

Evaluation on Effects of Intravenous Thiamine on Patients with Sepsis and Septic Shock**Rakesh Kumar¹, Arohi Kumar², Amit Kumar³, Rahul Kumar⁴**¹Senior Resident (Emergency Medicine), MD (Anaesthesia), Department of Medicine, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar.²Professor, Department of Medicine, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar.³Assistant Professor and HOD, Department of Medicine, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar.⁴Associate Professor and HOD, Department of Anaesthesia, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar.

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Abstract**Background:** There is growing evidence that thiamine alone or in combination with vitamin C and steroids may have benefits in patients with sepsis. The purpose of this study is to evaluate the effects of intravenous thiamine following creation of an institutional thiamine guideline for sepsis.**Methods:** The pre-intervention group consisted of patients 18 years or older admitted to Department of Medicine and Emergency Medicine of SKMCH, Muzaffarpur, Bihar with sepsis/septic shock who received intravenous thiamine plus standard care (n=26). In the retrospective phase, they were matched with patients with the same diagnosis who served as a control group (n=26). The primary endpoint was hospital mortality. Secondary endpoints were time to death, critical care length of stay, time to lactate level <2 mmol/L, vasopressor use and duration, renal replacement therapy (RRT) requirement, and PaO₂/FiO₂ ratio. An evidence-based thiamine guideline for sepsis, standardizing the dose, duration, and time of initiation, was developed and implemented. In the prospective phase, the post-intervention thiamine group was compared with both the pre-intervention thiamine and control groups measuring the same endpoints.**Results:** In the pre- and post-intervention phase, there was no difference in hospital mortality. However, more patients in the control group required RRT as compared to pre-intervention thiamine group (65.4% vs. 42.3%, P=0.013). The post-intervention thiamine group also showed decreased RRT requirement compared to the control group (36.8% vs. 65.4%, P=0.02).**Conclusion:** Thiamine did not show hospital mortality benefit. However, it may be considered for use in patients with renal dysfunction. Future studies should further explore renally-protective effects of thiamine.**Keywords:** Sepsis; Septic Shock; Thiamine; Mortality; Renal Replacement Therapy (RRT).This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Sepsis affects about 1.7 million people in the United States annually and results in over 270,000 deaths [1]. Despite advances in critical care practices, sepsis remains the most common cause of death in non-cardiac intensive care units (ICUs). Sepsis manifests as decreased systemic vascular resistance resulting in decreased organ perfusion, and ultimately impaired oxygen delivery [2].

Patients who survive may suffer from residual organ dysfunction [3]. Current management of sepsis focuses on administering intravenous (IV) fluids and vasopressors while treating the underlying infection and controlling the source of infection. Society of Critical Care Medicine

(SCCM) guidelines do not address IV thiamine use in sepsis [4]. Thiamine has recently been used in sepsis as a potential adjunct to antibiotics, infection source control, and supportive care for patients with sepsis and septic shock. Thiamine (vitamin B1) is a water-soluble vitamin and a cofactor for pyruvate dehydrogenase enzyme, essential for converting pyruvate to acetyl-coenzyme A for entry into the Krebs cycle.

Increased metabolic demand, parenteral or enteral nutrition, diuretics, as well as hemodialysis and hemofiltration can deplete thiamine levels. Thiamine deficiency rates range from 20% to 70% in septic shock patients [5,6]. At inadequate levels

of thiamine, pyruvate is unable to be converted to acetyl coenzyme A, which results in impaired aerobic respiration and a compensatory shift to the anaerobic pathway. This, in turn, results in elevated serum lactate levels [7]. Some studies show that thiamine deficiency may be associated with increased mortality [6,8-10].

Thiamine supplementation has not been associated with serious adverse effects, even at high doses [11]. Up to 500 mg per dose IV may be necessary for patients with septic shock. Anaphylaxis has been reported in rare instances [11]. Intravenous (IV) thiamine should be administered over a 15- to 30-minute interval in a mixture of saline solution or dextrose to avoid potential adverse reactions [12]. However, some studies suggest thiamine administration with doses up to 200 mg as an IV push with no evidence of anaphylactic reactions [13,14]. Thiamine supplementation can be a low-risk and potentially high-reward intervention for some patients with septic shock and increased baseline risk of thiamine deficiency.

