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Original Article

Effect of Thiamine on Serum Glucagon and Reactive Oxygen Species (ROS) in Perioperative Stress Response

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Abstract

Background: General anesthesia surgery induces a stress response, altering metabolic patterns and increasing glucagon and reactive oxygen species levels. Thiamine is hypothesized to mitigate this response. **Methods**: This randomized controlled trial employed a pretest-posttest control group design. Thirty patients undergoing surgery at Adam Malik General Hospital were randomized to receive either thiamine or normal saline. Serum glucagon and ROS levels were measured before and after intervention. Data were analyzed using SPSS 25.0 with a significance level of 0.05. **Results**: Baseline thiamine levels showed no significant difference between groups ($p = 0.896$). Post-intervention, the thiamine group exhibited significantly higher thiamine levels (8.69 ± 2.185 ng/ml) compared to the control group (4.52 ± 2.185 ng/ml, $p = 0.04$). ROS levels were significantly higher in the control group (363.2074 ± 103.74 ng/ml) than the thiamine group (343.239 ± 102.05 ng/ml, $p = 0.040$). **Conclusion**: Perioperative thiamine administration effectively suppressed the surgical stress response, demonstrated by decreased ROS levels. The higher thiamine levels in the treatment group suggest a potential mechanism for this effect. Further research is warranted to explore the clinical implications of these findings.

Keywords: Thiamine; Surgical stress response; Reactive oxygen species; Glucagon

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INTRODUCTION

General anesthesia surgery is a stressor that causes the body's stress response as a compensatory mechanism. The response to surgery includes large-scale hormonal and metabolic, neuroendocrine, and hemato-immunological changes.[1] The neuroendocrine response to surgery is described by two main pathways (hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis). Corticotropin significantly influences the stress response to the surgery. Corticotropin promotes the production of cortisol in the adrenal cortex. Its secretion increases in some moments after surgery. Its concentrations reach a maximum level approximately 4-6 hours after surgery, depending on the severity of the surgical trauma. Cortisol promotes protein breakdown and gluconeogenesis in the liver. It also inhibits glucose utilization by cells which triggers an increase in blood glucose concentrations. The cortisol increase is seen in open invasive surgical techniques, old age, female sex, and general anesthesia.[2]

Surgery may increase postoperative cortisol and blood glucose levels.[3] Changes in normal metabolic patterns due to surgery stimulate gluconeogenesis, glycogenolysis,

proteolysis, lipolysis, and cytogenesis. These result in hyperglycemia and ketosis conditions4. Surgery and anesthesia lead to an immunosuppressive effect. Increased secretion of proinflammatory cytokines may also occur after the surgery.[1]

Besides an increase in cortisol levels, surgery can also increase cytokine response and ROS production in patients who have undergone surgery under general anesthesia after 72 hours. ROS production can also be a useful indicator in assessing the severity of surgical trauma.[5]

In surgical procedures, there is an acute increase in reactive oxidative stress (ROS). This occurs when ischemia is followed by reperfusion. ROS can trigger tissue injury seen in transplantation (liver and heart), the release of aortic clamps during abdominal and thoracic aortic surgery, the release of limb tourniquets during orthopedic surgery, and reperfusion during and after cardiopulmonary bypass. There is a thiamine deficiency in 20% of patients treated in the intensive care unit (ICU). Thiamine deficiency is a source of lactic acidosis that does not seem in severe sepsis and septic shock.[6] An imbalance between the formation and removal of free radicals causes a pathological condition called oxidative stress. However, the human body uses antioxidants to suppress these free radicals. One of the antioxidants that can reduce oxidative stress is thiamine. Previous studies proved this finding. Thiamine has also been able to significantly prevent the expression of inflammatory cytokines and chemokines, depending on NF-B induced by thromboxane and PGI2 synthase.[7]

MATERIALS AND METHODS

This is a randomized controlled trial with a pretest-posttest control group design with randomization using a computer application (www.randomizer.org). The samples are taken from Adam Malik General Hospital of Medan from November to December 2021. The inclusion criteria are patients aged 18-65 years who undergo surgery under general anesthesia and those with ASA physical statuses 1 and 2. The patients will be included in the exclusion criteria if they refuse to participate. They may also suffer from diabetes mellitus, experience shock sepsis or lactic acidosis, and have a history of hypersensitivity (allergy) to thiamine. They have a thiamine deficiency, take immunomodulatory drugs, antiplatelet or anticoagulants surgery duration > 6 hours, and thiamin regularly. They experience massive bleeding and receive blood transfusions preoperatively, intraoperatively, or postoperatively. The subjects will be excluded from the research if their blood samples are damaged or they passed away before the observation is finished. The sampling uses the non-probability consecutive technique.

