International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 02 Issue 12 December 2022

Page No: 1547-1554

DOI: https://doi.org/10.47191/ijmscrs/v2-i12-33, Impact Factor: 5.365

Is Thiamine Administration Effective in Sepsis or Not? A Randomized Controlled Trial

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ABSTRACT

Background: Sepsis is the first leading cause of death in Myanmar and complications are also difficult to solve. This study aimed to detect the effect of thiamine on lactate clearance and mortality in patients with sepsis.

Method: A randomized controlled trial done in No.(1) Defence Services General Hospital, Yangon from October 2020 to June 2022. All patients > 18 years old admitted with suspected or documented infection and qSOFA score 2 or 3 were included but alcohol related cases were excluded. Total 80 patients were assigned 1:1 by block randomization. Intervention group was given IV thiamine 100 mg 6 hourly for 3 days. Primary outcome was lactate clearance and secondary outcomes, mSOFA score (both were assessed in day 1, day 3 and day 7), and mortality within 7 days. Intention to treat analysis with worst data imputation in missing value for expired cases.

Results: Significant lactate clearance was seen in intervention group compared with control group, in day 3, [23.53% (34.37) vs 16.67% (43.30), z = -2.353, p = 0.019] and day 7, [53.85% (28.90) vs 30.22% (38.61), z = -3.186, p = 0.001]. Lactate clearance over time was well observed in the intervention group, [X^2 (2) = 29.356, p < 0.001] but not in the control group, [X^2 (2) = 3.152, p = 0.207]. Significant mSOFA score reduction over time was also observed in the intervention group, [X^2 (3) = 39.330, p < 0.001]. All-cause mortality within 7 days was not different, [X^2 (1) = 0.949, p = 0.330, OR 0.949, 95% CI (0.51 – 7.12)].

Conclusion: Thiamine supplementation in sepsis patient was benefit in lactate clearance starting from day 3 and reduction of mSOFA score starting from day 7. But it did not show the mortality benefit within 7 days period.

ARTICLE DETAILS

Published On:
21 December 2022

Available on:
https://ijmscr.org/

KEYWORDS: Sepsis, thiamine, lactate clearance, mSOFA score

BACKGROUND

Sepsis is a common medical problem which causes life threatening condition. The global epidemiological burden of sepsis is difficult to estimate. According to WHO, more than 30 million people worldwide every year suffer from sepsis and about 6 million people lead to death (1). The burden of sepsis is estimated to be highest in low and middle-income countries. According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, there was an estimation of 60.2 million and 48.9 million sepsis cases worldwide in1990 and 2017, respectively (2). Incidence and mortality of sepsis is also high in southeast Asia (including Myanmar). The epidemiological data of sepsis in Myanmar is difficult to estimate. Sepsis is the first single leading cause

of death in Myanmar 7.4% in 2014, 8.0% in 2015 and 6.6% in 2016. Therefore, sepsis is the main problem of increasing mortality in Myanmar (3).

When the microorganisms invaded into the living body, immune defense mechanism is activated. If the microorganisms overcome the host's immunological defense system due to the weak defense system or due to higher infectious dose as well as increased virulency, microorganisms spread to the different tissue and organs through the blood stream causing bacteriemia and septicaemia. Then, exaggerated production of inflammatory mediators creates the cytokine storm, leading to failure of vital organs and finally death.

During sepsis, patient's metabolism has been changed and increased production of lactate due to increased glycolysis activity, which is aerobic glycolysis (Warburg effect) and increased reduction of pyruvate (4). Utilization of thiamine is increased and deficient during sepsis. The prevalence of thiamine deficiency in sepsis was 10% on admission, increased to 20% within the first 72 hour, and in septic shock 20% on admission and increased to 71.3% during the course (5)(6). This may be due to poor absorption, inadequate nutrition, increased requirements for thiamine (7).

