Serum Ascorbic Acid and Thiamine Concentrations in Sepsis: Secondary Analysis of the Swiss Pediatric Sepsis Study

Lucile Equey, MD[1]
Philipp K. A. Agyeman, MD[2]
Rosemarie Veraguth[3]
Serge Rezzi, PhD[3]
Luregn J. Schlapbach, MD, PhD[4,5]
Eric Giannoni, MD[1]
for the Swiss Pediatric Sepsis Study Group

OBJECTIVES: To determine circulating levels of ascorbic acid (VitC) and thiamine (VitB1) in neonates and children with blood culture-proven sepsis.

DESIGN: Nested single-center study of neonates and children prospectively included in the Swiss Pediatric Sepsis Study.

SETTING: One tertiary care academic hospital.

PATIENTS: Sixty-one neonates and children 0–16 years old.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: VitC and VitB1 were quantified in serum of patients (median age, 10.5 mo; interquartile range [IQR], 0.5–62.1 mo) with blood culture-proven sepsis. Median time between sepsis onset and sampling for measurement of vitamins was 3 days (IQR, 2–4 d). Median serum levels of VitC and VitB1 were 32.4 µmol/L (18.9–53.3 µmol/L) and 22.5 nmol/L (12.6–82 nmol/L); 36% of the patients (22/61) had low VitC and 10% (6/61) had VitC deficiency; and 72% (44/61) had low VitB1 and 13% (8/61) had VitB1 deficiency. Children with low VitC were older ($p = 0.007$) and had higher C-reactive protein ($p = 0.004$) compared with children with VitC within the normal range. Children with low VitB1 levels were older ($p = 0.0009$) and were less frequently receiving enteral or parenteral vitamin supplementation ($p = 0.0000003$) compared with children with normal VitB1 levels.

CONCLUSIONS: In this cohort of newborns and children with sepsis, low and deficient VitC and VitB1 levels were frequently observed. Age, systemic inflammation, and vitamin supplementation were associated with vitamin levels during sepsis.

KEY WORDS: children; newborn; organ dysfunction; sepsis; vitamin

Sepsis is a major global health issue. Forty percent of the estimated 48.9 million annual cases occur among neonates and children, leading to 2.9 million deaths (1). There is a need for novel effective and low-cost therapies to improve prevention and treatment of sepsis, for which vitamin-based therapies represent attractive candidates.

Ascorbic acid (VitC), a powerful anti-oxidant and immune response modulator, acts on multiple pathways that are affected during sepsis (2). Thiamine (VitB1) is an important cofactor of enzymes regulating key cellular metabolic processes (3). Low circulating levels of VitC and VitB1 have been reported in critical illness including sepsis (4–6). VitC and VitB1 are currently under investigation as potential adjunctive treatments for sepsis (7–9).

Low vitamin levels are not uncommon during growth and development, and there are limited data regarding VitC and VitB1 levels during pediatric sepsis. We determined circulating levels of VitC and VitB1 in neonates and children

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with blood culture-proven sepsis and assessed factors associated with low vitamin concentrations.

MATERIALS AND METHODS

This single-center study was based on a subset of the prospective observational Swiss Pediatric Sepsis Study (10, 11). Neonates and children 0–16 years old presenting with blood culture-proven bacterial sepsis were recruited at the University Hospital of Lausanne (Switzerland) between September 2011 and December 2015. After having obtained written informed consent, we collected arterial or venous blood in children with positive blood cultures and systemic inflammatory response syndrome (12). Blood was centrifuged within 30 minutes of sampling, and serum was immediately frozen at –80°C until analysis. The study was approved by the ethical review board, Swissethics KEK-029/11.

Vitamin levels were determined at the Swiss Vitamin Institute, an accredited medical analysis laboratory, using high-pressure liquid chromatography coupled to electrochemical detection for VitC and a microbiological assay for VitB1 (13–15).

We defined VitC levels less than 22.7 µmol/L and VitB1 levels less than 60 nmol/L as low (4, 5, 16). VitC deficiency was defined by levels less than 11.4 µmol/L, and VitB1 deficiency was defined by levels less than 9 nmol/L (4, 17).