Clinical Protocol and Participant

The research samples were taken after being approved by the Ethics Committee of the Faculty of Medicine, University of North Sumatra, and Haji Adam Malik General Hospital of Medan (RSUP HAM). The included subjects receive some explanations about the research objectives, advantages, disadvantages, and procedures. The researcher asks them to sign an informed consent if they are willing to participate in the research. The identity recording includes gender, age, body mass index, ASA grade, and type of surgery experienced by the subjects. The researcher asks them to fast for at least 6 to 8 hours before surgery. Before the intervention, a 6 ml blood sample is taken from the median cubital vein and put into a vacuum tube containing EDTA. The blood sample is sent to the laboratory, and the results of the examination of glucagon and ROS levels will be the basis for conducting the pretest or baseline.

The researcher gives an intervention two hours before surgery based on the available randomization table. The research subjects consist of two groups (thiamin and control (normal saline) groups). The subjects in the thiamin group receive 100 mg (1 ml) of thiamin intravenously, while the control group receives 1 ml of normal saline injection intravenously. The research subjects and intervention groups are divided in a double-blind

manner. In the operating room, there are standard monitoring tools (an ECG monitor, noninvasive arterial blood pressure (NIBP), and SpO2r). Oxygen is channeled via a nasal cannula at 3 liters/minute capacity to make sure the intravenous line operates smoothly. The hemodynamic recording includes blood pressure, pulse, respiratory rate, and oxygen saturation. To start the general anesthetic process, premedication covers midazolam 0.07-0.15 mg/kg BW and fentanyl 2-5 g/kg BW intravenously. Induction consists of propofol 2-2.5 mg/kg BW intravenously. Furthermore, a relaxation process includes the administration of rocuronium 0.6-1.2 mg/kg BW intravenously. Insertion of an endotracheal tube (ETT) ensures that airway patency runs smoothly. The ETT diameter size is number 7.5 for men and 7 for women. Then, the ETT is connected to the anesthesia machine connector. The anesthesia process runs until the end of surgery with a minimum alveolar concentration (MAC) of 1.0-1.5 volume% isoflurane. Intraoperative analgesia is given through intravenous injection of fentanyl 0.5-1.5 mg/kg BW.

There is a re-administration of intravenous thiamin or 0.9% NaCl two hours after the surgery. Post-anesthesia monitoring consists of hemodynamic monitoring (blood pressure, pulse, respiratory rate, oxygen saturation) and electrocardiography. Six hours after the second intravenous administration of thiamin or 0.9% NaCl, the blood is collected again to conduct post-test glucagon and ROS levels. Research data are collected, recorded, tabulated in Microsoft Excel, and then statistically analyzed.

Statistical Analysis

The data analysis uses a computer program called SPSS (Statistical Package for Social Science). The demographic data are presented in a frequency distribution table. Inferential data analysis aims to test the hypothesis using the independent T-test if the data are normally distributed, and the Mann-Whitney test if they are not. The data are significant if the p-value < 0.05.

RESULTS

This research is a clinical trial with a Randomized Controlled Trial (RCT) design. The purpose is to identify the effect of intravenous thiamine administration compared to normal saline placebo on glucagon levels in patients undergoing general anesthesia surgery at Haji Adam Malik General Hospital of Medan city. This research was carried out in April-May 2021.

Sample Characteristic

This research consists of 30 samples (15 samples of thiamin and 15 samples of normal saline) that met the inclusion criteria. The characteristics of the research sample are presented in frequency, mean with standard deviation, and median with minimum and maximum values. Table 1. shows the normality test results.

