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# Correlation between Oral Thiamine as an Opioid Adjuvant and Cathecol-O-Methyltransferase Enzyme Levels in Cervical Cancer Patients

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**Abstract**

**BACKGROUND:** The high prevalence of cancer pain shows that a lot of the patients are undertreatment. Vitamin B is one of the additional alternative substances studied in cancer pain management. Thiamine is believed to modulate pain mechanisms in lowering the Cathecol-O-Methyltransferase (COMT) enzyme level.

**AIM:** The aim of the study was to assess the correlation between Oral Thiamine as an Opioid Adjuvant and COMT Enzyme Levels in Cervical Cancer Patients

**METHODS:** This research is a quasi-experimental study with a pre-test and post-test control group design. Patients in this study were 32 cervical cancer patients who experienced cancer pain, divided into two groups (treatment and control groups). The treatment group received morphine plus thiamine 500 mg/8 h/oral, and the control group received morphine alone. Measurement and evaluation of pain scores were carried out after 72 h of thiamine administration and blood collection was carried out again 4 h after the last thiamine administration to check thiamine levels and COMT. Then, data collection and analysis is being evaluated.

**RESULTS:** From 32 cervical cancer patients studied, there were differences in changes in numeric rating scale (NRS) levels and COMT levels in the thiamine treatment group.

**CONCLUSIONS:** The administration of thiamine can reduce COMT enzyme levels and clinically reduce NRS in cervical cancer patients. If it confirmed by other findings, thiamine might be considered for its use in the treatment of cancer pain.

## Introduction

Human papilloma virus is a virus responsible for cervical cancer. It is estimated that one in eight women may get cervical cancer in their lifetime, Global Cancer Statistics 2018 estimates that there are 569,847 new cases of cervical cancer and 311,360 people die from the disease is scattered every year. In developing countries, cervical cancer is the second leading cause of death from cancer after breast cancer [1].

Indonesia as one of the developing countries also has a high prevalence of cervical cancer. According to Cancer Registry Indonesia data, 13% of all deaths in the country are caused by cervical cancer [2]. At 23.4/100,000 population, the incidence of cervical cancer in Indonesia in 2019 was followed by an average mortality rate of 13.9/100,000 population [3]. Cervical cancer is divided into two types, namely, squamous cell carcinoma and adenocarcinoma [1].

Cervical cancer is a disease with a high mortality rate so the treatment given must be adequate. The treatment given to each cervical cancer patient is based on its stage or severity. There are three treatment options for cervical cancer: Surgical excision, chemotherapy, and radiotherapy, according to IFGO (International Federation of Gynecology and Obstetrics) 2018 [4].

In a meta-analysis study (more than 100 studies), cancer pain was found to be 39.3% after curative treatment, 55% in cancer patients who were undergoing anti-cancer treatment, meanwhile, in advanced cancer patients, it was found as much as 66.4%. Moderate-to-severe pain degrees were found in 38% of all cancer pain patients. Data in the United States state that of the 4526 cancer patients who live, there are 1648 (34.6%) people who experience chronic cancer pain and there are 768 people (16.1%) who experience a decrease in quality of life due to pain aforementioned [5].

The number of cancer pain above shows that the management of cancer pain has not been maximized. This may be because pain management so far has only been limited to symptoms. Supposedly, pain

management based on the underlying pathophysiology should not only inhibit the transmission of pain but should affect the course of the disease [5]. In addition, access to the use and availability of opioid-class analgesic drugs such as morphine is very limited. Indonesia in terms of the use of morphine opioids is relatively small compared to other countries [6]. For this reason, other additional alternative treatments are needed that are considered to be abundant in availability and have good effectiveness.

The correlation between vitamin administration in cancer has been the focus of recent researcher's investigations. An additional treatment alternative that is widely studied in cancer patients today is B vitamins [6]. The B vitamin group has been researched for its ability to provide benefits for pain relief. Thiamine (Vitamin B1) is rated as having the anti-inflammatory ability through antinociceptive, anti-inflammatory, and antineuropathic mechanisms [7]. Especially in cancer patients, many studies have observed the role of thiamine administration on the outcomes of cancer patients. This was noticed because studies showed significant results that cancer lowered serum thiamine levels [7].