Descriptive statistics are presented as median and interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. For continuous variables, differences between groups with and without low levels of VitC and VitB1 were analyzed by Wilcoxon rank-sum test. For categorical data, we used Pearson chi-square test or Fisher exact test. We assessed correlations between VitC and VitB1 levels and clinical variables by the nonparametric Spearman test. We considered *p* values of less than 0.05 after Bonferroni correction significant. We performed statistical analyses with R Version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

VitC and VitB1 levels were measured in 61 patients with blood culture-proven sepsis, including 26 newborns (26/61, 43%) and 35 children (35/61, 57%). Median gestational age of newborns was 32 weeks (IQR, 28–38 wk). Median postnatal age at sepsis onset was 10.5 months (IQR, 0.5–62.1 mo) for all patients. The most common pathogens were coagulase-negative *Staphylococci* (25%, 15/61), *Escherichia coli* (15%, 9/61), *Staphylococcus aureus* (15%, 9/61), and *Streptococcus viridans* (8%, 5/61). Thirty-nine percent of the patients (24/61) were receiving parenteral or enteral substitution of VitC and VitB1 at sepsis onset. Median maximum C-reactive protein (CRP) level during sepsis was 83 mg/dL (IQR, 29–186 mg/dL). Twenty-six patients (43%, 26/61) had no organ dysfunction during the course of infection, 19 (31%, 19/61) had one organ dysfunction, and 16 (26%, 16/61) had multiple organ dysfunction. Three patients died (5%, 3/61) within 30 days after sepsis onset.

Median levels of VitC and VitB1 were 32.4 µmol/L (IQR, 18.9–53.3 µmol/L) and 22.5 nmol/L (12.6–82 nmol/L). Overall, 36% (22/61) and 72% (44/61) of the patients had low VitC and VitB1 (**Fig. 1**). Ten percent of the patients (6/61) had VitC deficiency and 13% (8/61) had VitB1 deficiency. Analysis of paired measurements revealed a correlation between VitC and VitB1 levels (R = 0.41; p = 0.001). Median time between sepsis evaluation by blood culture and blood sampling for measurement of vitamins was 3 days (IQR, 2–4 d). Children with low VitC were older (p = 0.007) and had higher CRP (p = 0.004) compared with children with VitC within the normal range (**Table 1**). Children with low VitB1 levels were older (p = 0.0009) and were less frequently receiving vitamin supplementation (p = 0.0000003) compared with children with normal VitB1 levels.

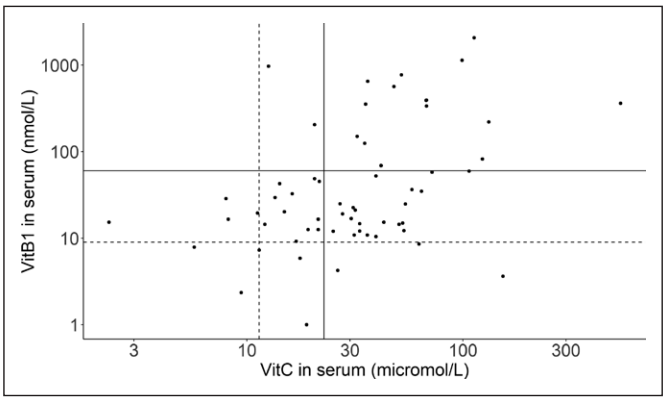

Figure 1. Vitamin C and B1 levels in newborns and children with sepsis. The *solid lines* represent the published thresholds for low vitamin levels, and the *dotted lines* represent the published levels for vitamin deficiency. Data are presented with a logarithmic scale. VitB1 = thiamine, VitC = ascorbic acid.

TABLE 1.
Demographics and Main Clinical Characteristics of Patients With Low or Adequate Vitamin Levels

Demographics and Clinical Characteristics	VitC < 22.7 µmol/L, *n* = 22	VitC ≥ 22.7 µmol/L, *n* = 39	*p*	VitB1 < 60 nmol/L, *n* = 44	VitB1 ≥ 60 nmol/L, *n* = 17	*p*
Median age at sepsis onset (mo)	55.0 (7.0–112.0)	1.3 (0.3–38.7)	0.007	42.1 (1.6–87.6)	0.3 (0.3–0.7)	0.0009
Female gender	11 (37)	19 (63)	1	18 (60)	12 (40)	0.23
Male gender	11 (36)	20 (65)		26 (84)	5 (16)	
Time between sepsis onset and vitamin measurement (d)	2 (2–3)	3 (2–4)	1	3 (2–4)	3 (2–4)	1
Vitamin supplementation at sepsis onset	5 (21)	19 (79)	0.28	8 (34)	16 (67)	0.0000003
No vitamin supplementation at sepsis onset	17 (46)	20 (54)		36 (97)	1 (3)	
Maximum C-reactive protein level (mg/dL)	181 (97–206)	52 (19–141)	0.004	119 (42–191)	64 (15–154)	0.59
Organ dysfunction during sepsis	11 (31)	24 (69)	1	22 (63)	13 (37)	0.37

VitB1 = thiamine, VitC = ascorbic acid.
Categorical variables are presented as frequencies (%) and continuous variables as median (25th and 75th percentiles).
p values from χ^2 test (or Fisher exact test) for categorical variables and from Wilcoxon test for continuous variables. We show *p* values after Bonferroni correction.

