

Research Article

# The Effect of Thiamine Administration on Catechol-O-Methyltransferase (COMT) Enzyme Level and Amsterdam Preoperative Anxiety and Information Scale (APAIS) Value in Patients with Preoperative Anxiety

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## Abstract

**Background:** Preoperative anxiety increases intraoperative and postoperative morbidity and mortality. Anxiolytic premedication drugs that exist so far have adverse side effects.

**Methods:** We conducted a study of thiamine administration in 20 preoperative anxiety patients (APAIS value  $\geq 11$ ) divided into 2 groups (thiamine and control groups) thiamine administered 500 mg orally per 8 hours for 72 hours. The study was conducted July 2019 until October 2019, randomized, and quasi-experimental controlled intervention study to investigate the effect of thiamine administration on COMT enzyme levels and APAIS values in patients with preoperative anxiety. The parameters measured were APAIS and COMT enzymes.

**Results:** In thiamine group, APAIS value decreased ( $p=0.001$ ) and COMT enzyme levels increased ( $p=0.001$ ) compared to the control group. There is a correlation between COMT with APAIS C ( $r=-0.673$ ;  $p=0.016$ ).

**Conclusion:** Thiamine administration improves anxiety (APAIS and COMT) in elective surgery patients with general anaesthesia.

**Keywords:** COMT enzyme levels; APAIS SUM C; APAIS SUM I; preoperative anxiety; thiamine

**Abbreviations:** COMT: Catechol-O-Methyltransferase; APAIS: Amsterdam Preoperative Anxiety and Information Scale

## 1. Introduction

Preoperative anxiety tends to cause perioperative complications, such as hypertension and tachycardia thus increasing the need for anesthesia and causing long recovery complications and more severe postoperative pain [1]. Information on preoperative anesthesia, adverse effects of anesthesia and sudden surgery

recommendations statistically have also been shown to be significantly related to overall preoperative anxiety increase [2]. In the present prospective cohort study, significant levels of patient-reported preoperative anxiety independently predicted a greater risk of mortality or major morbidity occurred postoperative in 55% of the anxiety group, 25% of the possible anxiety group, and 22% of the no anxiety group [3].

This preoperative anxiety can be treated with non-pharmacological and pharmacological therapies. Non-pharmacological therapy can be done in through preoperative education. Patients with anxiety disorders need support and attention to deal with their emotional problems related to anxiety disorders. However, according to studies conducted on 60 patients with preoperative anxiety were measured using Abbreviated Mental State Score, and state trait anxiety inventory (STAI) in Australia, 203 patients with preoperative anxiety were measured using STAI in Germany, 211 patients with preoperative anxiety were measured using STAI in Japan, and 209 patients with preoperative anxiety were measured using STAI in Germany, there were no significant changes related to the incidence of preoperative anxiety between groups given preoperative education and groups not given preoperative education, which means that preoperative education does not reduce the level of preoperative anxiety [4–8]. Because, based on these studies, non-pharmacological therapy alone

cannot reduce preoperative anxiety, pharmacological therapy with very minimal side effects is needed to be done. Currently pharmacological therapy is widely using benzodiazepines (alprazolam, lorazepam, diazepam and midazolam) which have many side effects, such as ataxia, hypnotics, sedation, and changes in mental status. Some reports even indicate severe toxicity – especially with the use of anxiolytic premedication, this therapy is thought to slow down patient recovery [9]. Therefore, alternative therapies that can minimize the use of benzodiazepines are needed, one of which is thiamine administration. Side effects of intravenous administration of thiamine are reported very rarely. According to a study conducted by Wrenn in a prospective evaluation study with a sample of 989 given thiamine 100 mg IV, an adverse reaction effect was reported as much as 1.1% with a minor reaction [10].

The incidence of anxiety is very high among preoperative patients. The incidence of preoperative anxiety is around 82%, with the higher percentage found in patients undergoing general anesthesia compared to undergoing regional anaesthesia and then more higher percentage found in female patients compared to male patients [11, 12]. In the preliminary study conducted at the Haji Adam Malik General Hospital Indonesia, which involved 121 patients planned to undergo elective surgery, we found preoperative anxiety using APAIS score around 48.3% [13]. The original research studies in Europe that reported the preoperative anxiety case is around 30.2% of 344 patients [14]. According to studies conducted on 149 patients undergoing elective surgery, preoperative anxiety was found to be 12.6% using Hospital Anxiety and Depression Scale (HADS), 10.9% using Visual Analogue Fear Scale (VAFS), and 57.7% using APAIS.