Changes in thiamine levels in cervical cancer patients are associated with decreased expression of the SLC19 gene which has a role in thiamine transport and homeostasis in the body. This decrease in thiamine levels has been shown to have many impacts, such as abnormalities in the transketolase process, the occurrence of DNA damage associated with the p53 gene, and a decrease in nuclear proteins Poly (ADP-ribose) Polymerase-1 which plays a role in cell defense under stress conditions [8].

Until now, thiamine administration in cancer patients is still controversial, there are studies writing thiamine at low doses will increase survival rate, the rate of proliferation of cells cancer, as well as resistance to chemotherapy. However, several other studies write that giving thiamine, especially in high doses, will have an inhibitory effect on the growth of cancer cells and have a good effect on changes in prostaglandin levels, Cyclooxygenase-2 (COX2), Reactive oxygen species (ROS), and nitric oxide synthetase (NOS) [9].

One of the effects of metabolic changes that are strongly affected by changes in thiamine levels in cancer cells is the transketolase reaction. This reaction has an important role in the use of carbon from glucose in the synthesis of ribose nucleotide acids in the tumor cell growth process. The transketolase reaction mainly works in the Krebs cycle whose changes depend on the presence of thiamine. The given thiamine will cause modulation in the transketolase so that the Krebs cycle will enter the non-oxidative pathway with little ATP production, while the presence of THIS ATP will affect levels of other enzymes, for example, in cervical cancer, namely, Cathecol-O-Methyltransferase (COMT) [10].

COMT is one of the enzymes that is involved in the body's physiological reactions such as mood, cognition, and stress response. One of the functions of the COMT enzyme is to degrade neurotransmitters, in this case, including dopamine, epinephrine, and norepinephrine [11]. Epinephrine and norepinephrine are neurotransmitters that play a role in the perception of pain. Low levels of COMT will increase epinephrine and norepinephrine levels so that it will increase the stimulus to adrenergic receptors, especially $\beta 2/\beta 3$ [12], [13].

According to experimental animal studies, thiamine can prevent the appearance of neuropathic pain symptoms while increasing the inhibition of TNF-$\alpha$ and IL-6. In addition, thiamine also has an anti-pain effect if used as a single drug even though its effects are still being invaded at the level of experimental animal studies, in addition to that thiamine when combined with other anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs and glucocorticoids, can increase the antinociceptive and anti-inflammatory work of the drug so that the anti-pain effect of the drug will increase. Meanwhile, thiamine administration will also reduce the transketolase reaction at the cellular level so that there is a decrease in activity and COMT levels in plasma [14]. Results from a literature search conducted found that the use of thiamine single in clinical practice was limited to case reports such as for cases of fibromyalgia and *cluster headache* even with varying doses. The use of thiamine for cancer pain is still not widely found including dosage, duration of its use, and side effects caused [15].

Based on the description above, it can be concluded that there seems to be a strong relationship between thiamine and the decrease in the enzyme COMT and the role of epinephrine and norepinephrine in the occurrence of pain. Thiamine administration and the association with cancer pain are still rare, let alone associated with COMT. However, research on thiamine to relieve pain in patients is still very limited so further research is needed. For this reason, many potential things can be studied regarding the relationship between thiamine, cancer pain, and adjuvant therapy. For this reason, in-depth research is needed on the administration of thiamine in cancer patients to see its effectiveness as a therapeutic adjuvant in lowering pain scores and seeing its ability to influence COMT levels as an early marker of neuropathic, especially in patients with cervical cancer pain [15].

