Original Article

Thiamine Could Decrease Lactate and Creatinine Level After Coronary Artery Bypass Surgery in Patients with Mild Systolic Dysfunction

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Abstract

Background: During cardiopulmonary bypass, oxidative stress happens in the patient's cells due to blood contact with various levels of synthetic materials. It can activate inflammatory process and release factors such as interleukin 6 (IL-6), C reactive protein (CRP) and neutrophilia, which may hurt different organs. In recent years, many efforts have been made to prevent this type of damage; however, no single treatment has been proposed to reduce this risk. Antioxidant substances such as Thiamine is important in cell defense against free oxygen radicals. Regarding this issue, in this study, effect of Thiamine on lactate levels in patients undergoing coronary artery bypass graft (CABG) surgery has been investigated.

Methods and materials: In this study, 140 patients, 25 to 65 years with mild systolic dysfunction (EF=45-55%) who were candidates for elective CABG surgery in two groups, control and purpose (patients receiving Thiamine), were examined. All of these patients anesthetized in an identical manner, and subjected to a heart-lung pump. Serum lactate levels were measured before, during and six, 12, 18, 24 hours after surgery. All data collected in a questionnaire recorded and evaluated using SPSS statistical software.

Results: Study groups showed no significant differences regarding demographics and underlying diseases. Serum lactate was significantly lower in Thiamine group during the first 24 hours after surgery (except before operation and 2 hours later) ($p < 0.05$). Creatinine level in two groups before surgery was not significantly difference, however, it was significantly lower in case group 24 hours after surgery (1.54±0.14 vs. 1.24±0.19; p: 0.001). In addition, dose of Inotropes in patients who received Thiamine, was significantly lower than the control group (p= 0.001). Extubation was longer in control group (15.4±4.9 vs. 13.15±4.1; p=0.003) while intensive care unit stay was not different.

Conclusion: It seems that Thiamine administration before cardiopulmonary bypass in patients with decreased left ventricular function could decrease serum lactate as tissue perfusion marker and improve kidney function.

Keywords: Thiamine, Coronary artery bypass graft, Systolic dysfunction, Lactate

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Introduction

During cardiopulmonary bypass (CPB) surgery, inflammatory responses occur for various reasons (surgical stress, ischemic reperfusion injury, gas micro embolic and particulate) that cause functional impairment in vital organs such as the heart, lungs and kidneys (1). In an accurate statement, it should be noted that stress of surgery leads to inflammatory reactions. However, using CPB exacerbates these inflammatory responses due to increased blood contact with external surfaces (2). These inflammatory responses cause oxidative stress, which is usually associated with the release of inflammatory factors such as C reactive protein (CRP), interleukin 6 (IL-6) and neutrophilia (3). Thus, complications of oxidative stress, by disturbing the balance between free radicals and antioxidants, could exacerbate complications in cardiopulmonary bypass (4). All of these cases indicate that use of antioxidant substances can help to balance effects of increased oxidative stress in patients undergoing cardiopulmonary bypass surgery.

One of the most important markers for improving index of tissue perfusion is serum lactate, which increases during CPB and it is more significant in patients with systolic dysfunction (5). Antioxidant substances such as Thiamine and Glutathione in a form of remission (GSH) have a high degree of cellular defense against oxygen free radicals (6). Thiamine (vitamin B1) have antioxidant effects, and with an unknown mechanism, can improve tissue perfusion and thus improve the index of tissue perfusion, the serum lactate (7). Despite its extracellular function, glutathione plays an important role in purifications of free radicals. High level of GSH reduces loss of oxygen radicals during reperfusion (8). Intracellular GSH is made up of Glycine and Glutamate amino acids and Cysteine containing Thiol (9).

In recent years, many efforts have been made to reduce the damage to organs following cardiopulmonary bypass surgery. Due to spread of different sciences and techniques, there is still no specific method for reducing immunological complications and inflammatory effects of this type of surgery. However, it seems that prescribing antioxidants and drugs during CPB can resolve this problem.

Considering that in patients undergoing cardiopulmonary bypass surgery, serum Thiamine levels are reduced and there has not been any specific research on effects of thiamine administration on heart function and lactate levels; the research team decided to investigate its effect on serum lactate levels in patients undergoing cardiopulmonary bypass surgery.

Methods

This study designed as a clinical trial and registered in the Iranian clinical trial registry with this code: IRCT2016051412642N24 (dual blinded). Initially, 140 patients with mild heart failure who were selected for coronary artery bypass graft (CABG) surgery (by obtaining consent and the criteria" Aged 25 to 65 years, candidate for elective CABG surgery, mild heart failure (EF between 45% and 55%), thiamine insensitivity, lack of brain problems and lack of post-surgical infections entered the study phase. These patients divided to two groups with 70 participants. At all stage's patients divided between two groups randomly. Two groups including; screening group (300 mg thiamine in 100 ml normal saline 0.9% before CPB) and control group (100 ml normal saline 0.9% before CPB). All patients received a same premedication group (1 mg of lorazepam (P0)) 2 hours and (Morphine 0.1 mg/kg/intramuscular) an hour before surgery. For induction of anesthesia used from Fentanyl, Propofol and Atracurium. Infused Propofol, Fentanyl and Atracurium to maintain anesthesia. Surgery performed using standard on-pump method and patients transferred to the intensive care unit (ICU) intubated and later weaned from ventilator according to standard protocol.