Findings on the efficacy of IV thiamine are not consistent. In small, retrospective studies of septic ICU patients, the combination of thiamine (200 mg IV every 12 hours), ascorbic acid (1,500 mg IV every six hours), and hydrocortisone (50 mg IV every six hours) improved organ injury, time to shock reversal, increased lactate clearance and decreased mortality (3,15). APACHE-adjusted ICU mortality was lowest when combination therapy was initiated within six hours of presentation with sepsis and in the subgroup of patients with SOFA scores of greater than 10 or with hypoalbuminemia (albumin below 3 g/dL) [16,17].

Material and Methods

The study consisted of retrospective (January through July 2023) and prospective (November 2023 through March 2024) phases.

In the pre-intervention phase, critical care patients with sepsis or septic shock diagnosis, who did not receive thiamine, were matched with patients who received average daily thiamine dose of 200 mg for the period of January 1st through July 15th, 2023.

Twenty-six patients in the control group were matched with 26 patients who received any dose of IV thiamine, with a total of 52 patients in the retrospective phase, based on receiving standard of care (IV fluids and antibiotics within three hours of diagnosis) and ventilation. An evidence-based, thiamine guideline for sepsis, standardizing the dose, duration, and time of initiation was developed, approved by the Pharmacy &

Therapeutics Committee and implemented in November. Per the guideline, the post-intervention phase patients received 200 mg of thiamine intravenously every 12 hours within six hours of sepsis or septic shock diagnosis for a minimum of 72 hours or six doses. The guideline recommends thiamine discontinuation upon sepsis or septic shock resolution and/or discontinuation of vasopressors.

The primary endpoint was hospital mortality. The secondary endpoints were time to death, time to lactate level less than 2 mmol/L, vasopressor use, ICU length of stay, vasopressor duration, renal replacement therapy (RRT) requirement, PaO₂/FiO₂ ratio at discharge, as well as SOFA score at 72 hours. The inclusion criteria were: age of 18 years or older, critical care unit (ICU/IMCU) admission with sepsis or septic shock diagnosis. The exclusion criteria were: allergy or anaphylactic reaction to thiamine, clinical indication for thiamine (e.g., alcoholism, Wernicke's encephalopathy), and pregnancy.

In the prospective phase, the same primary and secondary endpoints were then compared between the post-intervention (thiamine dose of 200 mg every 12 hours) and pre-intervention (thiamine at any dose and frequency) thiamine patients, as well as between post-intervention thiamine and control patients.

Statistical tests for data analysis included chi-square and Fisher's Exact (when 50% of the values had expected counts less than five for categorical data. Continuous data were analyzed using Wilcoxon Rank Sum test and presented using median and interquartile range. Alpha level for statistical significance was set at 0.05 or less. Time to event analysis was presented as Kaplan-Meier survival curves for time to hospital mortality and time to discharge from critical care unit.

Results

In the retrospective phase of the study, out of 345 patients screened 52 patients meeting the eligibility criteria were random selected. For the retrospective pre-intervention phase, baseline characteristics were similar between the thiamine (n=26) and control groups (n=26), except for gender, vasopressor use, AKI at baseline and antibiotic initiation within three hours of sepsis diagnosis (Table 1).

Another difference in baseline characteristics between the groups was steroid use: 50% in the control group received steroids vs. about 70% in the thiamine group.

