


## Catechol-O-Methyltransferase (COMT) Enzyme Level In Preoperative Anxiety Patients

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### ABSTRACT

**Background:** Incidence of perioperative anxiety is very high, many preoperative patient experience anxiety. Thiamine acts as an essential nutrition functionate as cofactor enzyme in most of mitochondria in brain. Brain is very susceptible to thiamine deficiency because its dependency on mitochondrial ATP production. Decreased ATP production result in inhibition of COMT activity. Low COMT levels indicated tendency for anxiety. The aim of this study is to determine the effect of thiamine in increasing COMT enzyme levels in patient with preoperative anxiety

**Methods :** A true experiment with pretest-posttest control group and double-blind design conducted at the Department of Anesthesia and Intensive Care of University of North Sumatra in August 2019. The 60 patients were analyzed which were planned for and done an elective surgery under general anesthesia. Preoperative anxiety was measured with Amsterdam Preoperative Anxiety and Information Scale (APAIS) and COMT enzyme level measured by ELISA assays.

**Results :** The results showed that from 64 patients had incidence of preoperative anxiety in this study was 48.3%. We found that there is significant differences in COMT enzyme levels in thiamine group compared to control ( $p$  value = 0.001). In addition, it was seen that in thiamine group had an increased COMT levels from 0.96 ng/dL to 1.78 ng/dL, while in control group there also slight increasing from 0.44 ng/dL to 0.78 ng/dL. This show that increase in COMT levels is greater in thiamine group than control group.

**Conclusion :** COMT enzyme levels increase in patients scheduled for elective surgery with preoperative anxiety under general anesthesia

### Keywords

Preoperative Anxiety, General Anesthesia, COMT Enzyme

## INTRODUCTION

The incidence of preoperative anxiety is very high, many preoperative patients experience anxiety. The incidence of preoperative anxiety is about 82% where the highest anxiety is found in patients undergoing general anesthesia compared to regional anesthesia, and women are more anxious than men (1). A preliminary study conducted at the Haji Adam Malik General Hospital (HAM) on 121 patients Those who planned for elective surgery had preoperative anxiety as measured by the APAIS score, which was reported to be very high with a percentage of 48.3%. Anxiety conditions will result in perioperative complications in the form of hypertension and tachycardia thereby increasing the need for anesthesia, causing complications of a long

recovery and greater postoperative pain (2). Patient-related factors such as age, gender, education level and economic status, pain tolerance, Previous surgery history and exposure to anesthetics, psychiatric problems, social security can affect anxiety levels. Procedure-related factors such as major surgery, chronic illness, and unscheduled emergency procedures play an important role in preoperative anxiety development in patients. The attitude of health care providers, communication skills of doctors, beliefs and opinions of patients also have an influence on the onset of anxiety. In addition, information on preoperative anesthesia, adverse effects of anesthesia, and sudden surgical advice were shown to be statistically significantly associated with increased overall anxiety levels (3).

A study found that low COMT levels indicate a tendency to anxiety. The main function of COMT is the metabolism of catecholamine degradation. Decreased activity of this enzyme can increase the high plasma catecholamines associated with anxiety. This could explain that excessive and prolonged anxiety response can be triggered by exposure to emotional stress in patients with genetically low COMT enzyme activity. The study concluded that low levels of COMT may be a genetic marker for anxiety (4).

In anxiety, there is also the production of toxic dopamine metabolism so that the influx of  $Ca^{+}$  will increase into brain cells and eventually increase tyrosine hydroxylase and decrease ATP production, which in turn increases the release of cortisol and catecholamines. High circulating cortisol levels can result in mitochondrial dysfunction and apoptosis, which in turn reduces ATP production again, thus tending to create a vicious cycle (5–8). A study has shown that COMT plays an important role in suppressing anxiety through the reduction of catecholamines (9). The role of catecholamines is impaired in a number of medical conditions including anxiety, so some pharmaceutical drugs target COMT as a therapeutic target (10,11). This study aims to determine the levels of the COMT enzyme in preoperative anxiety patients.

## **METHOD**

This study is a pure experimental study with a pretest-posttest control group design and double-blind. The measurement of COMT enzyme levels was carried out using the ELISA technique. Blood samples were taken from preoperative anxiety patients who were assessed by the Amsterdam Preoperative Anxiety Information Scale (APAIS) as many as 64 patients. This research was conducted at Haji Adam Malik Central General Hospital and Regional General Hospital dr. Pirngadi Medan, and the Integrated Laboratory of the Faculty of Medicine, University of North Sumatra. After obtaining permission from the USU/RSUP Medical Faculty Research Ethics Committee. H. Adam Malik Medan, Head of Section/SMF Anesthesia and Intensive Therapy, FK USU/RSUP. H. Adam Malik Medan, USU Medical Faculty Integrated Laboratory, and Pirngadi Regional General Hospital Medan carried out protocol preparation, filling out research forms and APAIS examination to assess preoperative anxiety, tools and materials for serum COMT examination.