In all patients, serum Lactate levels measured before, during and after surgery (2, 4, 6, 12, 18 and 24 hours after surgery). All data collected in a questionnaire and evaluated using SPSS statistical software (T-test used to compare parametric variables, Mann-Whitney U test, Chi-square tests and Fisher exact test used to compare non-parametric variables in two groups).

Results

The most patients in the study were men and male to female ratio was 63.7% to 36.3% in the control group and 65.5% to 34.5% in the case one. Results of

Table 1: Demographic variables, ASA class, and Ejection fraction of patients in two groups.

	Control (n=70)	Thiamine (n=70)	P-value
Age (year)	56.3±10.2	58.4±9.4	0.25
Height (cm)	167.3±11.4	164.5±12.0	0.33
Weight (Kg)	72.3±15.8	70.1±17.3	0.17
BSA (m2)	1.6±0.16	1.7±0.21	0.39
preoperative EF (%)	45.9±7.3	44.8±6.6	0.48
ASA Class (I/II)	24/46	22/48	0.11
Sex (male/female)	63.7%/36.3	65.5%/34.5%	0.32

EF: Ejection Fraction. ASA: American Society of Anesthesiologists

Table 2: Underlying diseases in two groups of patients.

	Control (n=70)	Thiamine (n=70)	P-value
Diabetes	36(52%)	30(42.5%)	0.22
Hypertension	41 (58.6%)	43 (62.5%)	0.56
Hyperlipidemia	19 (27%)	16 (23%)	0.31
Cigarette smoking	12 (17%)	16 (23%)	0.19
MI	1(1.4%)	1(1.4%)	-
CVA	1(1.4%)	0	-

MI: myocardial Infarction, CVA: Cerebrovascular Accident

this study showed that there was no significant difference between two groups regarding age, sex, height and weight. In addition, according to Table 1, factors such as body surface area (BSA), ejection fraction (EF) and the American society of anesthesiologists (ASA) class had no statistically significant difference (P>0.05).

Table 2 compares underlying diseases in two study groups. Results indicated the meaningless relationship between patients in mentioned groups regarding these issues.

Serum lactate surveyed in patients (before surgery and during 24 hours after surgery) showed a statistically significant difference between two groups (except before and 2 hours after surgery) and this factor was significantly lower in the treatment group than the control group (Table 3).

Results showed that creatinine level in two groups before surgery was not significantly different. However, there was a significant difference in serum creatinine, 24 hours after surgery (p<0.05). Table four shows mechanical ventilation time after surgery had a

Table 3: Postoperative serums lactate in two groups of study.

Lactate	Control (n=70)	Thiamine (n=70)	P-value
Before operation (mmol/L)	2.54±0.67	2.63±0.73	0.34
After 2h in ICU	2.25±0.79	2.61±1.7	0.23
After 4h in ICU	3.55±0.64	2.49±0.33	0.001
After 6h in ICU	2.82±0.34	2.28±0.43	0.001
After 12h in ICU	2.29±0.44	2.06±0.41	0.0062
After 18h in ICU	1.96±0.36	1.75±1.25	0.013
After 24h in ICU	1.68±0.61	1.36±0.62	0.032

MV: mechanical ventilation, ICU: Intensive Care Unit

Table 4: Postoperative Base excess (BE) in two groups of study.

	Control (n=70)	Thiamine (n=70)	P-value
Creatinine			
Preoperative (mg/dL)	1.06±0.29	1.01±0.34	0.40
24 h postoperative	1.54±0.14	1.24±0.19	0.001
Duration of MV (hours)	15.4±4.9	13.15±4.1	0.003
Duration of ICU stay (days)	3.73±0.98	3.47±0.93	0.22

MV: mechanical ventilation, ICU: Intensive Care Unit

significant difference in two groups, but duration of ICU stays in two groups did not show any significant difference.