Lactate is a typical biomarker in sepsis and lactate dynamic strongly correlate with disease severity, and mortality (8). Lactate clearance during the first 6 hour of sepsis treatment, is highly associated with survival benefit (9).

According to the previous studies, thiamine supplementation to patients with sepsis causes rapid improvement in SOFA score, lactate clearance, 7 days mortality. In a randomized controlled trial of intravenous thiamine in patients with septic shock, there was significant decrease in lactate from baseline within 24 hours (5). In a matched cohort study, patients with septic shock admitted to the ICU, receipt intravenous thiamine within the first 24 hours of admission was associated with improved lactate clearance and a reduction in 28-day mortality (10). But in a study, there was no significant improvement in relative lactate change, SOFA score and ICU Mortality (11). This study was aimed to detect the effect of thiamine on lactate clearance and mortality in patients with sepsis.

METHODS

Study Design and Population

A randomized controlled trial done in No.(1) Defence Services General Hospital, Yangon from October 2020 to June 2022. All patients above 18 years old admitted with suspected or documented infection and qSOFA $\geq$ 2 were included. Patients with known drug allergy to thiamine, alcohol used disorder who needed IV thiamine therapy and pregnant women were excluded in this study.

Randomization, Study Drug and Research Procedure

The written informed consents were taken from patients or a legally authorized his/her relative. Patients were assigned to either thiamine group or control group according to the block randomization order. There were total of 80 patients; 40 patients were assigned to intervention group and another 40 were assigned to control group. Patients in intervention group were given IV thiamine hydrochloride 100 mg 6 hourly for 3 days. Before administration, intradermal thiamine allergy test was performed. Patients in control group were not given any placebo. Empirical antibiotic therapy, fluid resuscitation, inotrope therapy and other supportive as in hospital guideline were given to both groups.

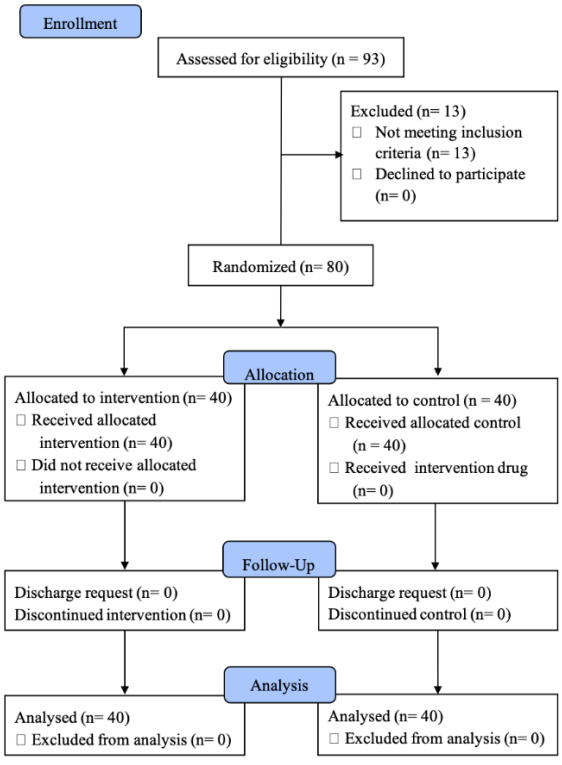

Figure 1. CONSORT diagram

Outcome Measures

The primary outcome was the lactate clearance, which was percent changes of lactate at day 1, day 3 and day 7 from initial lactate level by using following formula:

Lactate clearance = (lactate initial – lactate delayed) /lactate initial × 100

Unit is expressed in percentage and a negative lactate clearance indicates an increase in lactate over time, while a positive lactate clearance indicates a decrease of lactate over time.

Secondary outcomes were mSOFA score at day 1, day 3 and day 7, and 7 day mortality. mSOFA score was assessed according to the Table (1).

