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Research Article

The Influence of Oral Thiamine as an Adjuvant to Morphine on Catechol-O-Methyltransferase (COMT) in Pain Associated with Breast Cancer

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Abstract

Background: The number of cancer pain sufferers above indicates that the management of cancer pain is not optimal.
Method: The study was conducted in April-December 2020 using a randomized quasi-experimental design with a pretest-posttest control group study aimed to analyze the role of thiamine in regulating COMT enzyme levels in breast cancer-related pain patients. All patients who were hospitalized with complaints of breast cancer pain. Patients to be given intervention (thiamine 500 mg orally 8 hours) or not to be given intervention were determined based on a random.
Results: COMT enzyme levels before treatment in the two groups had a homogeneous value (P = 0.838). Meanwhile, the COMT enzyme levels after treatment in the thiamine and control groups had a significant difference with a value of P = 0.019.
Conclusion: Oral thiamine as an adjuvant to morphine can decrease catechol-o-methyltransferase (COMT) in pain associated with breast cancer patients.

Keywords

Cancer Pain, COMT, Thiamine, Morphine

1. Introduction

Cancer-related pain should be managed well because since 1986 WHO has issued guidelines for the management of cancer pain which are claimed to be able to control the pain by 70-90% [1]. However, the facts in daily clinical practice still show that there are cancer patients who still feel pain due to their disease. More than 50% of cancer patients suffer from cancer-related pain [2]. In a meta-analysis (more than 100 studies) of cancer-related pain, it was found that 39.3% of the cancer patients had undergone curative treatment, 55% were on anti-cancer treatment, and 66.4% were advanced cancer patients. Moderate to severe pain was found in 38% of all patients with cancer pain [3].

The number of cancer pain sufferers above indicates that the management of cancer pain is not optimal. This may be due to pain management which has been limited to symptoms. Supposedly, pain management should be based on the underlying pathophysiology; it should involves not only inhibition of pain transmission but it should also influence the course of the disease [4]. In addition, access to the use and availability of analgesic drugs in the opioid class such as morphine is very limited. The use of morphine opioids in Indonesia is very small compared to other countries [5]. Therefore, it is necessary to have alternative treatments which are widely available and have good effectiveness.

The most researched alternative treatment in cancer patients today is the administration of B vitamins. The ability of B vitamin group to provide pain relief has long been studied. Thiamine (Vitamin B1) is considered to have anti-pain properties through antinociceptive, anti-inflammatory and anti-neuropathic mechanisms [6]. According to research with human subjects conducted by Nasution et al. (2019) thiamine is able to increase the work and levels of the enzyme Catechol-O-Methyltransferase (COMT).

COMT is an enzyme that is involved in many physiological reactions in the body, such as mood, cognition and stress response [8]. One of the functions of the COMT enzyme is to degrade the dopamine, epinephrine and norepinephrine neurotransmitters. Epinephrine and norepinephrine are neurotransmitters that play a role in pain perception. Low levels of COMT increase levels of epinephrine and norepinephrine, thereby increasing stimulation of adrenergic receptors, especially β2/β3. This means that patients who have low COMT levels will experience pain more easily [9,10].

The use of thiamine for cancer pain, including dosage, duration of use and side effects, has not been widely found. Based on the description above, it can be concluded that there may be a strong relationship between thiamine (vitamin B1) and the increase in the COMT enzyme.

2. Methods

The study was conducted in April-December 2020 using a randomized quasi-experimental design with a pretest-posttest control group study aimed to analyze the role of thiamine in regulating COMT enzyme levels in breast cancer-related pain patients.

All patients who were hospitalized with complaints of breast cancer pain and had met the inclusion criteria were asked to be research subjects. Examination was carried out on the patients to determine the pain score using VAS, and blood draw was done to check the levels of thiamine and COMT in the blood.