DISCUSSION

In this cohort of newborns and children with blood culture-proven sepsis, low levels of VitC and VitB1, and vitamin deficiency were commonly observed. Based on published adult/pediatric reference values, a third of the patients had low VitC levels, and almost three quarters had low VitB1. There was a moderate correlation between low VitC and VitB1 levels. Low VitC and VitB1 levels were associated with older age. In addition, low VitC was associated with higher CRP during sepsis, and low VitB1 level was associated with absence of vitamin supplementation at sepsis onset.

A sufficient supply of vitamin is important to support metabolism during growth and development. There are limited data regarding adequate levels of VitC and VitB1 in neonates and children (18). Higher levels of VitB1 have been described during the first months of life, possibly indicating higher demand (19). Vitamin requirements may increase during critical illness including sepsis, due to reduced intestinal absorption, alterations in tissue distribution, and greater metabolic demand (2–4, 20).

Studies conducted mainly in adults have identified low circulating levels of VitC and VitB1 during critical illness (4, 5, 16, 17, 20–22). In a study of 44 adults, 88% of septic shock cases had low VitC (4). A trial conducted in 167 adults showed low median VitC levels at baseline and during the course of sepsis in the placebo group (21). In a study conducted in India, VitB1 levels were low in all of 76 children with septic shock at presentation and further decreased during the disease course (20). In a Brazilian cohort, 28% of 202 children had low VitB1 upon admission to the ICU (16). In our study, patients with low VitC had a higher CRP during sepsis, in line with previous studies (16, 23). We found higher VitB1 levels in patients receiving vitamin supplementation. VitB1 levels were low in the vast majority of children beyond neonatal age, and older age was associated with low VitC levels. Differences in age, comorbidities, vitamin intake, disease severity, and methods for determination of vitamin levels might explain the different proportions of patients with low vitamin levels between studies.

Classically, VitC deficiency is known as scurvy, and VitB1 deficiency causes the disease named beriberi.

While different states of subclinical or relative deficiency exist, the impact of low VitC and VitB1 levels on the outcome of sepsis remains unclear (3, 5, 16, 17, 24, 25). We did not find an association between VitC or VitB1 and organ dysfunction.

Our study has several limitations. The relatively small sample size and heterogeneity of patients limited our capacity to determine the relationship between vitamin levels and outcomes. Timing of sampling varied in relation to admission to hospital/intensive care and sepsis onset, and the proportion of patients with multiple organ dysfunction was relatively low. Vitamins were quantified in serum (3); therefore, we could not analyze intracellular VitB1 diphosphate levels. In addition, storage time prior to quantification of vitamins was relatively long, and precautions to support vitamin VitC stability during storage were not implemented and could thus add to the variability observed for this vitamin. Furthermore, cutoffs used in the literature to define levels associated with increased risks of developing adverse outcomes are not based on strong evidence (15).

CONCLUSIONS

Low and deficient VitC and VitB1 concentrations are frequent in neonates and children with sepsis and are associated with older age. In addition, systemic inflammation is associated with low VitC, and absence of vitamin supplementation is associated with low VitB1. The clinical relevance of these findings and the impact of VitC and VitB1 on the outcome of sepsis remains to be determined in future studies optimizing specific sample preanalytical requirements.

1 *Department Mother-Woman-Child, Clinic of Neonatology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.*

2 *Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.*

3 *Swiss Vitamin Institute, Lausanne, Switzerland.*

4 *Paediatric Intensive Care Unit, Queensland Children's Hospital, Child Health Research Centre, The University of Queensland, Brisbane, QLD, Australia.*

5 *Department of Intensive Care and Neonatology, Children`s Research Center, University Children's Hospital Zürich, Zürich, Switzerland.*

The Swiss Pediatric Sepsis Group are as follows: Professor Christoph Aebi (Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland); and Christoph Berger (Division of Infectious Diseases and Hospital Epidemiology, and Children's Research Center, University Children's Hospital Zurich, Switzerland).

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For information regarding this article, E-mail: Eric.Giannoni@chuv.ch

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