Table 1: Baseline characteristics in retrospective phase: control vs. pre-intervention thiamine group

Variable	Control group (n=26)	Pre-intervention thiamine group (n=26)	P value
Age, mean±SD, years	65.7±3.3	62.6±12.9	0.386
Weight, mean±SD, kg	84.7±31.5	80.6±18.9	0.400
Sex, male, n(%)	22 (84.6)	16 (61.5)	0.007
Admission diagnosis, n(%)			
Community acquired pneumonia	8(30.8)	6(23.1)	0.395
Pneumonia due to COVID	9(34.6)	11 (42.3)	0.410
Surgical site infection	0(0)	1(3.85)	0.845
UTI/pyelonephritis	4(15.4)	3(11.5)	0.587
GI infection	2(7.7)	2(7.7)	1.0
HCAP	0(0)	1(3.8)	0.845
Respiratory distress	0(0)	2(7.7)	0.695
SSTI	3(11.5)	1(3.8)	0.220
Unknown	0(0)	1(3.8)	0.845
Comorbidities, n(%)			
CAD/MI	6(23.1)	8(30.8)	0.3352
Hypertension	14 (65.4)	15(57.7)	0.410
Hyperlipidemia	7(26.9)	11 (42.3)	0.077
Diabetes	9(34.6)	10 (38.5)	0.680
Heart failure	2(7.7)	3(11.5)	0.462
CVA	3(11.5)	1(3.85)	0.220
COPD	3(11.5)	2(7.7)	0.539
CKD	2(7.7)	2(7.7)	1.0
PVD	0(0)	1(3.85)	0.845
Immunocompromised	5(19.2)	4(15.4)	0.619
Cirrhosis	0(0)	1(3.85)	0.845
Opioiduse	3(11.5)	1(3.85)	0.220
None/unknown	3(11.5)	4(15.4)	0.539
Mechanical ventilation	18 (69.2)	21 (80.8)	0.202
Vasopressors	14 (53.8)	24 (92.3)	0.004
Positive blood cultures	17 (65.4)	16 (61.5)	0.680
Acute kidney injury	11 (42.3)	22 (84.6)	0.005
Laboratory values			
Lactate, median(IQR), mmol/L	2.7(1.3–4.2)	2.2(1.5–5.7)	0.543
Procalcitonin, median (IQR), mcg/mL	0.51(0.19–1.94)	0.81(0.19–5.00)	0.488
PaO ₂ /FiO ₂ ratio, mean±SD, mmHg	212.7778±123.5588	195.3444±142.7044	0.445
Treatment timing and duration			
Fluids within 3 hours of sepsis diagnosis, n(%)	21 (80.8)	18 (69.2)	0.135
Antibiotics within 3 hours of sepsis diagnosis, n(%)	24 (92.3)	15 (57.7)	<0.0001
Timing of thiamine initiation, mean±SD, h	–	155.2±183	–
Number of thiamine doses, mean±SD	–	8.8±5.7	–
Thiamine dose, mean±SD, mg	–	220±110	–
Receipt of steroid, n(%)	13 (50.0)	18 (69.2)	0.049
Daily steroid dose (hydrocortisone equivalent), median (IQR), mg	200[200–530]	200[100–300]	0.330
Duration of steroid therapy, median (IQR), h	96 [38–240]	72 [24–144]	0.290
COVID presence at diagnosis, n(%)	11 (42.3)	12 (46.2)	0.691

There was no statistically significant difference between the two groups with respect to the primary outcome. There was no difference between groups with respect to secondary outcomes, with the

exception of RRT requirements: more patients in control group required RRT as compared to the treatment group (65.4% vs. 42.3%, P=0.013) (Table 2).

Table 2: Outcomes in retrospective phase : control vs. pre-intervention thiamine group

Primary outcome	Control group (n=26)	Pre-intervention thiamine group (n=26)	P value
Hospital mortality, n(%)	9(34.6)	10 (38.5)	0.680
Secondary outcomes			
Time to death, median (IQR), days	9[8–21]	7.5[3–12]	0.93
Time to lactate levels <2mmol/L, median (IQR), hours	21 [10–24]	37.5[24–48]	0.06
ICU/IMCU length of stay, median(IQR),days	9(4–17.3)	11.5(6.8–25.3)	0.479
Vasopressor duration, median (IQR), h	48 (23.5–117.8)	51.5[24–151]	0.75
RRT required, n(%)	17 (65.4)	11 (42.3)	0.013
PaO ₂ /FiO ₂ ratio, median (IQR), mmHg	244[127–305]	197[107–327]	0.59

