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Thiamine Level in Out-of-hospital Cardiac Arrest Patients

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Abstract

BACKGROUND: Thiamine deficiency is more common in critically ill patients. Administration of thiamine in cardiac arrest mice has improved survival and neurological outcomes. Evidence for thiamine deficiency in cardiac arrest humans is insufficient to support routine use of thiamine in cardiac arrest patients.

AIM: This study aimed to determine thiamine blood levels in cardiac arrest patients to understand whether the presence of thiamine deficiency is common in cardiac arrest patients.

METHODS: A prospective descriptive study from April 2017 to March 2018, on 24 adult out-of-hospital cardiac arrest patients. We used the high-performance liquid chromatography technique to determine whole blood thiamine pyrophosphate levels in cardiac arrest patients who arrived at the emergency department within 1 h of the onset of a cardiac arrest.

RESULTS: The mean thiamine pyrophosphate level within 1 h of the onset of a cardiac arrest was 170.9 ± 56.7 nmol/L. Only one participant had thiamine deficiency according to the cut-off level for thiamine pyrophosphate in whole blood of <70 nmol/L. Fourteen patients had spontaneous return of circulation. Thiamine pyrophosphate levels were not different between the two groups of patients who had and did not have the return of spontaneous circulation at the emergency department.

CONCLUSION: Little evidence was found to support thiamine deficiency as a feature among our cardiac arrest patients. A study with a larger population is required for more meaningful statistical analysis. As there is no consensus on cut-off level for thiamine deficiency diagnosis, the level of thiamine pyrophosphate in specific populations should be evaluated to establish reference values.

Introduction

Thiamine works as a coenzyme in carbohydrate metabolism in three major pathways in our body: Pyruvate dehydrogenase, transketolase, and alpha-ketoglutarate dehydrogenase [1]. In the circumstance of lack of thiamine, the body will produce lactic acidosis from the anaerobic pathway. The accumulation of lactic acidosis can lead to death. Thiamine deficiency is predominant in low-income countries and populations, where polished rice is a primary dietary component [2], [3]. High incidence of thiamine deficiency is found in South-East of Asia [2], [3], [4] and in North-East Thailand, where anti-thiamines in traditional foods, such as glutinous rice and raw fermented fish, lowers thiamine levels [5].

Earlier studies showed high rates of thiamine deficiency in patients with congestive heart failure and sepsis [6], [7], [8], [9], [10]. Costa *et al*. reported a high incidence of thiamine deficiency, as high as 71.3%, in septic shock patients admitted to intensive care [9]. The thiamine deficiency in critical illness could happen either before, or, after the illness. Attaluri et al. proposed three possibilities for thiamine deficiency occurring after illness [8]. First, it could be a result of inadequate nutrition during illness. Second, an increase in thiamine excretion, for instance, diuretic use in patients with congestive heart failure, could enhance thiamine excretion from their bodies. Third, during a critical illness, patients are in hyper-metabolic states, with increased bodily thiamine requirement. Administration of intravenous thiamine has been shown to benefit the washing out of lactic acidosis in sepsis patients who had a low level of serum thiamine [11].

Animal studies have shown that animal cardiac arrest is associated with low pyruvate dehydrogenase and thiamine pyrophosphate levels. Adult mice subjected to cardiac arrest had decreased thiamine phosphate blood levels 2 h after cardiac arrest. Giving thiamine in cardiac arrest, mice increased their 10-day survival rate and neurological outcomes [12]. In a human study, comparing pyruvate dehydrogenase (PDH) levels in healthy participants and cardiac arrest patients, the PDH level was lower in the cardiac arrest group [12]. However, a randomized controlled trial with post-cardiac arrest patients did not show any benefit of thiamine administration [13].

Previous studies have investigated the possible benefit of giving thiamine as a resuscitation drug for cardiac arrest patients. To date, only evidence from animal

studies shows benefits, the impact on human cardiac arrest is still unclear. Our study aimed to determine evidence for thiamine deficiency in out-of-hospital cardiac arrest patients to support the role of thiamine administration during cardiac arrest resuscitation.

Methods

Study design

Our study was a prospective descriptive study. We aimed to determine the thiamine pyrophosphate levels in out-of-hospital cardiac arrest patients who presented at the emergency room within 1 h from the onset of cardiac arrest. The study was conducted in two tertiary hospitals in Khon Kaen, North-East of Thailand from April 2017 to March 2018.

Study population

We included out-of-hospital cardiac arrest patients aged over 18 who required ongoing resuscitation. We excluded patients who were currently taking thiamine supplements and patients with trauma.

Outcomes

The primary outcome was to determine the thiamine status in out-of-hospital cardiac arrest patients. The secondary outcome was to compare the thiamine level in patients who survived and did not survive at the emergency department, admission, and discharge. However, the number of patients who survived to admit and discharge was too small to compare between groups.