Patients to be given intervention (thiamine 500 mg orally 8 hours) or not to be given intervention were determined based on a random table (www.randomizer.org). Patients in the intervention group were given thiamine 500 mg orally per 8 hours for 72 hours. All patients in the control group and the thiamine group received morphine as the standard drug for cancer pain management. After 72 hours, the patients was again examined for pain scores using the VAS score. Blood draws were also repeated 4 hours after the last administration of thiamine to check the levels of thiamine and COMT in the blood.

Patients included in this study were patients with metastatic/stage IV breast cancer pain, VAS Pain Score ≥ 7, and age range of 19-60 years, and they and their family agreed to participate in the study. Patients who had previously consumed psychopharmaceuticals, consumed alcohol, had a history of head injury and were unable to complete the questionnaire independently were excluded from the study.

Patients' blood was tested to see the levels of COMT (Elisa kit, Antibody-Sunlong Biotech Co. Ltd). This study protocol was approved by our Institutional Review Board of the Medical Faculty of the University of North Sumatra (No 54/KEP/USU/2020) and was carried out in accordance with the ethical standards set out in the Declaration of Helsinki. All data were analyzed using SPSS 25.0 package program. T-test was performed to see the differences before and after treatment. The spearman test was used for the correlation test which was conducted to see the strength of the correlation between variables. The results were considered statistically significant if $p < 0.05$.

3. Results

Demographic and clinical parameters from septic patients (n=19) is shown in Table 1. Table 1 shows that the distribution of patient characteristics in this study had a mean patient age of 47.0 ± 7.0 years, all patients had undergone surgery and the most had undergone chemotherapy (84.2%).

Table 2 shows that the COMT enzyme levels before treatment in the two groups had a homogeneous value ($P = 0.838$). Meanwhile, the COMT enzyme levels after treatment in the thiamine and control groups had a significant difference with a value of $P = 0.019$. In addition, the difference in COMT enzyme levels before and after treatment in the two groups experienced a significant difference ($P = 0.001$), with the COMT enzyme levels in the thiamine group experiencing a greater decrease than the control group.

4. Discussion

Table 2 shows the value of COMT enzyme levels in 19 breast cancer patients, with a higher mean difference in reduction in the thiamine group (0.06 ± 0.04 ng/ml) than in the control group (0.01 ± 0.04 ng/ml). This suggests that thiamine may actually decrease COMT levels in the thiamine group, with the exact mechanism not yet known.

One possible cause is an abnormality in the Krebs cycle due to thiamine administration. The thiamine will modulate transketolase so that the Krebs cycle will enter the non-oxidative pathway with little ATP production [11]. Meanwhile, ATP is the main factor that improves COMT function [12]. Perhaps this could explain why COMT was lower in the thiamine group.

The relationship between thiamine and COMT is different from the research results of Nasution et. al (2020), where the administration of thiamine in patients with preoperative anxiety showed increased levels of the COMT enzyme. However, that study was conducted on research non-cancer subjects. The results of this study were different from those of Nasution et. al (2020). This is because the COMT enzyme activity tends to be low in breast cancer patients.

Cancer patients tend to have 3-4 times lower COMTMet allele coding enzyme activity due to changes in amino acids in codon 108/158 [13,14]. The COMT gene is located on chromosome 22q11.1-q11.2 [15,16]. All of them resulted in the accumulation of two catechol estrogen, namely 2-OHE2 and 4-OHE2 which are agents involved in the carcinogenic process of breast cancer [17–19]. These catecholestrogens should be metabolized by COMT to 2-methoxyestraidol which can reduce pain clinically in breast cancer [20].

The decrease in COMT in this study may also be caused by low thiamine doses and the inadequate duration of administration. Indeed, so far the safe and effective dosage and the appropriate duration of thiamine administration are still controversial, and clinical reports on the use of single thiamine are still limited to case reports, such as case reports in 3 patients who used oral thiamine 600 mg to 1800 mg for 20 days [21]. In terms of dosage, thiamine given about 12.5 to 37.5 times the recommended daily allowances (RDA) resulted in a higher stimulatory effect on cancer cell proliferation; however, giving thiamine at a higher dose turned out to have a better inhibiting effect on cancer cell growth [22]. This study used 1500 mg of thiamine per day which is about 75 to 2500 of the recommended daily allowances (RDA). ComõÂn-Anduix et. al (2001) in a metabolic control analysis study conducted on experimental animals reported that giving thiamine at a dose of 2500 times higher than the RDA was found to produce better cancer cell growth inhibiting effects [22]. However, that study was carried out in experimental animals, so the side effects of giving very high doses of thiamine in humans have not been proven safe.