Table 1. mSOFA score

Organs	mSOFA Score				
	0	**1**	**2**	**3**	**4**
Respiratory SpO_2/FiO_2 (mmHg)	≥ 400	< 400	< 315	< 235	< 150
Liver	No scleral icterus or jaundice			Scleral icterus or jaundice	
CVS (dopamine, dobutamine, epinephrine and nor-epinephrine doses in µg/kg/min)	No Hypo-tension	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)	Dopamine > 5 or epinephrine ≤ 0.1 or nor-epinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or nor-epinephrine > 0.1
CNS GCS	15	13-14	10 - 12	6 - 9	< 6
Renal Creatinine mg/dL (µmol/L)	< 1.2 (< 110)	1.2-1.9 (110-170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440)	> 5 (> 440)

Statistical Analysis

Statistical analysis was done by using IBM® SPSS® Statistic version 26. Data were analyzed using intention to treat approach and missing values were treated as single imputation by worst observation carried forward method for the patients who died during the study period. All the continuous variables for both groups were accessed normality by skewness and kurtosis in descriptive as well as by the Shapiro-Wilk test. When the variables in either group was in non-normal distribution, the comparative data were expressed as median (IQR), and both met normal distribution, expressed as mean ± SD. All the categorical data were described as frequency and percentage. Lactate clearance and mSOFA score were analyzed by Mann-Whitney U test for between group analysis, and non-parametric Friedmann's two-way analysis of variance for within group analysis and post-hoc analysis by Wilcoxon signed ranked test using the Bonferroni correction. Mortality within 7 days was analyzed by Pearson's chi-square test. For all the statistical tests, the significant level, alpha was set as p value < 0.05.

RESULTS

The mean age was 53.70 ± 18.77 vs 62.68 ± 16.91 years, mean BMI 24.57 ± 4.89 vs 24.92 ± 4.68 kg/m^2, male/female ratio 1:1 in intervention vs control group. Half of the patients in each group were having history of hypertension and one-third having diabetes mellitus. The majority of patients, 72.5% in the intervention group and 80% in the control group were due to lower respiratory tract infection, severe pneumonia. Nine patients in each group presented with hypotension at initial and 8 out of 9 in intervention group as well as 4 out of 9 in control group required inotrope therapy at initial; [Table (2)].

Significant lactate clearance was seen in the intervention group compared to the control group, in day 3, [23.53% (34.37) vs 16.67% (43.30), z = -2.353, p = 0.019] and day 7, [53.85% (28.90) vs 30.22% (38.61), z = -3.186, p = 0.001], [Table (3) & Figure (2)]. Lactate clearance over time was well observed in the intervention group, [X^2 (2) = 29.356, p < 0.001] but not in the control group, [X^2 (2) = 3.152, p = 0.207]; [Table (4) & (5)].

The median mSOFA score and IQR was 3.5 (4) in both groups at day 1, (Z = -0.024, p = 0.981) and 3 (5) in both groups at day 3, Z = -0.427, p = 0.669, ; and both were not statistically significant. The day 7 median mSOFA score and IQR in intervention group was 0 (5) which was less than that in the control group although it did not reach to statistically significant level, (Z = -1.920, p = 0.055); [Table (6) & Figure (3)]. The significant mSOFA score reduction over time was also observed in the intervention group, [X^2 (3) = 39.330, p < 0.001], but not in the control group; [Table (7) & (8)].

Four patients in the intervention group and seven patients in the control group died within the 7 days period, however, there was not statistically significant difference in 7 day mortality between the two groups, [X^2 (1) = 0.949, p = 0.330, OR 0.949, 95% CI (0.51 – 7.12)]; [Table (9) & (10)]. All the patient who got IV thiamine did not have any adverse reaction.