Data collection

We used whole blood thiamine pyrophosphate to determine thiamine status, because it is an active form of thiamine and directly measures thiamine storage levels. The blood for thiamine pyrophosphate analysis was drawn within 1 h of the patient's arrival at the hospital. The whole blood was stored in a tube containing ethylenediaminetetraacetic acid (EDTA) and kept refrigerated below 4°. Analysis of thiamine pyrophosphate in the whole blood was directly measured using high-performance liquid chromatography. The suggested cut-off of < 70 nmol/L of thiamine pyrophosphate in the whole blood was applied to define thiamine deficiency [14].

Data analysis

Patient characteristics are reported using percentage and mean + SD. The Kolmogorov–Smirnov Test was applied for testing normal distribution. The mean difference was used for testing the difference between thiamine pyrophosphate levels in two groups of patients; those who had, or did not have return of spontaneous circulation on admission to the emergency department. p-value lower than 0.05 was considered statistically significant. All analyses were done using SPSS (IBM, SPSS for Windows, Version 26).

Ethical review

This research was reviewed and approved by the Khon Kaen University Human Research Ethics Committee (HE 591536). Written informed consent was obtained from all patient's families.

Results

Twenty-four patients were enrolled in the study. The thiamine pyrophosphate level of out-of-hospital cardiac arrest patients was measured at the respective emergency department within an hour of the onset of a cardiac arrest. Males made up 66.7% of all participants. The majority of participants cardiac arrested at home with cardiac etiology as presumed cause of arrest. Only six of twenty-four patients regularly consumed alcohol. Nearly 90% of the participants had initial EKGs with non-shockable rhythms. Almost 60% of the participants had spontaneous return of circulation at the emergency department. However, only one of the 24 survived to hospital discharge (Table 1).

Table 1: Baseline characteristics of participants

Characteristics	n = 24, n (%)
Male	16 (66.7)
Age, mean (SD)	64.2 ± 14.4
Place of cardiac arrest	
Home	14 (58.3)
Public	2 (8.3)
Paddy felid	1 (4.2)
Others	7 (29.2)
Presume cause cardiac arrest	
Presumed cardiac etiology	15 (62.5)
Respiratory	2 (8.3)
Others	7 (29.2)
Chronic alcohol drinking	6 (25)
Witnessed cardiac arrest	20 (83.3)
Bystander CPR	10 (41.7)
EKG (initial rhythm)	
Shockable	3 (12.5)
Non-shockable	21 (87.5)
Return of spontaneous circulation	14 (58.3)
Sustain ROSC	10 (41.7)
Survival to discharge	1 (4.2)
Thiamine pyrophosphate level (nmol/L), mean (SD)	170.9 ± 56.7
Hemoglobin (g/dL), mean (SD)	11.4 ± 2.5
Hematocrit (percent), mean (SD)	37.4 ± 7.6
Serum lactate (nmol/L), mean (SD)	14 ± 2.7
Serum pH, mean (SD)	6.9 ± 0.9
Serum bicarbonate (nmol/L), mean (SD)	11.6 ± 5.2

SD: Standard deviation, ROSC: Return of spontaneous circulation, CPR: Cardiopulmonary resuscitation, EKG: Electrocardiography

The mean thiamine pyrophosphate level in 24 participants was 170.9 ± 56.7 nmol/L (Table 1). The mean serum pH was 6.9 ± 0.9; and serum lactate was

14 ± 2.7 nmol/L. The thiamine pyrophosphate level for each participant is shown in Figure 1. Only one patient would have thiamine deficiency according to thiamine pyrophosphate cut-off of <70 nmol/L.

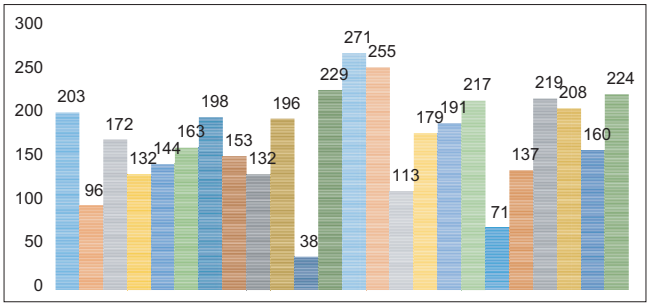

Figure 1: Whole blood thiamine pyrophosphate level (nmol/L) in each participant

The mean thiamine pyrophosphate level, as shown in Table 2, was lower in the group of participants who survived in the emergency department (153.1 ± 58.8 nmol/L) compared to patients who did not survive (195.7 + 43.4 nmol/L). However, the number of participants was too small to make a statistically significant difference.