## Research Methods

The control group before and after the test in this study was used to test the effect of oral thiamine administration as an opioid adjuvant on COMT enzyme levels in patients with cervix cancer. This research was conducted from December 2021 to June 2022 and was carried out at Unhas State Hospital and other education network hospitals. Cervical cancer

patients who received therapy at RSPTN Unhas and Makassar Teaching Network Hospital were included in this study, successive sampling was used to collect data from all eligible participants. To be eligible for the trial, participants must be between the ages of 16–90, have cervical cancer pain, and be willing to participate in the study. Patients who have used psychopharmaceutical drugs, drank alcohol, or had a history of head injuries were not included in the inclusion criteria of this study. When a patient has difficulty in the treatment or chose to withdraw from the study, the dropout criteria are fulfilled. The Faculty of Medical Hasanuddin University and the Education and Research Section of Wahidin Sudirohusodo Hospital obtained ethics permit with number 126/UN4.6.4.5.31/PP36/2022 from the Biomedical Research Ethics Commission on Human. To participate in the trial, all patients who met the inclusion criteria were given verbal reviews and a written consent form for signature. Both treatment and control groups received thiamine 500 mg 8 h/oral for those who qualified in the inclusion and exclusion criteria and were randomized into two groups. Patients who met the inclusion and exclusion criteria were randomly divided into two groups, namely, the treatment group that received thiamine 500 mg/8 h/oral, and the control group was given morphine only. This study also involved research assistants who had been trained as many as one person who played a role in taking samples and ensuring that the drug (thiamine) was taken by patients. Patients who will be given the intervention (thiamine 500 mg/8 h/orally) or not given the intervention are determined based on a random table that has been previously created. Subsequently, patients who entered the intervention group were given thiamine 500 mg/8 h and administered orally for 72 h by the research assistant. All patients in the control group and thiamine group continued to receive morphine as a standard drug for cancer pain management. After 72 h, the patient was re-examined for pain scores by researchers using numeric rating scale (NRS) scores, and blood draws were carried out again 4 h after the last administration of thiamine by the research assistant for COMT examination. Then, the researcher collects and performs data analysis with the help of software on the computer. Age, weight, height, and BMI were tested with Independent t-test and the Mann–Whitney U-test. Comparison between NRS and COMT before and after the treatment was analysed with Wilcoxon test. The meaningfulness level used is <0.05 with a 95% confidence interval.

## Research Results

The results of the sample homogeneity test based on the characteristics of the research sample are shown in following table:

A comparison of average age, weight, height, and body mass index (BMI) is shown in Table 1. As determined by the Independent t-test and the Mann–Whitney Test, there were no significant differences between the samples of the two groups in terms of age prevalence, body weight, height, and BMI ($p > 0.05$).

**Table 1: Sample characteristics**

| Group | CP | | CT | | p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age | 44.69 | 9.30 | 48.38 | 8.89 | 0.261[(a)ns] |
| Weight | 51.18 | 9.88 | 51.75 | 9.55 | 0.868[(a)ns] |
| Height | 154.56 | 4.56 | 152.69 | 5.02 | 0.332[(b)ns] |
| BMI | 21.34 | 3.38 | 22.24 | 3.54 | 0.468[(a)ns] |

The data are displayed with mean ± standard deviation. Data tested with Independent t-test (a) and Mann–Whitney U-test (b); ns: not significant test, BMI: Body mass index.

Using the data in Tables 2-4, researchers were able to compare NRS levels before and after the treatment, changes in NRS and COMT between control and treatment groups, and compare COMT levels between control and study groups.

Table 2 shows the $p < 0.001$ values in the control and study group using the Wilcoxon test for NRS variables in post-treatment conditions. This illustrates that the study group is more likely to decrease compared to the control group.

**Table 2: Comparison of NRS before and after the treatment in the control and study groups**

| Variable | Group | Before | | After | | p |
|---|---|---|---|---|---|---|
| | | Median | Min-Max | Median | Min-Max | |
| NRS | CP | 5.5 | 4-7 | 2 | 1-3 | <0.001* |
| | CT | 5 | 4-7 | 3 | 2-4 | <0.001* |

The data are displayed with mean ± standard deviation. The data were tested with the Wilcoxon test; *: $p < 0.05$, significantly different, NRS: Numeric rating scale.

