared with intravenous hydrocortisone alone [20]. Though there is no information on the thiamine status of the enrolled patients, the trial was conducted in a population with supposedly normal thiamine status. With *post hoc* analysis of a randomized control trial, Donnino *et al.* [11] demonstrated significant reduction in the absolute lactate values at 24 h [2.1 mMol/l (1.4, 2.5) vs. 3.1 (1.9, 8.3); $p = 0.03$], faster reduction in lactate in first 24 h (repeated measure model $p = 0.006$) and a trend towards survival

Table 2. Clinical characteristics, critical care needs and outcome of children with septic shock (cases)

Primary clinical diagnosis	
Acute pyogenic infections, *n* (%)	18 (23.7)
Scrub typhus (IgM positive), *n* (%)	17 (22.4)
Pneumonia, *n* (%)	9 (11.8) (H1N1 positive; $n = 3$)
Dengue shock syndrome (IgM positive), *n* (%)	6 (7.9)
Toxic shock syndrome, *n* (%)	6 (7.9)
Enteric fever, *n* (%)	1 (1.3)
Others (including suspected scrub typhus and dengue shock syndrome), *n* (%)	19 (25)
Positive cultures at admission, *n* (%)	11 (14.5)
Staphylococcus aureus (blood and/or pus)	9 (11.8)
Salmonella typhi	1 (1.3)
Pseudomonas aeruginosa	1 (1.3)
Septic shock and critical illness characteristics	
PRISM III at PER admission	10 (6, 15)
PRISM III at PICU admission	9 (5, 15)
PIM 2 at PER admission	−3.8 (−4.4, −3.1)
PIM 2 at PICU admission	−3.4 (−4.05, −2.8)
pSOFA score on day 1	9 (7, 12)
PeLOD score on day 1	12 (10, 21)
pH at admission	7.35 (7.2, 7.4)
Serum bicarbonate at admission	20.5 (16.07, 25.4)
SerumlLactate at admission	2.2 (1.22, 3.3)
VIS	
At 6 h	20 (10, 30)
At 24 h	20 (14.8, 40)
Maximum VIS	40 (20, 85)
Duration of vasoactive drug use (hours)	65 (45, 95)
Time to reversal of shock (hours)[a]	75 (54.7, 100.5)
Culture positive healthcare-associated infections ($n = 6$)	
Acinetobacter baumanii	4 (tracheal aspirate-3; pleural fluid-1)
Escherichia coli	1 (peritoneal dialysis fluid)
Klebsiella pneumoniae	1 (urine)
Outcomes	
Acute care area free days in 14 days	3.0 (0.0, 9)
Acute care area free days in 28 days	17.0 (0.0, 23.2)
Adverse outcome	35 (46.1%) (Deaths 30; LAMA 5)

Notes: All values are in median (IQR) unless specified otherwise. PeLOD score, paediatric logistic organ dysfunction score [25]; pSOFA, paediatric sequential organ failure assessment score [24]; PER, paediatric emergency room; PICU, paediatric intensive care unit; LAMA, leave against medical advice; PRISM, the paediatric risk of mortality; PIM, paediatric index of mortality.

[a]Reversal of septic shock was defined as off inotropes for >24 h.

Table 3. Longitudinal behaviour of WBTT levels (nMol/l) in children during septic shock

Variables, reference [23] [Mean (range)]	Day 1 ($n = 76$)	Day 10 ($n = 45$)[a]	1-month post-discharge ($n = 41$)[b]	p value[c]	p value[d]
Free thiamine [7.4 (3.3–12.4)]	1.54 (1.26, 1.76)	1.23 (1.10, 1.70)	2.24 (1.99, 2.61)	$p < 0.001$	$p1 = 0.7$ $p2 < 0.001$ $p3 < 0.001$
TMP [3.5 (1.6–6.5)]	1.00 (0.81, 1.10)	0.92 (0.80, 0.97)	1.80 (1.48, 2.07)	$p < 0.001$	$p1 = 0.7$ $p2 < 0.001$ $p3 < 0.001$
TPP [114 (70.3–178.6)]	20.4 (19.2, 23.8)	18.7 (16.10, 21.05)	32.1 (28, 32.1)	$p < 0.001$	$p1 = 0.03$ $p2 < 0.001$ $p3 < 0.002$
Total thiamine [124.8 (75.2–193.8)]	23.08 (21.83, 26.26)	20.86 (18.1, 21.05)	35.55 (31.19, 36.6)	$p < 0.001$	$p1 = 0.02$ $p2 < 0.001$ $p3 < 0.001$

Notes: All values are in median (IQR). TMP, thiamine monophosphate; TPP, thiamine pyrophosphate (thiamine diphosphate).
[a,b]The number of surviving patients at the respective points.
[c]Comparative analysis was done with Friedman test.
[d]$p1$ (day 1 vs. day 10), $p2$ (day 1 vs. 1-month post-discharge) and $p3$ (day 10 vs. 1-month post-discharge) represent *post hoc* pairwise intergroup comparisons.