Several pathophysiologic processes have been proposed to explain the relation between anxiety and Catechol-O-Methyltransferase (COMT). One previous study found that low COMT levels indicated a tendency for anxiety. COMT is the main enzyme needed for catecholamine metabolism/degradation [15]. Decreased activity of this enzyme can increase the high plasma catecholamines associated with anxiety. This explains that excessive and prolonged anxiety responses can be triggered by emotional stress exposure in patients with genetically low COMT enzyme activity. The study concluded that low COMT levels could be genetic markers for anxiety [16–18].

Recent studies demonstrated that patients with anxiety had low blood thiamine levels [19–21]. Previously, thiamine was not known as anti-anxiety drug, but supplementation of thiamine can be thought to reduce anxiety in patients with preoperative anxiety [22]. A review of current literature on the role of thiamine in the anxiety, thiamine plays a critical role regulating carbohydrate metabolism in the brain acts as an essential nutrient that works as a cofactor in a number of enzymes that are mostly found in mitochondria. The brain is an organ that is very susceptible to thiamine deficiency because it is

very dependent on mitochondrial ATP production. A decrease in ATP production will result in the inhibition of COMT activity and will result in disruption of the hypothalamic–pituitary–adrenal axis (HPA) function and increase catecholaminergic activity, resulting in the greater release of hypothalamic corticotrophin-releasing hormone (CRH) [23]. Based on a previous study, we want to determine the effect of thiamine administration on COMT enzyme levels and APAIS values in patients with preoperative anxiety.

## 2. Methods

### 2.1. Participants

The study was conducted July 2019 until October 2019, randomized, and quasi-experimental controlled intervention study to investigate the effect of thiamine administration on COMT enzyme levels and APAIS values in patients with preoperative anxiety. Patients with preoperative anxiety were recruited between July until September 2019 at the Haji Adam Malik General Hospital and Hospital Networks, Indonesia. All patients included in the study were randomized using a computer-generated list of random numbers (*randomizer.org*). Patients with mental and psychological problems, psychopharmaceuticals, alcohol consumption, history of head injury, patients unable to communicate and complete questionnaires independently, patients with impaired kidney function, patients with impaired liver, pregnant and breastfeeding patients were excluded from this study. Study protocol was approved by our Institutional Review Board Medical Faculty of University of Sumatera Utara (No 619/TGL/ KEPK FK USU RSUP HAM/2019) was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

### 2.2. Amsterdam Preoperative Anxiety and Information Scale (APAIS)

Preoperative anxiety was measured using APAIS values. APAIS was further subdivided to assess anxiety about anesthesia (SUM A), anxiety about surgery (SUM S) and a combined anxiety total (SUM C = SUM A plus SUM S). APAIS SUM A is an APAIS questionnaire that assesses preoperative anxiety related to anesthesia (SUM A = questions number 1 and 2). APAIS SUM S is an APAIS questionnaire that assesses preoperative anxiety related to surgical procedures (SUM S = questions number 4 and 5). APAIS SUM C is a combination of anxiety components in the form of total anxiety components related to anesthesia and surgical procedures. APAIS SUM I is a component of information needs which is the sum of question number 3 and question number 6. Anxiety score was obtained by calculating the total scores assigned to the expressions “ I am worried about the anesthetic”, “ The anesthetic is on my mind continually”, “I am worried about the procedure”, “ The procedure is on my mind continually”, to measure the patient’s level of anxiety regarding the anesthesia and surgery.

Desire for information score is obtained by calculating the total scores assigned to the expressions “I would like to know as much as possible about the anesthetic “ and “I would like to know as much as possible about the procedure “to measure the patient’s level of desire for information regarding the anesthesia and surgery. Higher scores indicate higher levels of anxiety and desire for information. Answers to the statements were evaluated with Likert Scale [24, 25]. APAIS assessment was performed in an outpatient clinic as well as visit during hospitalization after patient received treatment 72 hours.

### 2.3. Catechol-O-Methyltransferase (COMT)

Catechol-O-Methyltransferase (COMT) enzyme levels are one of several enzymes that decrease catecholamines such as dopamine, epinephrine, and norepinephrine. COMT enzyme levels were measured using duplex enzyme-linked immunosorbent assays (ELISA’s) (Elisa kit, Antibody-Sunlong Biotech Co. Ltd). Blood sampling for examination of COMT enzyme levels is done 4 hours after the last consumption of thiamine. Blood was collected from peripheral venous using EDTA as an anticoagulant. Centrifuge sample for 15 minutes within 30 minutes of collection. The detection range of detection for COMT enzyme levels can be determined 0.156-10 ng/ml [1, 26].

### 2.4. Thiamine

Patients received 500 mg of oral thiamine (Solgar inc., USA) per 8 hour during 72 hours before anesthesia [27, 28].

### 2.5. Statistical analysis

All data were analyzed by SPSS 25.0 package program. Mann-Whitney test was used for intergroup comparison of the parametric data that have been distributed normally, whereas Mann-Whitney U test was used for intergroup comparison of data that the data are not normally distributed. The Spearman's rank correlation test was

performed to see the strength of the correlation between variables. The results were considered statistically significant if  $p < 0.05$ .