Table 1. shows that each group consists of 15 subjects with more females than males in the thiamin and normal saline groups. The mean BMI value in the thiamin group is 23.49 ± 2.834 kg/m2, and the normal saline group is 22.89 ± 1.944 kg/m2. The average age of the subjects is 39.87±13.28 years, and the normal saline group is 43.26±10.10 years. The subjects in the thiamin group and 0.9% NaCl on ASA 1 are 46.7% and 60%, respectively. Meanwhile, in ASA 2, it is 53.3% and 40%, respectively. Based on the type of operation, in the thiamine group, 12 persons are undergoing digestive surgery (63.2%), two persons for obgyn (10.5%), three persons for orthopedic (15.8%), and two persons for ENT surgery (10.5%). Meanwhile, in the normal saline group, 11 persons (57.9%) have had digestive surgery, two persons (10.5%) have experienced obsgyn, four persons (21.1%) have undergone orthopedic surgery, and only one person (5.3%) have had plastic surgery and BTKV. Based on the leukocyte levels, in the thiamine group, the mean leukocyte value is 11291 ± 6864.131 cells/mm3. In the normal saline group, the mean leukocyte is 10692.11 ± 5945.552

cells/mm3. Statistically, all research subject characteristics variables have a p-value higher than 0.05. It means all of them are homogeneous.

Table 1. Baseline characteristics of the study population

Characteristic	Thiamin	Normal Saline	P-value
Gender (n,%)			
Male	5 (33,2%)	3 (20 %)	0,433[a]
Female	10 (66,7%)	12 (80%)	
Age	39,87±13,2	43,26± 10,1	0,391[b]
IMT	23,49±2,8	22,89 ±1,9	0,559[b]
ASA			
ASA I	7 (46,7%)	9 (60%)	0,610[b]
ASA II	8 (53,3%)	6(40%)	
Type of Surgery, n (%)			
Digestive	12(63,2%)	11(57,9%)	
Obsgyn	2(10,5%)	2 (10,5%)	
Orthopedic	3(15,8%)	4(21,1%)	0,801[c]
ENT	2(10,5%)	0 (0%)	
Plastic	0 (0%)	1 (5,3%)	
BTKV	0 (0%)	1 (5,3%)	
Leukocyte	11291 ± 6864,1	10692,1± 5945,5	0,779[b]

Serum thiamin levels before and after intervention

The differences in serum thiamine levels before and after the intervention. The average value of thiamine levels before intervention in the two groups does not have a statistical difference (p = 0.896). However, during the intervention, the average thiamine level after the intervention is higher in the thiamine group (8.69 ± 2.185 ng/ml) than in the normal saline group (4.52 ± 2.185 ng/ml) with a P value of 0.04. It can be concluded that there is a significant difference between both groups.

Table 2. Comparison of glucagon levels before and after thiamine administration

Glucagon level (ng/ml)	Thiamin IV	NaCl 0,9 % IV	P value
Before intervention			
Mean ±SD	336,4 ± 154,7	332,3 ± 88,4	0,913[b]
Median (min-max)	337 (145,7-681,6)	337 ± 88,4	
After intervention			
Mean ±SD	285,4 ± 187,4	364,6 ± 84,5	0,03[b]
Median (min-max)	200,8 (94,3 - 724,9)	360 (200,8 -508,9)	
Difference			
Mean ±SD	50,9 ± 185,5	-32,2 ± 109,2	0,04[b]
Median (min-max)	185,5 (-313,2-360,7)	-58,2 (-230,3-231,6)	
P-value	0,305[a]	0,272[a]	

Differences in Glucagon Levels before and After Thiamine Intervention

Table 2. presents the differences in serum glucagon levels before and after the intervention. The average value of serum glucagon levels after intervention in the thiamine group (285.462 ± 187.465 ng/ml) is lower than the normal saline group (364.613 ± 84.515 ng/ml). It has a statistical difference (p = 0.03). It means there is a significant difference between the two groups after the intervention.

The glucagon levels in the thiamine group decreased by (50.97 ± 185.567 ng/ml) after the intervention but were not significant. Meanwhile, in the normal saline group, the glucagon levels increase (32.273 ± 109.262 ng/ml) but were not significant (Table 3).

Differences in ROS levels before and after thiamine intervention

Table 3. shows that the average baseline ROS levels are higher in the 0.9% NaCl group (356.212 ± 96.80 ng/ml) than in the thiamine group (350.36 ± 116.31 ng/ml). However, there is no significant comparison between the two groups (p = 0.128). After the intervention, the saline group has higher ROS levels (363.2074 ± 103.74 ng/ml) than the thiamine group (343.239 ± 102.05 ng/ml). There is a significant comparison between the two groups (p = 0.040).