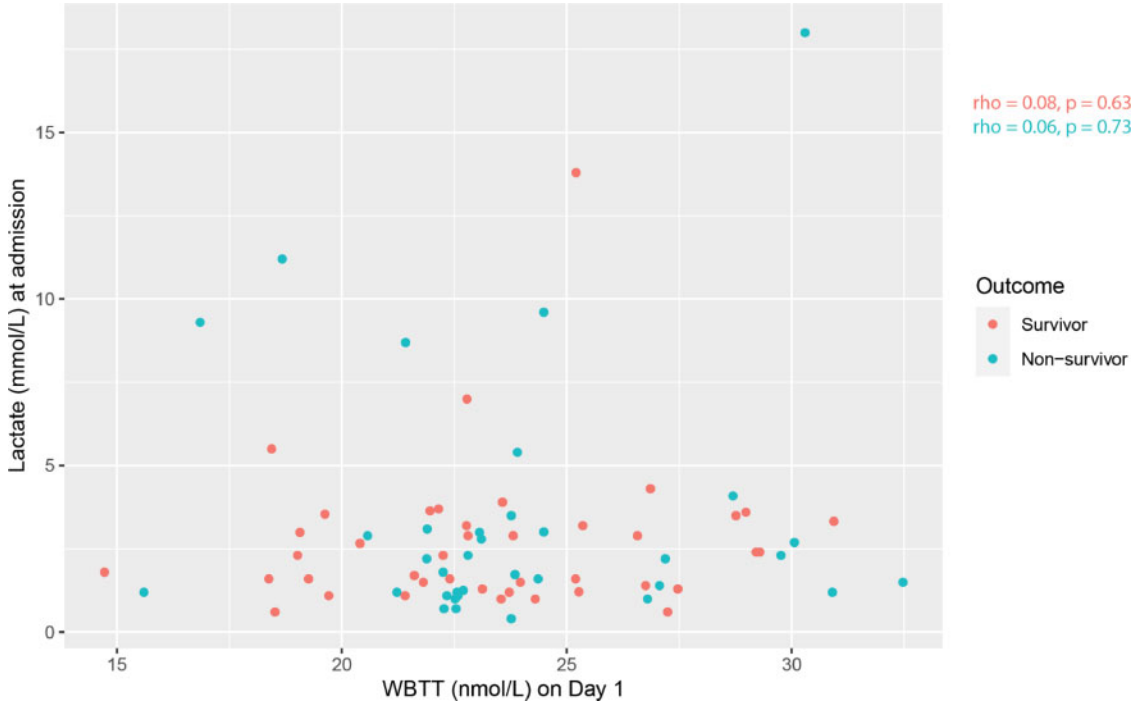

Fig. 2. Scatterplot to show relationship between day 1 WBTT levels and admission serum lactate levels among survivors and non-survivors of septic shock cases (*rho* represents the Spearman's correlation coefficient).

benefit (2/15 vs. 6/13, $p = 0.10$; log rank test, $p = 0.047$) with thiamine therapy in a subset of thiamine-deficient adult patients ($n = 28$). Similar data are accumulating in paediatric literature as well [36, 37]. TD has been shown to be associated with higher lactate levels [12], CRP and mortality in patients with septic shock [13, 29]. On the contrary, we noted relatively lower lactate levels [2.25 (1.22–3.29)] in the cases. Overall, nearly half (47%) of the patients had lactate values <2.0 mMol/l, even though these children required high inotropic support. The reasons for this observation are not clear.

We utilized WBTT level which is superior to the functional assays [38]. It is a more sensitive and specific indicator of body thiamine stores during systemic inflammation, as compared with the plasma levels [7]. There is a felt need of interventional studies on thiamine therapy in children with septic shock [5], which is likely to be more relevant in a population with pre-existing TD. This study is an attempt to provide information on longitudinal behaviour of thiamine levels during fluid-refractory septic shock and its recovery in a developing country. The immunization clinic controls and sibling controls provided an idea about the thiamine status in the general population and the patients' family, respectively. Considering the lack of thiamine data in normal childhood population, large community-based local studies are required to assess the prevalence and severity of TD. Pre-existing TD may provide a strong argument to study the role of thiamine in metabolic resuscitation of paediatric septic shock and associated MODS in developing countries.

CONCLUSION

We conclude that children with septic shock, in our cohort from a developing country, had significantly low levels of thiamine, which worsened during septic shock. Observed severe deficiency might have precluded any further association of thiamine levels with the severity of septic shock and its outcome. Data obtained from our study may inform trials on metabolic resuscitation in paediatric septic shock in developing countries.

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