This is also supported by Kambur and Männistö (2010) who reported that in experimental pain models studies in humans in acute pain conditions, increased pain sensitivity was found in patients with low COMT activity. However, in cancer pain, low COMT activity can increase the availability of opioid receptors and increase opioid analgesia, thereby decreasing the need for opioids and reducing side effects [23].

5. Conclusion

In conclusion, the novel findings of our study were that oral thiamine as an adjuvant to morphine can decrease catechol-o-methyltransferase (COMT) in pain associated with breast cancer patients.

6. Acknowledgement

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7. Conflict of Interest

The authors declare that there is no conflict of interest.

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Table 1: Baseline clinical and biochemical characteristics of patients.

Characteristics	Thiamine (n=10)	Control (n=9)	Total (n=19)	p Value
Age, Mean (SD), Years	45.3 ± 8.0	48.8 ± 5.5	47.0 ± 7.0	0.280[a]
Chemotherapy, n (%)				
Yes	8 (50.0)	8 (50.1)	16 (84.2)	0.780[b]
No	2 (66.6)	1 (33.3)	3 (15.7)	
Operation history, n (%)				
Yes	10 (52.6)	9 (47.4)	19 (100.0)	1.000[b]
No	0 (0)	0 (0)	0 (0)	

Table 2: Comparison of COMT Serum Enzyme Levels in the Thiamine and Control Groups.

COMT Enzyme Level (ng/ml)	Thiamine (n=10)	Control (n=9)	p Value[a]
Before			
Mean ± SD	0.10 ± 0.05	0.11 ± 0.04	
Median (min-max)	0.08 (0.05-0.19)	0.11 (0.05-0.18)	0.838
After			
Mean ± SD	0.04 ± 0.02	0.09 ± 0.05	
Median (min-max)	0.04 (0.01-0.09)	0.09 (0.02-0.19)	0.019*
Difference			
Mean ± SD	0.06 ± 0.04	0.01 ± 0.04	
Median (min-max)	0.05 (0.02 - 0.15)	0.01 (-0.08 - 0.07)	0.038*
p Value[b]	0.001*	0.346	

Note: p[a] (comparison of COMT enzyme levels between thiamine and control groups, independent t-test); p[b] (comparison of COMT enzyme levels before and after, dependent t-test); * Significance $\alpha<0.05$

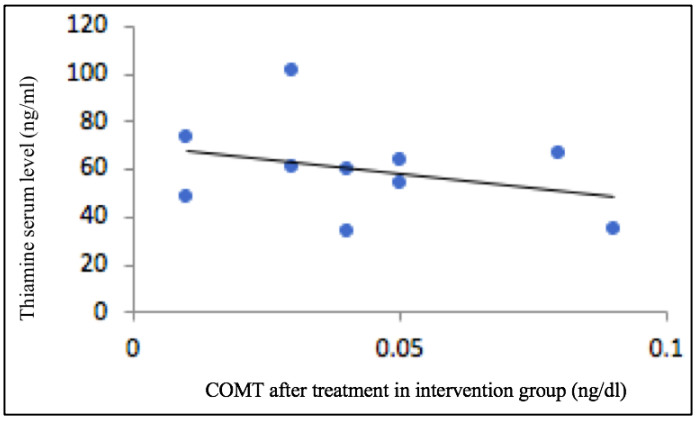

Figure 1: Scatterplot Graph of Changes in COMT Enzyme Levels with Increased Serum Thiamine Levels in the Thiamine Group

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