Table 2. Baseline clinical characteristics of the patients with sepsis

Clinical Characteristics	Intervention (n = 40)		Control (n = 40)	
	n (%)	Mean ± SD	n (%)	Mean ± SD
Age (yrs)		53.70 ± 18.77		62.68 ± 16.91
Sex				
Male	20 (50)		22 (55)	
Female	20 (50)		18 (45)	
BMI (kg/m^2)		24.57 ± 4.89		24.92 ± 4.68
Comorbidities				
CAD	6 (15)		12 (30)	
Hypertension	20 (50)		23 (57.5)	
CCF	2 (5)		0 (0)	
COAD	2 (5)		0 (0)	
Diabetes	13 (32.5)		13 (32.5)	
Stroke	7 (17.5)		11 (27.5)	
CKD	4 (10)		2 (5)	
Malignancy	2 (5)		0 (0)	
SLE	0 (0)		1 (2.5)	
Source of infection				
Respiratory tract	29 (72.5)		32 (80.0)	
Urinary tract	0 (0)		2 (5)	
Gastrointestinal	7 (17.5)		1 (2.5)	
Soft tissue	3 (7.5)		3 (7.5)	
CNS	0 (0)		2 (5)	
Septic Abortion	1 (2.5)		0 (0)	
GCS, *Median (IQR)*		15 (2)		15 (2)
Temp (˚F)		100.93 ± 1.73		100.39 ± 1.27
SpO_2/FiO_2 (mmHg)		319.80 ± 110.56		305.73 ± 103.67
RR (/min)		28.85 ± 6.82		29.10 ± 6.23
HR (bpm)		98.33 ± 16.16		91.68 ± 15.07
SBP (mmHg)		116.00 ± 26.00		114.75 ± 23.31
DBP (mmHg)		73.38 ± 17.30		69.75 ± 14.41
MAP (mmHg)		87.50 ± 19.76		84.58 ± 17.17
Hypotension	9 (22.5)		9 (22.5)	
Inotrope required	8 (20)		4 (10)	
Jaundice present	5 (12.5)		6 (15.0)	

Table (3) Comparison of day 1, day 3 and day 7 lactate clearance between intervention and control groups

Day	Median (IQR) of Lactate clearance (%)		Z statistics	*p* value*
	Intervention n = 40	Control n = 40		
Day 1	16.67 (32.98)	14.86 (35.85)	-0.188	0.851
Day 3	23.53 (34.37)	16.67 (43.30)	-2.353	0.019
Day 7	53.85 (28.90)	30.22 (38.61)	-3.186	0.001

*Mann Whitney's U test

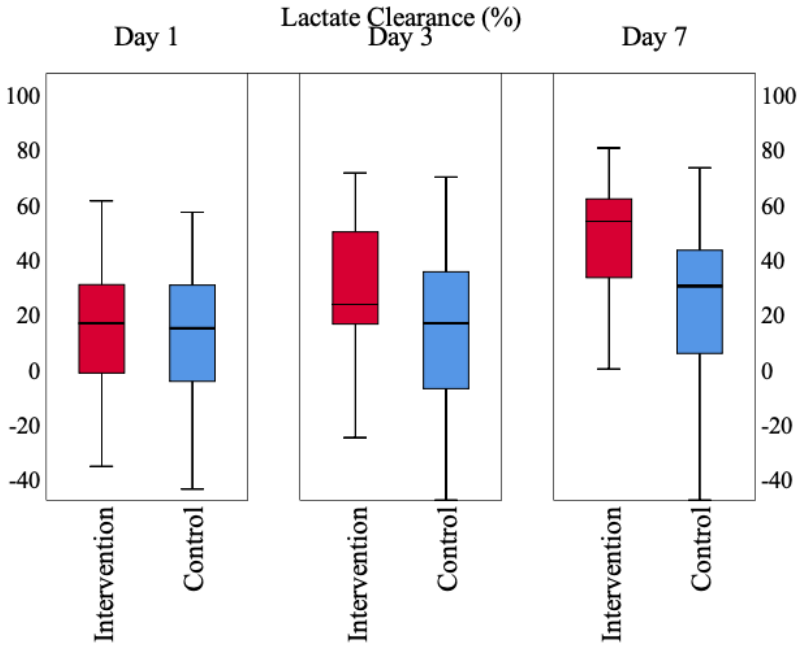

Figure 2. Box and Whisker Plot diagram showing the lactate clearance (%) in day 1, day 3 and day 7 in the intervention group and in the control group