Table 3 shows that there were statistically significant differences between the study group and control groups in changes in NRS levels and COMT levels, with $p < 0.05$, indicating that the differences it is likely meaningful statistically. This means that the treatment given, in this case, the administration of thiamine, can affect changes in the level of pain and COMT levels.

**Table 3: Comparison of changes in NRS and COMT levels between control groups and study groups in patients with cervical cancer pain**

| Variable | CP | | CT | | p-value |
|---|---|---|---|---|---|
| | Median | Min-Max | Median | Min-Max | |
| NRS changes | −4 | −6–(−2) | −2 | −4–(−1) | 0.003* |
| COMT changes | −3.01 | −20.42–(−1.39) | 0.48 | −6.19–14.73 | <0.001* |

The data are displayed with mean ± standard deviation. The data were tested with the Mann–Whitney test; *: $p < 0.05$, meaningfully different, NRS: Numeric rating scale, COMT: Cathecol-O-Methyltransferase.

Table 4 shows the difference in the control group's COMT enzyme levels before and after giving an insignificant result at a significant degree of 5% ($p = 0.569$). Thus, it can be concluded that the COMT enzyme levels tend to increase in the control group, while in the study group shows a meaningful difference

**Table 4: Comparison of COMT changes before and after the treatment in the control group and study group**

| Variable | Group | Before | | After | | p-value |
|---|---|---|---|---|---|---|
| | | Median | Min-Max | Median | Min-Max | |
| COMT | CP | 11.30 | 8.03–34.15 | 8.65 | 5.00–25.06 | <0.001* |
| | CT | 12.84 | 8.71–27.37 | 12.83 | 8.77–33.76 | 0.278ns |

The data are displayed with mean ± standard deviation. The data were tested with the Wilcoxon test; *: $p < 0.05$, meaningfully different; ns: not significant, COMT: Cathecol-O-Methyltransferase.

before and after the treatment with $p < 0.001$, which showed that the COMT enzyme levels of the study group have decreased.

Table 5 shows that between NRS and COMT levels after the treatment in the control group, there was a moderate positive correlation ($r = 0.518$, $p = 0.04$), while the study group shows a strong positive correlation ($r = 0.715$, $p = 0.002$).

**Table 5: Correlation of NRS with decreased levels of COMT enzymes in the control group and study group in patients with cervical cancer pain**

| Group | NRS-COMT | |
|---|---|---|
| | R-value | p-value |
| CP | | |
| Before | 0.073 | 0.789$^{ns}$ |
| After | 0.715 | 0.002* |
| Delta | 0.502 | 0.047* |
| CT | | |
| Before | 0.123 | 0.650ns |
| After | 0.518 | 0.040* |
| Delta | −0.039 | 0.135$^{ns}$ |

Data tested with spearman correlation test;*: $p < 0.05$, meaningfully different; ns: not significant, COMT: Cathecol-O-Methyltransferase.

## Discussion

The test results in the control group and study group for the NRS variable in the after conditions showed a meaningful difference from the previous conditions with $p < 0.001$. This is due to the administration of morphine as an analgetic in both groups. An interesting finding in this study was that it reveals a greater and statistically significant decrease in NRS in the study group (which was given thiamine as an adjuvant) than in the control group (in which thiamine is not given as an adjuvant). This shows that thiamine has a decreasing effect on NRS when given as an adjuvant to morphine opioids.

Thiamine administration can lower the levels of prostaglandins and COX2 that contribute to the inflammatory process. In addition, thiamine is also able to reduce the number of ROS and NOS which play a role in activating transcription factors and increasing various protein expressions that control transformation, proliferation, and invasion of tumor cells and become an initiator in the formation of various tumor cells [16].

Differences in COMT enzyme levels in the control group before and after the treatment showed insignificant results at a significant degree of 5% ($p = 0.569$). This showed that in the control group, COMT enzyme levels tended to increase, while in the treatment group, there was a meaningful difference in the difference before and after the treatment with $p = 0.00$, which showed that the COMT enzyme levels of the treatment group had decreased.