## 3. Results

### 3.1. Sample

The sample in this study amounted to 20 samples that according to inclusion and exclusion criteria. Social characteristics are shown in Table 1. Characteristics of the sample in this study were spread homogeneously in both groups.

### 3.2. Changes in COMT enzyme levels in the thiamine and control groups

Changes in COMT enzyme levels in the intervention and control groups are shown in Table 2. It shows that changes of COMT enzyme levels between the intervention and control groups had significant differences ( $p=0.001$ ), which in intervention group increased COMT enzyme levels  $1.74 \pm 1.25$  ng/ml while in the control group only increased  $0.04 \pm 0.17$  ng/ml. There was a 6-fold increase in the mean increase in COMT enzyme levels in the thiamine group while the control group had no change.

### 3.3. APAIS SUM C, and SUM I values in the intervention and control groups

Table 3 shows the changes in APAIS SUM C score was comparable between groups. Immediately after intervention, APAIS SUMC value decreased in thiamine groups with differences statistically significant ( $p=0.005$ ).

### 3.4. Correlation between changes of COMT enzyme levels with APAIS SUM C in intervention and control groups

Table 4 shows that in thiamine group, a strong negative correlation in the thiamine group between changes in COMT enzyme levels and changes in APAIS SUM C, meaning that the higher the COMT enzyme levels followed by the lower the APAIS SUM C value. It was

**Table 1:** Sample characteristics.

Sample Characteristics	Group		P
	Thiamine (Mean±SD); n=10	Control (Mean±SD); n=10	
Sex, (female/male)	4/6	3/7	
Age, (years)	40.0±7.9	34.4±13.1	0.088 <sup>a</sup>
Operating history, n (%)			
yes	0 (0)	2 (20)	0.481 <sup>b</sup>
no	10 (100)	8 (80)	
Type of anesthesia			
General anesthesia	10 (100.0)	10 (100.0)	1.000 <sup>b</sup>
APAIS value			
SUM A	6.3 ± 1.7	6.7 ± 2.1	0.739
SUM S	8.2 ± 1.3	8.4 ± 1.5	0.739
SUM C	14.5 ± 3.06	15.1 ± 3.6	0.739
SUM I	8.8 ± 1.3	9.0 ± 1.2	0.739
COMT (ng/ml)	0.31 ± 0.56	0.14 ± 0.08	0.684

**Note:** <sup>a</sup>T-independent test; <sup>b</sup>Mann-Whitney test; Anxiety associated with anesthesia (SUM A); Anxiety associated with surgery (SUM S); total anxiety components related to anesthesia and surgical procedures (SUM C); Component of information needs (SUM I).

**Table 2:** COMT enzyme levels in the thiamine and control groups.

COMT	Group		p <sup>a</sup>
	Thiamine (Mean±SD); n=10	Control (Mean±SD); n=10	
Before	0.31 ± 0.56	0.14 ± 0.08	0.684
After	2.06 ± 1.17	0.19 ± 0.18	0.001*
Change	1.74 ± 1.25	0.04 ± 0.17	0.001*
p <sup>b</sup>	0.005*	0.575	

Note: p<sup>a</sup>: (thiamine group versus control group, Mann Whitney test); p<sup>b</sup>: (before versus after every groups, Wilcoxon test)

**Table 3:** APAIS SUM C values in the thiamine and control groups

SUM C	Group		p <sup>a</sup>
	Thiamine (Mean±SD); n = 10	Control (Mean±SD); n = 10	
Before	14.5±3.06	15.1±3.6	0.684
After	11.2±2.5	13.4±2.5	0.001*
Change	3.3±1.6	1.7±1.1	0.001*
p <sup>b</sup>	0.005*	0.006*	

Note: p<sup>a</sup>: (thiamine group versus control group, Mann Whitney test); p<sup>b</sup>: (before versus after every groups, Wilcoxon test)

**Table 4:** Correlation of changes in COMT enzyme levels with APAIS SUM C score in the thiamine and control groups

APAIS	Thiamine		Control	
	r	p	r	p
SUM A	-0.674	0.016*	0.071	0.423
SUM S	-0.590	0.036*	0.201	0.289
SUM C	-0.673	0.016*	0.201	0.289
SUM I	0.174	0.315	-0.028	0.470

Note: Anxiety associated with anesthesia (SUM A); Anxiety associated with surgery (SUM S); total anxiety components related to anesthesia and surgical procedures (SUM C); Component of information needs (SUM I). Spearman's rank correlation, \*p<0.05

found for correlation between changes in COMT enzyme levels with changes in APAIS SUM A and SUM S. However correlation between changes of COMT enzyme levels with APAIS SUM I was found a weak positive correlation in thiamine group as well as control group.