## **PATIENT PREPARATION**

Patients enrolled for elective surgery under general anesthesia, who met the inclusion criteria, were asked to be research subjects. Patients were given an explanation of the research procedure and asked to sign an informed consent to participate in the study. Three days before the scheduled outpatient surgery, the patient was checked for anxiety using the APAIS score and blood was taken for COMT examination. Perform data collection and perform data analysis with the help of software on the computer.

## **STATISTIC ANALYSIS**

After all the required data has been collected, the data is then re-examined for completeness before being tabulated and processed. After that, coding is given to the data to make it easier to tabulate. The data is tabulated into a master table using computer software. Numerical data is shown in mean + SD (standard deviation) and median (minimum-maximum) values, while categorical data is shown in sum (percentage). The normality test used the Kolmogorov-Smirnov normality test. The research hypothesis was tested using an independent t-test, Mann-Whitney and Spearman correlation test was performed to see the strength of the correlation between variables. 95% confidence interval with  $p < 0.05$  was considered significant.

## RESEARCH RESULTS

The sample in this study amounted to 64 samples according to the inclusion and exclusion criteria . Sample characteristics are shown in Table 1.

**Table 1** Sample characteristics

Characteristics	thiamine	Control	Total	p value
Gender, n (%)				
Man	4 (30.8)	2 (33.3)	6 (31.6)	0.966
Woman	9 (69.2)	4 (66.7)	13 (68.4)	
Age, Mean (SD)	44.5 (17.3)	41.3 (12.8)	43.5 (14.5)	0.966
Economic status, n (%)				
Not enough	12 (92.3)	6 (100)	18 (94.7)	0.323
More	1 (7.7)	0 (0)	1 (5,3)	
Last education, n (%)				
Bachelor	2 (15.4)	1 (16.7)	3 (15.8)	0.467
Senior High School	6 (46.2)	4 (66.7)	10 (52.6)	
Junior High School	2 (15.4)	1 (16.7)	3 (15.8)	
SD	3 (23.1)	0 (0)	3 (15.8)	
Operation history, n (%)				
There is	2 (15.4)	1 (16.7)	3 (15.8)	0.988
There isn't any	11 (84.6)	5 (83.3)	16 (84.2)	

Description: Mann-Whitney Test

Based on Table 1 shows that the distribution of sample characteristics in this study has a mean patient age of  $43.5 \pm 14.5$  years. Most of the patients were female with a percentage of 68.4%. Most patients with high school education are 10 people (52.6%) and with less economic status are 18 people (94.7%). Most of the samples in this study had never had surgery before, as many as 16 people (84.2%).

## COMT ENZYME LEVELS IN PREOPERATIVE ANXIETY AND NON-ANXIETY PATIENTS PREOPERATIVE

**Table 2.** Effect of thiamine on COMT . levels

COMT (ng/dl)	Anxiety	Not anxious	p value
Before			
SD mean $\pm$	0.14 (0.08)	0.96 (1.11)	0.014*
Median (min-max)	0.1 (0.05-0.35)	0.59 (0.1-3.09)	

Description: T-independent test ; \*Significant  $\alpha < 0.05$

Based on Table 2, it was found that the levels of COMT in the anxiety and control groups had differences with p value = 0.014. In addition, the levels of COMT in the preoperative anxiety group were lower when compared to the non-anxiety group preoperatively, where the anxiety group had COMT enzyme levels of  $0.14 \pm 0.08$  ng/dl, while the control group had higher COMT levels  $0.96 \pm 1.11$  ng/dl. Figure 1 shows that patients who did not experience preoperative anxiety based on the APAIS score had higher COMT levels.