Following thiamine guideline implementation and completion of the prospective post-intervention phase, out of 66 patients, 38 met the eligibility criteria with guideline-directed thiamine use. The primary and secondary outcomes were compared between the pre-intervention thiamine and post-intervention thiamine groups. Baseline

characteristics were similar between the two groups, except the timing of antibiotic initiation: less patients in the retrospective thiamine group received antibiotics within 3 hours of sepsis or septic shock diagnosis compared to the post-intervention thiamine group (57.7% vs. 92.1%, P=0.001) (Table 3).

Table 3: Baseline characteristics in prospective phase: pre-intervention vs. post-intervention thiamine groups

Variable	Pre-intervention thiamine group (n=26)	Post-intervention thiamine group (n=38)	P value
Age, mean±SD, years	62.6±12.9	67.3±12.9	0.11
Weight, mean±SD, kg	80.6±18.9	81.1±23.9	0.85
Sex, male, n(%)	16 (61.5)	27 (71.1)	0.63
Admission diagnosis, n(%)			
Septic shock due to pneumonia	17 (65.4)	17 (44.7)	0.05
Septic shock due to UTI	3(11.5)	3(3.79)	0.68
GI infection	2(7.7)	1(2.6)	0.99
SSTI	1(3.8)	1(2.6)	0.99
Comorbidities, n(%)			
CAD/MI	8(30.8)	5(13.2)	0.09
Hypertension	15 (57.7)	24 (63.2)	0.66
Hyperlipidemia	11 (42.3)	18 (47.4)	0.69
Diabetes	10 (38.5)	15 (39.5)	0.94
Heart failure	3(11.5)	6(15.8)	0.73
COPD	2(7.7)	3(7.9)	0.98
CKD	2(7.7)	6(15.8)	0.46
Immunocompromised	4(15.4)	5(13.2)	0.80
None/unknown	4(15.4)	4(10.5)	0.71
Other, n(%)			
Mechanical ventilation	21 (80.8)	34 (89.5)	0.29
Vasopressors	24 (92.3)	38 (100)	0.16
Positive blood cultures	16 (61.5)	20 (52.6)	0.48
Acute kidney injury	22 (84.6)	26 (68.4)	0.27
Laboratory values			
Lactate, median(IQR), mmol/L	2.2(1.5–5.7)	3.7(2.2–8.3)	0.06
PaO ₂ /FiO ₂ ratio, mean±SD, mmHg	195.3±142.7	134.5±80.3	0.20
SOFA score on day 1, median (IQR)	7(4.7–9.5)	9(7.8–9)	0.22
Treatment timing and duration			
Fluids within 3 hours of sepsis diagnosis, n(%)	18 (69.2)	29 (76.3)	0.53
Antibiotics within 3 hours of sepsis diagnosis, n(%)	15 (57.7)	35 (92.1)	0.001
Number of thiamine doses, mean±SD	8.8±5.7	10±6.9	0.31
Daily thiamine dose, mean±SD, mg	220±110	400±0	–
Received steroids, n(%)	18 (69.2)	32 (84.2)	0.15

Daily steroid dose (hydrocortisone equivalent), median (IQR), mg	200[100–300]	200[200–200]	0.80
Duration of steroid therapy, median (IQR),h	72 [24–144]	99 [72–192]	0.10
COVID presence at diagnosis, n(%)	12 (46.2)	18 (71.1)	0.92

In the prospective phase, the post-intervention thiamine group with standardized thiamine dosing did not reveal any mortality benefit (Table 4). In addition, no difference in secondary outcomes between the pre-intervention and post-intervention thiamine groups were observed.