Table 4. Comparison of day 1, day 3 and day 7 lactate clearance within the intervention group (n = 40)

Day	Median (IQR) of Lactate clearance (%)	X^2 statistics (df)	*p* value*
Day 1	16.67 (32.98)		
Day 3	23.53 (34.37)	29.356 (2)	< 0.001
Day 7	53.85 (28.90)		

*Friedman's test

Table 5. Comparison of day 1, day 3 and day 7 lactate clearance within the control group (n = 40)

Day	Median (IQR) of Lactate clearance (%)	X^2 statistics (df)	*p* value*
Day 1	14.86 (35.85)		
Day 3	16.67 (43.30)	3.152 (2)	0.207
Day 7	30.22 (38.61)		

*Friedman's test

Table 6. Comparison of day 0, day 1, day 3 and day 7 mSOFA score between intervention and control groups

Day	Median (IQR) of mSOFA score		Z statistics	*p* value*
	Intervention n = 40	Control n = 40		
Day 0	4 (4)	4 (4)	-0.107	0.915
Day 1	3.5 (4)	4 (4)	-0.024	0.981
Day 3	3 (5)	3 (5)	-0.427	0.669
Day 7	0 (5)	2 (6)	-1.920	0.055

*Mann-Whitney U Test

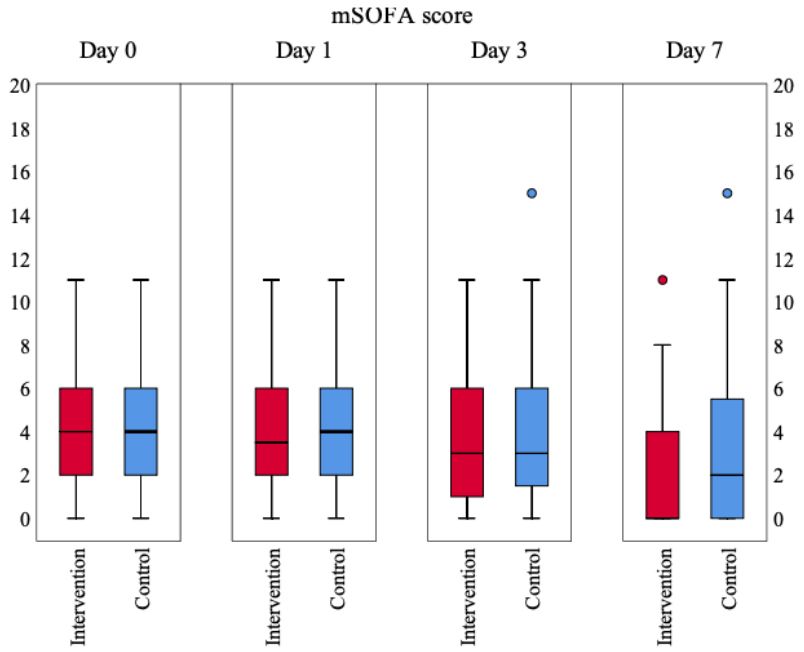

Figure 3. Box and Whisker Plot diagram showing mSOFA score in day 0, day 1, day 3 and day 7 in the intervention group and in the control group

Table 7. Comparison of day 0, day 1, day 3 and day 7 mSOFA score within intervention group (n = 40)

Day	Median (IQR) of mSOFA score	X^2 statistics (df)	*p* value*
Day 0	4 (4)	39.330 (3)	< 0.001
Day 1	3.5 (4)		
Day 3	3 (5)		
Day 7	0 (5)		

*Friedman's test

Table 8. Comparison of day 0, day 1, day 3 and day 7 mSOFA score within control group (n = 40)