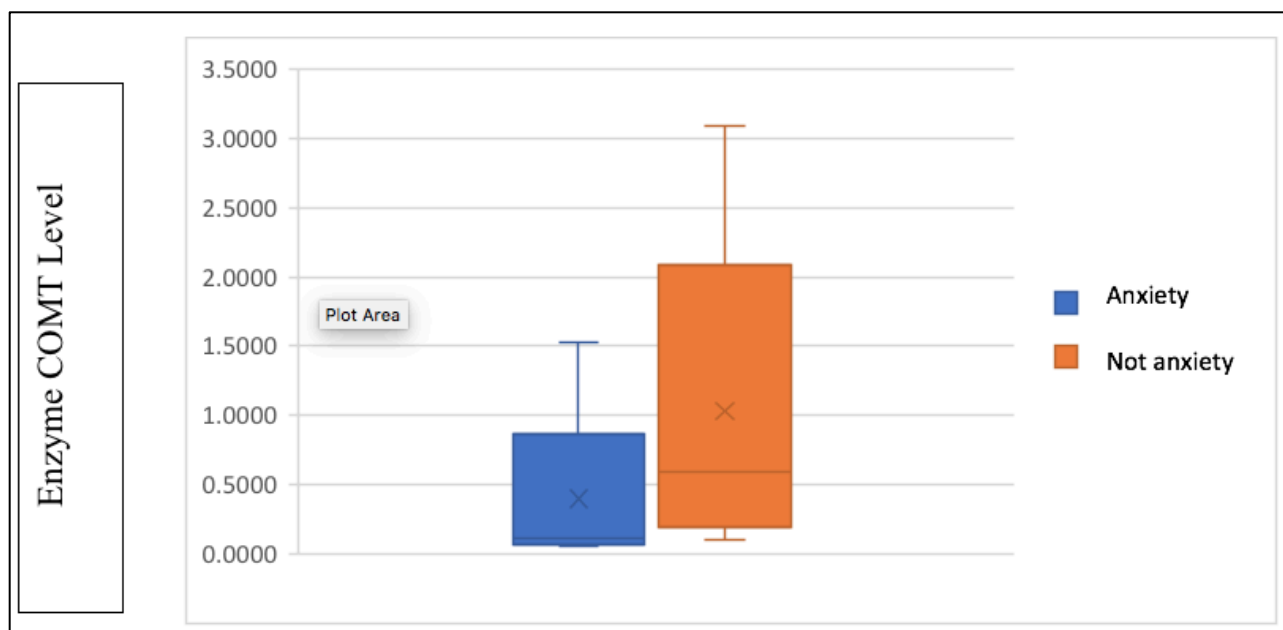


Figure 1. Comparison of COMT enzyme levels in preoperative and non-anxiety preoperative patients

## Discussion

Based on the results of the study, it was found that the levels of COMT in the preoperative anxiety group were lower than those in the non-preoperative anxiety group. This indicates that the anxiety condition can be caused by low levels of the COMT enzyme. When viewed from the research conducted by Luong and Nguyễn, it was found that anxiety patients had very low thiamine levels, namely  $25.06 \text{ nmol/L} \pm 6.0 \text{ nmol/L}$ , so that it was suspected that this could lead to a decrease in APT production which could lead to a decrease in COMT (12) enzyme levels. Anxiety can occur sympathetic stimulation. Excessive sympathetic stimulation can cause the release of epinephrine and norepinephrine, stimulating the hypothalamus as a compensatory response through activation of the HPA axis regulation (2,13). Thiamine acts as a co-factor in all organ systems, especially the cells of the nervous system. Decreased ATP production in the brain increases the production of toxic dopamine metabolism and decreases the work of COMT (6). Inhibition of COMT activity will result in impaired HPA function and increase higher catecholenergic activity, resulting in a greater release of hypothalamic CRH (14). From this explanation, it can be seen that decreased activity COMT also plays an important role in the development of preoperative anxiety. It is proven in this study that the levels of COMT in preoperative anxiety patients have very low levels (15,16).

Another theory supports that thiamine also acts as a coenzyme in ACh synthesis, where a decrease in thiamine levels will result in a significant decrease in ACh levels in neurons. This is evidenced in experimental animal studies, where ACh synthesis damage occurs in thiamine-deficient mice (17). Thiamine is able to bind to nicotinic receptors which are thought to play a role in inhibiting anticholinesterase activity, so that thiamine administration also increases ACh synthesis. Anxiety patients have been shown to have low levels of thiamine, this has also been shown to result in low ACh (17) synthesis and result in the release of catecholamines 18. High levels of catecholamines in anxiety will result in increased autonomic nervous responses. The administration of thiamine actually plays a role in increasing the levels of COMT which is responsible for the degradation of catecholamines into inactive metabolites, namely norepinephrine which is methylated by COMT to normetanepinephrine, epinephrine is methylated by COMT to metanephrine, and dopamine is converted to homovanilic acid through the combined action of MAO and COMT.

## Conclusion

Preoperative anxiety patients had lower levels of the COMT enzyme compared to patients who did not experience preoperative anxiety. Researchers suspect that there is a role for the COMT enzyme in causing preoperative anxiety.

## **ABBREVIATIONS**

COMT, Catechol-O-Methyltransferase; HAM, Haji Adam Malik General Hospital.

## **ETHICS APPROVAL AND INFORMED CONSENT**

The study protocol complies with the requirements of the institute's committee of Haji Adam Malik Hospital, Medan, Indonesia.

## **CONSENT FOR PUBLICATION**

The Authors agree to publication in Journal of Society Medicine.

## **DATA AVAILABILITY**

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

## **FUNDING**

None.

## **COMPETING INTERESTS**

None.

## **AUTHORS' CONTRIBUTIONS**

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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