Table 4: Outcomes in prospective phase: pre-intervention vs. post-intervention thiamine groups

Primary outcome	Pre-intervention thiamine group (n=26)	Post-intervention thiamine group (n=38)	P value
Hospital mortality, n(%)	10 (38.5)	23 (60.5)	0.08
Secondary outcomes			
Time to death, median (IQR), days	7.5[3–12]	11.5[7–21]	0.26
Time to lactate levels <2mmol/L, median (IQR), hours	37.5[24–48]	28 [18–86]	0.47
ICU/IMCU length of stay, median (IQR), days	11.5(6.8–25.3)	13 [8–19]	0.86
Vasopressor duration, median (IQR),h	51.5[24–151]	79.8[34–203]	0.29
RRT required, n(%)	11 (42.3)	14 (36.8)	0.66
PaO ₂ /FiO ₂ ratio, median (IQR), mmHg	197[107–327]	178[93–250]	0.77
SOFA score at 72 hours	8(6.5–12)	8(4.8–12)	0.90

The control (n=26) and post-intervention thiamine groups (n=38) had some differences in baseline characteristics. It is worth noting that at baseline, all patients in post-intervention thiamine group required vasopressors at baseline, had higher lactate levels, higher SOFA scores, and lower

PaO₂/FiO₂ ratio (Table 5). When comparing the two groups, the primary outcome of hospital mortality showed difference in favor of the control group (34.6% vs. 60.5% control vs. post-intervention thiamine groups, respectively; P=0.04) (Table 6).

Table 5: Baseline characteristics in prospective phase: control vs. post-intervention thiamine group

Variable	Control (n=26)	Post-intervention thiamine group (n=38)	P value
Age, mean±SD, years	65.7±16.8	67.3±12.9	0.58
Weight, mean±SD, kg	84.7±31.5	81.1±23.9	0.87
Sex, male, n(%)	22 (84.6)	27 (71.1)	0.21
Admission diagnosis, n(%)			
Septic shock due to pneumonia	9(34.6)	17 (44.7)	0.42
Septic shock due to UTI	4(15.4)	3(7.9)	0.43
GI infection	2(7.7)	1(2.6)	0.56
SSTI	3(11.5)	1(2.6)	0.30
Comorbidities, n(%)			
CAD/MI	6(23.1)	5(13.2)	0.30
Hypertension	14 (53.8)	24 (63.2)	0.46
Hyperlipidemia	7(26.9)	18 (47.4)	0.10
Diabetes	9(34.6)	15 (39.5)	0.69
Heart failure	2(7.7)	6(15.8)	0.34
COPD	3(11.5)	3(7.9)	0.62
CKD	2(7.7)	6(15.8)	0.34
Immunocompromised	5(19.2)	5(13.2)	0.51
None/unknown	3(11.5)	4(10.5)	0.90
Other, n(%)			
Mechanical ventilation	18 (69.2)	34 (89.5)	0.05
Vasopressors	16 (61.5)	38 (100)	<.0001
Positive blood cultures	17 (65.4)	20 (52.6)	0.31
Acute kidney injury	11 (42.3)	26 (68.4)	0.04
Laboratory values			
Lactate, median(IQR), mmol/L	2.7(1.3–4.1)	3.7(2.2–8.2)	0.01
PaO ₂ /FiO ₂ ratio, mean±SD, mmHg	212.3±123.6	134.5±80.3	0.02

SOFA score on day1, median (IQR)	6.5[4–8]	9[7–10]	0.045
Treatment timing and duration			
Fluids within 3 hours of sepsis diagnosis, n(%)	21 (80.8)	29 (76.3)	0.67
Antibiotics within 3 hours of sepsis diagnosis, n(%)	24 (92.3)	35 (92.1)	0.98
Number of thiamine doses, mean±SD	–	10±6.9	–
Daily thiamine dose, mean±SD, mg	–	400±0	–
Received steroids, n(%)	13 (50.0)	32 (84.2)	0.003
Daily steroid dose (hydrocortisone equivalent), median (IQR), mg	200[200–530]	200[200–200]	0.06
Duration of steroid therapy, median (IQR),h	96 [38–240]	99 [72–192]	0.53
COVID presence at diagnosis, n(%)	11 (42.3)	18 (71.1)	0.69