The ROS levels in the thiamine group decreased by (7.122 ± 149.519 ng/ml) after the intervention but were not significant. Meanwhile, in the normal saline group, the ROS increased (6.9954 ± 137.924 ng/ml) after the intervention but was not significant (Table 3).

Table 3. Comparison of ROS levels before and after the administration of thiamine

ROS level (ng/ml)	Thiamin	NaCl 0,9 %	p-value
Baseline			
Mean ± SD	350,3 ± 116,3	356,2 ± 96,8	0,128[a]
Median (min-max)	354,6(176,4 -569,9)	354,6 (196 – 453)	
After intervention			
Mean ± SD	343,239 ± 102,05	363,2 ± 103,7	0,040[a]
Median (min-max)	343,1 (176,3-576,9)	357,9 (158,7 – 505,7)	
Difference			
Mean ± SD	-7,1± 149,5	6,9 ± 137,9	0,030[b]
Median (min-max)	-22.9 (222,2-286.9)	11,7 (208,3-360,2)	
p-value	0,535[c]	0,535[c]	

DISCUSSION

This research aims to explain the effect of thiamine administration on serum levels of glucagon and ROS in patients experiencing a stress response during the perioperative period. The subjects are 30 patients who have undergone elective surgery with PS ASA 1 and 2 status at the Central Surgical Installation of Haji Abdul Malik Hospital of Medan city from November to December 2021. The glucagon and ROS levels are examined at the USU Medical Faculty Integrated Laboratory. After being screened according to the inclusion and exclusion criteria, their subjects are divided into two groups of fifteen patients. The groups are called thiamine and normal saline group.

The findings show that the administration of thiamine can decrease glucagon levels. Meanwhile, the normal saline group performs contradicts the result, although it is not statistically significant. The results are similar to Luong and Nguyen's (2012) that thiamine administration can reduce glucagon levels in people with diabetes mellitus. Thiamine has a crucial role in energy production. Thiamine is an important component in cellular metabolism8. It functions as a cofactor in the diphosphate-ester form. Thiamin pyrophosphate (TPP) is a cofactor for some enzymatic reactions in oxidative decarboxylation in the

mitochondrial complex, namely pyruvate dehydrogenase (PDH), alpha-ketoglutarate dehydrogenase (KGDH), and (BCKDH), as well as a cofactor for the cytosolic enzyme transketolase that influences pentose cycle9. Thiamin also has an important role in lipid metabolism. There is also a suspected non-cofactor role of the thiamine component in the immune system, gene regulation, oxidative stress response, cholinergic activity, chloride channels, and neurotransmission10.

The results also indicate a significant comparison in the ROS levels after the intervention ($p = 0.04$) and the difference in the thiamine group ($p = 0.03$). These are in line with Goncalves et al., (2019) in rats that were given benfotiamine supplementation and swimming exercise. They showed lower levels of ROS in the group of rats consuming benfotiamine supplementation and exercise compared to the group receiving benfotiamine alone and swimming training alone. The group of rats receiving benfotiamine supplementation performed an increasing level of antioxidant enzymes in general. This means that benfotiamine effectively increases antioxidant protection and reduces oxidative damage in rats undergoing endurance swimming exercises. Similar results are also presented by Karkabounas et al., (2018). They showed that the combination of α-lipoic acid, carnosine, and thiamine supplementation can reduce glucose and HbA1C levels and significantly reduce serum hydroperoxide levels in obese patients with type 2 diabetes mellitus11. Nasution et al., (2020) explained that thiamine is a response to the levels of the COMT enzyme and influences the stress response in triggering the flight or fight response12. Lubis et al., (2021) stated that thiamine also plays a role in regulating the balance of MMP-9 and TIMP-1 as enzymes that regulate cell proliferation, differentiation, and apoptosis processes13.

CONCLUSION

The administration of thiamine has a positive effect and benefit in suppressing the stress response, which is indicated by a decrease in glucagon and ROS levels during perioperative thiamine administration.

Abbreviations: ROS, Reactive oxygen species; PDH, pyruvate dehydrogenase; KGDH, alpha-ketoglutarate dehydrogenase; DNA, deoxyribonucleic acid.

Supplementary Materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions: The datasets generated All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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