The results of this study also showed that there was a difference in COMT levels between the study group and the control group with $p < 0.05$, which means that the difference is meaningful statistically. This means that the treatment given, in this case, the administration of thiamine, can affect changes in COMT levels.

The results showed that the value of COMT enzyme levels from 32 cervical cancer patients with a higher average decrease in the study group compared to the average difference in the control group. This suggests that thiamine is likely to lower COMT levels in the study group with a mechanism that is not yet known for certain. One of the causes may be the presence of an abnormality in the Krebs cycle due to the administration of thiamine. The administered thiamine will cause modulation of the transketolase, so the Krebs cycle will go into the non-oxidative pathway by slightly producing ATP [17]. Meanwhile, ATP is the main factor that plays a role in improving the function of COMT [18]. Perhaps this could explain why COMT could be lower in the study group.

The decrease in COMT levels after thiamine administration in cancer patients has also previously been studied by Hamdi *et al*. gave results that were in line with this study, namely, a decrease in COMT in the treatment group that received thiamine. In addition, in the study group, a significant decrease in NRS was obtained compared to the control group [19].

However, this correlation between thiamine and COMT is different from the research Nasution *et al*. held before, which states that thiamine administration in pre-operative anxiety patients showed an increase in COMT enzyme levels in the study group compared to the control group. However, in contrast to this study, the study was conducted on non-cancer patients [8].

The decrease in COMT levels in this study may also be caused by low thiamine doses and the duration of administration that has not been maximized. So far, the safety and effectiveness of the doses and the duration of thiamine administration are still controversial and clinical reports of single thiamine use are still limited.

This study is also supported by Kambur and Männistö, in experimental pain models studies in humans with acute pain conditions, there was an increase in pain sensitivity in patients with low COMT activity. However, in cancer pain, low COMT activity can increase the availability of opioid receptors and increase opioid analgesia, thus reducing the need for opioids and lowering the side effects. In addition, thiamine that inhibits COMT activity may have its properties, such as the capacity to resist oxidative stress, which can interfere with at least some forms of pain [20].

Between NRS and COMT levels after the treatment have a positive correlation overall. This shows that NRS after low treatment is associated with low levels of COMT. Overall, there is also a weak negative correlation between NRS changes and decreased

COMT levels, which illustrates a relationship between NRS and COMT levels, yet very weak. Based on other results from this study, there is a moderate correlation between changes in NRS and changes in COMT levels, and there is no correlation between the two variables in the group control. This shows that the decrease in NRS that occurred in this study was related to the decrease in its COMT and was caused by the administration of Thiamine.

This is also in line with research conducted by Sadhasivam *et al*., which provided supporting results that explained the relationship between the COMT genotype and postoperative pain and opioid use in children. In his research, it was explained that decreased COMT levels have been shown to affect pain sensitivity and post-operative morphine needs in children, although post-operative pain and opioid response can be affected by many different factors [21].

In addition, Matsuoka *et al*. also explained the results of their research that COMT affects morphine treatment outcomes, even an increase in certain COMT genotype levels can provide relatively high residual pain when measured by NRS, as well as increasing the need for more morphine, therefore, can be used as a predictive biomarker for the treatment of morphine, which according to its work can regulate the number of catecholamines, especially in some areas of the brain and peripheral tissues, which plays a role in influencing pain ducts in another place [22].

The main limitation of this study is the small number of participant who participate in the trial. We suggest to conduct this study in more hospitals to accommodate more participant. We also suggest in the next study to asses other factor that may involve in the pathway of pain. As we know cancer, pain is associated with multifactorial pathway.

## Conclusion

Thiamine administration can lower COMT enzyme levels and clinically lower NRS in patients with cervical cancer. If it confirmed by other findings, thiamine might be considered for its use in the treatment of cancer pain.

### *Suggestion*

Researchers expect to provide recommendations for thiamine as an adjuvant in clinical practice guidelines for cancer pain treatment and can explain the role of COMT as a therapeutic target in treating cancer pain.

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