Based on observations made on patients, there

Table 5: Postoperative Base excess (BE) in two groups of study

BE (mEq/L)	Control (n=70)	Thiamine (n=70)	P-value
At entry to ICU	-2.42±2.9	-2.42±2.46	0.99
After 2h in ICU	-3.05±2.2	-3.4±2.65	0.42
After 4h in ICU	-3.8±2.22	-3.41±3.12	0.51
After 6h in ICU	-3.56±2.1	-3.2±2.28	0.50
After 12h in ICU	-2.4±1.99	-1.90±2.20	0.22
After 18h in ICU	-1.21±1.98	-0.78±2.52	0.38
After 24h in ICU	-0.77±2.84	0.45±2.29	0.032

Table 6: Postoperative vasopressor uses in two groups of study

Vasopressor	Control (n=70)	Thiamine (n=70)	P-value
Epinephrine (n)			
After CPB	45	42	0.18
In ICU	45	42	0.18
Epinephrine dose (µ /min)	10.5±1.2	5.46±1.34	0.001
Epinephrine total usage (µg)	36.6±6.8	15.5±4.7	0.001
Dopamine (n)			
After CPB	16	9	0.16
In ICU	19	10	0.075
Dopamine dose (µg/kg/min)	9.7±1.12	4.5±0.98	0.001
Dopamine total usage (µg)	288.5±34.6	112.2±26.6	0.001

were no significant differences in both groups regarding central venous pressure (CVP) during the first 24 hours after ICU admission and the data from these two groups was very close ($p>0.05$). Although base excess (BE) level was higher in the thiamine recipient group, however, except at 24 hours after

surgery, no significant difference observed (Table 5).

Regarding the percentage of patients who received epinephrine and dopamine during and after separation from the CPB and in ICU, there was no significant difference between the two groups ($p> 0.05$). It should be noted that in patients under screening of thiamine, the dose of these two drugs was significantly lower than the control group ($p< 0.005$) (Table 6).

Discussion

Inflammation and accumulation of inflammatory factors, such as cytokines, associated with decreased renal function and increased serum lactate, are common in cardiopulmonary bypass surgery (10). Important factors for starting and continuing inflammation following CPB are not exactly specified. With the onset of inflammation, a large number of inflammatory factors and cells are activated. In the case of CPB, expression of cytokines and inflammatory factors such as endotoxins, tumor necrosis factors (TNFs), Antrodia cinnamomea fruiting bodies (NAKFB) and anaphylatoxins are increased (11). These agents release oxygen-free radicals and proteases by stimulating inflammatory cells, including polymorphonuclear neutrophils (PMN), platelets, and endothelial cells. Inflammation and release of free oxygen radicals followed by tissue damage (12).

Different methods have been proposed to reduce inflammation. Reducing contact time with emergency cardiac care (ECC) (such as off-pump coronary artery bypass (OPCAB) without pump) is one of the ways to reduce inflammation. Of course, along with this method, other methods (such as managing bleeding during surgery, less aortic manipulation in patients with atherosclerosis, using ultrafiltration, reducing prime volume, reducing the CPB duration, using heparin to cover the inner surfaces of tubes and filtering Selection of leukocytes from circulation) are used (13).

About CPB, we could say that cause of increased lactate during cardiac surgery is the reduction of tissue perfusion and low pressure during the pump (11). Mainly, CPB reduces perfusion and reperfusion, however, with the exception of lactate; there are no diagnostic molecular markers for ischemic reperfusion injury. Increased lactate (>3) has proven to be a prognostic factor of mortality in open-heart surgery (14). Results of this study, showed that serum lactate (as a tissue perfusion index) in treatment group in comparison to control group decreased significantly (24 hours after surgery) ($p<0.05$). These results can be important to improvement of patients' condition following the CPB. Reducing free radicals will lead to increased success in surgery outcome and accelerate patient recovery. Thus, based on results, thiamine may play a role in reducing complications and improving the efficiency of patients undergoing cardiopulmonary bypass surgery. However, the effectiveness of thiamine on cardiac factors and its performance has been proven in previous studies. For example, DiNicolantonio and colleagues in 2013 showed that use of thiamine supplements could improve heart function (15). Results of another study, performed by Luger et al. showed that lactate levels were significantly decreased in thiamin-treated patients (48 hours before surgery) (16). Our research results indicate that thiamine reduced creatinine levels. In this case, results are contradictory. For example, in previous studies, it demonstrated that thiamine did not significantly affect acute renal failure (ARF) reduction in patients under CPB (15, 16) and these findings confirmed by Wang et al. (17). However, in the present study only creatinine levels was examined (as a kidney function index). Overall, this decrease in serum levels could be attributed to controlling oxidative and inflammatory factors in the kidneys (18).

In this study, inotropic drug used in thiamine-screened patients was lower than the control group based on Lukienko et al. study. They stated that these results could be linked to the antioxidant properties of thiamine and lower level of lactate in treated group, which can cause better cardiovascular function (19). Meanwhile and based on Maddali and colleagues' observations in 2006, that less inotropic use has provided conditions for reducing the patient's extubating time (20) whereas these results are also observed in our study.

This study has been accompanied by limitations such as inability to measure serum thiamine levels in our country and no assessment of other kidney function markers, which can be addressed more precisely by fixing them.

Conclusion

Use of thiamine before cardiopulmonary bypass can decrease lactate serum level as a marker of reperfusion injury and serum creatinine as a factor for kidney function in patients who have decreased left ventricle function, but the effect of thiamine seems to be limited and higher doses may be needed to further compensate for this damage.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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