Day	Median (IQR) of mSOFA score	X^2 statistics (df)	*p* value*
Day 0	4 (4)	13.256 (3)	0.004
Day 1	4 (4)		
Day 3	3 (5)		
Day 7	2 (6)		

*Friedman's test

Table 9. Comparison of 7-day Mortality between intervention and control groups

Survival outcome at day 7	n (%)		X^2 (df)	*p* value*
	Intervention n = 40	Control n = 40		
Alive	36 (90)	33 (82.5)	0.949 (1)	0.330
Expired	4 (10)	7 (17.5)		

*Pearson's Chi-square test

Table 10. Mode of death in expired patients

Mode of death	Intervention (n = 4)	Control (n = 7)
ARDS	2 (50)	3 (42.9)
Multiorgan Failure	2 (50)	4 (53.1)

DISCUSSION

All the baseline demographic characteristics were comparable and small discrepancies were due to by chance. The non-significant finding in day 1 lactate clearance was consistent with the previous findings (5) (11) (12). However, it was against a study in which 24 hour lactate clearance in

the thiamine group was more than in the placebo group (13). Day 3 lactate clearance was seen more in the intervention group than in the control group and which was statistically significant and day 3 lactate clearance was against the previous findings (11) (12). Day 7 lactate clearance was also significantly more in the intervention group than in the control group and it was consistent with the previous finding (10). The overall lactate clearance in repeated measured analysis was statistically significant in the intervention group but not in the control group. This finding was consistent with the previous study, in which thiamine did not effect on lactate level in the first 24 hours, but significant improvement within the first 72 hours (5). The non-significant difference in day 1 and day 3 mSOFA score was similar with the previous studies (5) (11) (12). The 7 day mortality was not significant as the previous studies (5) (10) (13) (14).

CONCLUSIONS

Thiamine supplementation in sepsis patient had benefits in lactate clearance starting from day 3 and reduction of mSOFA score starting from day 7. Therefore, biochemical changes at cellular level came first when compared with clinical changes. However, it did not show the mortality benefit within 7 days period. Thiamine was generally safe to use and no remarkable adverse event was found.

LIMITATION OF STUDY

In this study, patients' thiamine status couldn't be assessed and the pretreatment thiamine level variance could reflect the outcomes. Although the aetiology distribution was almost equal between the intervention and the control group, majority of patients (72.5% in intervention group and 80% in control group) were due to respiratory aetiologies (aspiration pneumonia and severe community acquired pneumonia). So that the sample population could be represented as sepsis patients with respiratory aetiologies.

RECOMMENDATION

Initial lactate level reflects the severity of sepsis and higher clearance of lactate in serial monitoring is associated with better clinical outcome. Lactate level should be accessed on admission as well as serial monitoring in all the patients with sepsis. Increased utilization of thiamine may cause relative thiamine deficiency in sepsis and thiamine administration should be given to all patients at least 7 days or until discharge.

ACKNOWLEDGEMENT

We are deeply grateful to Professor Khin Phyu Pyar, Professor and Head of Department of Medicine and Nephrology, for her generous support and valuable advice. We would like to extend my gratitude to Dr. Sai Aik Hla, Consultant Nephrologist, Department of Nephrology and Professor Khin Ohnmar Kyaing, Consultant Pharmacologist, Head of Department of Pharmacology for their invaluable support and guidance.

DECLARATION OF CONFLICT OF INTEREST

The authors declared no potential conflict of interests with respect to authorship and publication of this article

ETHICAL APPROVAL

This study was approved by both Ethical Review Committee of Defence Services Medical Academy, Yangon, Myanmar and Hospital Research and Ethic Committee from Defence Services General Hospital (1000-Bedded) Yangon, Myanmar. The written informed consent was taken from the patients or a legally authorized his/her relative.

FUNDING

The authors received no financial support for this research and publication of this article.

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