Table 6: Outcomes in prospective phase: control vs. post-intervention thiamine group

Primary outcomes	Control (n=26)	Post-intervention thiamine group(n=38)	P value
Hospital mortality, n(%)	9(34.6)	23 (60.5)	0.04
Secondary outcomes			
Time to death, median (IQR), days	9[8–21]	13 [8–19]	0.83
Time to lactate levels<2mmol/L, median(IQR), hours	18 [10–24]	28 [18–84]	0.08
ICU/IMCU length of stay, median (IQR), days	9[4–16]	11.5[7–21]	0.28
Vasopressor duration, median (IQR),h	47.5(23.0–94.5)	79.8(37.0–194.5)	0.18
RRT required, n(%)	17 (65.4)	14 (36.8)	0.02
PaO ₂ /FiO ₂ ratio, median (IQR), mmHg	244[127–305]	178.6(95.9–334.0)	0.41
SOFA score at 72 hours, median (IQR)	7[6–9]	8[7–10]	0.41

Discussion

More patients in the control group were initiated on antibiotics in a timely manner compared to the thiamine group during the retrospective phase. While this is a confounding factor, it is unknown to what extent this contributes to the frequency of the primary outcome in each group. Differences in some baseline characteristics in the pre-intervention group along with the small sample size limit the generalizability of the study results. In the retrospective phase, time to discharge was also longer in thiamine group, which can be explained by the fact that patients who survived were more likely to stay in ICU or IMCU before being discharged or downgraded.

In the post-intervention phase, when comparing the pre-intervention thiamine group with the post-intervention thiamine group, there was no difference in baseline characteristics except for more timely antibiotic initiation in the post-intervention thiamine group. When comparing the retrospective control group with post-intervention thiamine group, the groups were significantly different in terms of some key baseline characteristics such as the number of patients on vasopressors, baseline lactate levels, SOFA score, as well as PaO₂/FiO₂ ratios. As the post-intervention thiamine group had sicker patients with higher lactate levels, higher SOFA scores, and lower PaO₂/FiO₂ ratio, this can help explain the lack of mortality benefit in the intervention group.

In the retrospective or pre-intervention phase of the current study, thiamine groups did not show benefit

compared with the control group with respect to primary and most of the secondary outcomes, with the exception of RRT requirement. This can be a potential benefit of thiamine therapy, suggesting renally protective effects in critically ill patients. However, RRT requirement was a secondary outcome of the retrospective phase of the study and the latter finding is only exploratory in nature. This finding of the present study corresponds to findings from a randomized, double-blind trial, where thiamine reduced the need for RRT [18]. As for the prospective or post-intervention phase, the study did not find statistically significant differences between standardized and unspecified thiamine dosing strategies. While this study was unable to demonstrate a mortality impact, given the risk vs. benefit profile, thiamine may be considered with current study limitations. Giving some thiamine may have masked the effect of guideline-based thiamine, decreasing the magnitude of the difference between no thiamine and thiamine at evidence-based doses.

Study limitations, such as small sample size and different baseline characteristics for some variables, limit applicability of study results. However, of note, the post-intervention thiamine group had sicker patients, which could be a contributing factor to more timely antibiotic initiation. Since this is one of the most important driving factors in reducing mortality, that benefit could have outshined the benefits of a standardized thiamine dosing approach. It is an important confounder that could not be adequately controlled for in this study. Even a marginal benefit of

thiamine in this patient population can make a difference in mortality with a properly conducted large-scale study. Thiamine with or without IV steroids and vitamin C may be a promising therapy for sepsis or septic shock, however, currently lacks robust evidence to support its use. The rationale behind using thiamine in this patient population is supported by its effect on the pentose phosphate pathway, facilitating carbohydrate metabolism and shifting anaerobic cellular metabolism to aerobic [5-7].

Conclusion

Future studies should further investigate thiamine effects on hospital mortality in septic patients when combined with other therapies, such as IV steroids and vitamin C. Another potential area of investigation for thiamine benefits can be septic patients with renal dysfunction.

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