#### 4. Discussion

The results of the study show that thiamine could increase the levels of the enzyme COMT and reduce the values of APAIS in patients with preoperative anxiety were not influenced by sample characteristics (Table 1). But for the type of surgery and type of anesthesia according to the literature can affect the level of patient anxiety [29]. This difference in results can be caused by almost all patients classified as minor surgery and planned general anesthesia.

Table 2 shows the change in the average increase in COMT enzyme levels in the thiamine group is greater than the control group significantly. Comparison with a similar study conducted revealed that patients with preoperative anxiety had very low levels of COMT [30, 31]. The mechanism underlying this pathophysiology is likely caused by decreased production of ATP in the brain increases the production of toxic dopamine metabolism and decreases the work of COMT [32, 33]. Barriers to COMT activity will result in disruption of HPA function and increase higher catecholenergic activity, resulting in greater hypothalamic CRH release [23]. Beside it, Luong and Nguyễn found that anxiety patients had very

low thiamine levels, which were 25.06 nmol/L ± 6.0 nmol/L (normal value is 70 nmol/L-180 nmol/L) [28]. Thiamine will prevent the onset of HPA axis stimulation which plays a role in stimulating sympathetic. Excessive sympathetic stimulation can cause epinephrine and norepinephrine release and hypothalamic stimulation as a compensatory response through the activation of the HPA axis regulation [1, 26]. Thiamine works as a co-factor in all organ systems, especially nerve system cells. Thiamine pyrophosphate (TPP), which is an active form of thiamine, is a co-factor in two enzymes that mediate carbohydrate metabolism and pentose phosphate pathway so that it plays a role in producing adenosine triphosphate (ATP) molecules, which provide energy for various cellular processes and reactions. From this explanation it is seen that indirectly thiamine deficiency will reduce COMT activity [34]. This was proven in this study that patients with preoperative anxiety had very low levels of COMT [30, 31].

Other theories also support the statement 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 animal studies, where damage to ACh synthesis occurs in mice with thiamine deficiency [35–37]. Thiamine is able to bind to nicotinic receptors which are thought to play a role in inhibiting anticholinesterase activity, so thiamine administration also increases ACh synthesis. Patients with anxiety are shown to have low thiamine

levels, which have been shown to result in low ACh 17 synthesis and lead to the release of catecholamine [38]. High levels of catecholamine in anxiety will result in an increase in the autonomic nervous response [39]. The administration of thiamine actually plays a role in increasing levels of COMT responsible for the degradation of catecholamine into inactive metabolite compounds, namely norepinephrine, which is methylated by COMT to normetanepinephrine, epinephrine to methanephrine, and dopamine to homovanilic acid through a combination of actions of Monoamine oxidases (MAO) and COMT [40].

Table 3 shows the change in the decrease mean APAIS SUM C in the intervention group is greater than in the control group and strong negative correlation (Table 4). Anxiety study in patients with non-cardiac surgery by Kuzminskaitė et al. concluded that the average APAIS score for anxiety (SUM A) reached 11 and the median APAIS median score for information (SUM I) reached 6 [40]. Kampouroglou showed that anxiety was positively related to clinical pathology patients, and information needs [41]. The results of this study indicate that COMT enzyme levels that increase after administration of thiamine can reduce preoperative anxiety levels as evidenced by decreasing APAIS SUM C. Many studies have proven that COMT enzymes can play a role in anxiety through biochemical effects on the hippocampus is described as the first emotional circuit or papez circuit [42]. The role of the hippocampus in anxiety is also evidenced in human functional studies and imaging studies by Ploghaus et al. which uses Functional magnetic resonance imaging (fMRI) where increased activation of the hippocampal occurs during unexpected situations and conditions of fear, conditions of uncertainty that occur during anxiety [43]. The results of Hasler et al. [44] also prove that interventions that result in an increased role of COMT can in fact increase cerebral blood flow in the anterior hippocampus of humans during anxiety [44].

The basis for making APAIS by Moerman [24] is that an increase in preoperative anxiety is followed by an increase in information needs (APAIS SUM I), but this study cannot be demonstrated. We found that there was a weak positive correlation between changes in COMT enzyme levels and changes in APAIS SUM I (Table 4).

## 5. Conclusion

We believe that thiamine administration improves preoperative anxiety (APAIS value and COMT enzyme levels) in elective surgery patients with general anesthesia.

## 6. Acknowledgement

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Medicine, University Sumatera Utara, Indonesia.

## 7. Conflict of Interest

The authors declare that there is no conflict of interest.

## 8. Ethical Clearance

Taken from Adam Malik General Hospital Health Research Committee, 07/30/2019, No 619/TGL/ KEPK FK USU RSUP HAM/2019.

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