Table 2: The mean thiamine pyrophosphate levels in the group of participants who survived in the emergency department and patients who did not survive

Parameters	ED ROSC group (*n* = 14)	No ED ROSC (*n* = 10)	Mean difference (95% CI)	*P*
Thiamine pyrophosphate level (nmol/L), mean (SD)	153.14 ± 58.77	195.70 ± 45.35	42.56 (−88.7–3.5)	0.069

SD: Standard deviation, CI: Confidence interval, ROSC: Return of spontaneous circulation

Discussion

Previous studies have shown that thiamine deficiency is common in critical care patients [6], [7], [8], [9], [10]. In mice, thiamine pyrophosphate levels 2-h after cardiac arrest have been shown to be significantly lower than levels for a naïve group [12]. The present study aimed to establish thiamine deficiency levels in out-of-hospital cardiac arrest patients. The difficulty for thiamine deficiency diagnosis is that there is no wide consensus on cut-point for thiamine pyrophosphate deficit [4]. We used a recommended cut-off of < 70 nmol/L of thiamine pyrophosphate in the whole blood [14]. Thiamine deficiency prevalence in Thai children and adults is commonly presented through indirect measures of erythrocyte transketolase (ETK) activity, which prevents our study results being directly compared with reference ranges for Thai populations.

Sixteen percentage of North-eastern Thai school children and 42% of obese children have been found to have thiamine deficiency [15], [16]. Thiamine deficiency among Thai workers has also been reported at 26.7% [17]. However, those studies did not use thiamine pyrophosphate level for diagnosis of thiamine deficiency. Our study found that the mean thiamine pyrophosphate level was about 170 nmol/L. According to Lu and Frank's healthy participants, mean whole blood thiamine pyrophosphate levels were between 70 and 179 nmol/L [14]. We used a thiamine deficiency cut-off point of 70 nmol/L thiamine pyrophosphate based on their study. However, based on this, only one of our participants had thiamine deficiency and all six patients who regularly consumed alcohol did not have thiamine deficiency. This cut point level resulted in a lower rate of thiamine deficiency in our study, compared to previous thiamine deficiency prevalence data in Thailand.

In addition to the lack of a clear Thai reference value for thiamine pyrophosphate, the low number of thiamine deficiency in our study may be related the higher number of males than females in our study. A previous study showed males had a higher mean whole blood thiamine pyrophosphate than females [18]. Evliyaoglu et al. and Ihara et al. pointed out that thiamine pyrophosphate level can also be affected by hemoglobin (Hb) or red cell count [18], [19]. An Hb of more than Hb 14 g/dL could under diagnose thiamine deficiency. The mean of Hb in our participants was normal (11.4 g/dL). However, the thiamine deficiency could be masked in the participants who had Hb over 14 g/dL. Thiamine deficiency may also be reduced by consumption of thiamine fortified foods. The increasing trend of consuming unpolished rice and whole grains may also relate to a lower incidence of thiamine deficiency.

In an animal study, plasma thiamine pyrophosphate decreased 2 h after cardiac arrest [12]. In humans, Pradita-Ukriy and Vattanavanit measured thiamine pyrophosphate levels in cardiac arrest patients within 24 h after the patients had return of spontaneous circulation (ROSC). Their study revealed thiamine pyrophosphate levels between 70 and 125.8 nmol/L [13]. However, we cannot compare our findings as their thiamine levels were measured at different times after cardiac arrest. Mean thiamine phosphate levels in neither study met the 70 nmol/L cut-off point for thiamine deficiency, showing no support for the hypothesis of a high incidence of thiamine deficiency in cardiac arrest patients.

Our results found no difference in thiamine pyrophosphate levels between the survival and non-survival groups, though the sample sizes were too small for statistical significance. There is one randomized controlled trial administering thiamine in cardiac arrest patients who had ROSC; it also showed no statistically significant survival difference between the groups receiving thiamine or placebo. Further studies using larger populations would be useful for determining whether thiamine levels affects the survival of cardiac arrest patients or not. Better neurological outcomes

may be another potential benefit from administering thiamine to cardiac arrest patients, as this has been shown in animal studies.

Limitation

Our study had a small number of cases, limiting our ability to show the association between thiamine deficiency and cardiac arrest. The results showed only one patient had thiamine deficiency, lower than other reports of thiamine deficiency incidence in Thai population especially in North-East of Thailand. There is no consensus cut-off level for thiamine pyrophosphate deficit for the Thai population. Most previous studies in Thai population used the ETK activity method which is no longer available and is not a direct measure of thiamine level. Thus, we did not know whether the cut-off level that we used may be an under diagnosis of thiamine deficiency or not.

Conclusion

Our study found only one of 24 cardiac arrest patients had thiamine deficiency on admission, insufficient to show the association between thiamine deficiency and cardiac arrest, or to support the routine use of thiamine for cardiac arrest patients. A study with a much larger population is needed for more thorough investigation. There is also a lack of consensus on the cut-off level for thiamine deficiency, and on reference values for the Thai population to enable a clear diagnosis of thiamine deficiency. Further studies of normative thiamine pyrophosphate levels for different populations are required for better diagnosis of thiamine deficiency.

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