PHARMACOLOGY, MEDICAL REPORTS, ORTHOPEDIC, AND ILLNESS DETAILS
(COMORBID)
VOLUME 1 ISSUE 1 (2022)

CATECHOL-O-METHYLTRANSFERASE (COMT) ENZYME LEVELS IN PATIENTS WITH PREOPERATIVE ANXIETY

Akhyar Hamongan Nasution[1], Aznan Lelo[2]

[1] The Head of Department of Anesthesia and Intensive Care, Faculty of Medicine, University of Sumatera Utara, Medan 20155, Indonesia
[2] Professor on Department of Pharmacology & Therapeutics, Faculty of Medicine, University of Sumatera Utara, Medan 20155, Indonesia

E-mail: [1)] primadr212@gmail.com

Abstract

The preoperative anxiety's incidence is very high and mostly preoperative patients have anxiety. It was found that low COMT levels indicate a tendency to develop anxiety. Hence, this study aims to investigate COMT enzyme levels in patients with preoperative anxiety. This research is a purely experimental research with a pretest-posttest control group design and double-blind. Measurement of COMT enzyme levels was executed by utilizing ELISA technique. Blood samples were taken from preoperative anxiety patients who were assessed with the Amsterdam Preoperative Anxiety Information Scale (APAIS). The research was carried out at Haji Adam Malik General Hospital and Regional General Hospital dr. Pirngadi Medan, and Integrated Laboratory of the Faculty of Medicine, University of North Sumatra. The were 64 samples involved in this research that fit the inclusion and exclusion criteria. The findings show that COMT levels in the anxiety and control groups had differences with p values = 0.014. In addition, COMT levels in the preoperative anxiety group were lower when compared to those without the preoperative anxiety group, where in the anxiety group had COMT enzyme levels of 0,14 ± 0,08 ng/dl, while in the control group had higher COMT levels 0,96 ± 1,11 ng/dl. The results showed that patients with preoperative anxiety had lower levels of the COMT enzyme compared to patients without preoperative anxiety. Researchers suspect there is a role for the COMT enzyme in causing preoperative anxiety.

Keywords: *Preoperative anxiety, COMT enzyme levels, APAIS, Elective surgery*

1. INTRODUCTION

Anxiety is extremely common among individuals undergoing preoperative treatments. Preoperative anxiety affects approximately 82% of patients, with a higher percentage seen in patients getting general anesthesia compared to those undergoing regional anesthesia, and in female patients compared to male patients (Mitchell, 2013). In the preliminary study conducted at the Haji Adam Malik General Hospital (HAM) which involved 121 patients planned to undergo elective surgery, the preoperative anxiety, which was measured with APAIS score, and found to be very high, which was 48.3% (Tinambunan et al., 2019). Anxiety tends to cause preoperative complications, such as hypertension and tachycardia thus increasing the need for anesthesia and causing long recovery complications and more severe postoperative pain (Pohjavaara et al., 2003). Factors related to patients such as age,

sex, level of education and economic status, pain tolerance, history of previous operations, exposure to anesthesia, psychiatric problems, and social security can affect anxiety levels. Procedure-related factors such as major surgery, chronic illness, and unscheduled emergency procedures play an important role in the emergence of anxiety in preoperative patients. The attitude of health care providers, the communication skills of doctors, and the beliefs and opinions of patients also have an influence on the emergence of anxiety. In addition, information on preoperative anesthesia, adverse effects of anesthesia, and sudden surgery recommendations statistically have also been shown to be significantly related to overall anxiety increase (Celik & Edipoglu, 2018).

One previous study found that low COMT levels indicated a tendency for anxiety. COMT is the main enzyme needed for catecholamine metabolism/degradation. 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 (Mathew et al., 1980).

Anxiety also triggers the production of toxic dopamine metabolism so that influx Ca will increase into brain cells and ultimately increase tyrosine hydroxylase and reduce the production of ATP, which ultimately increases cortisol and ketekolamin release. High levels of circulating cortisol can result in mitochondrial dysfunction and apoptosis, which in turn decreases ATP production again, so it tends to create a vicious cycle (Biddiss et al., 2014; Dhir et al., 2019; Osiezagha et al., 2013; Pittman & Kridli, 2011). A study showed the important role of COMT in suppressing anxiety by decreasing catecholamines (Desbonnet et al., 2012). The role of catecholamines is disrupted in a number of medical conditions including anxiety so that some pharmaceutical drugs target COMT as a therapeutic target (Tunbridge, 2010; Ursini et al., 2011). This study aims to look at COMT enzyme levels in patients with preoperative anxiety.

2. RESEARCH METHOD

This research is a pure experimental research with a pretest-posttest control group design and double-blind. Measurement of COMT enzyme levels was done by ELISA technique. Blood samples were taken from patients with preoperative anxiety who were assessed with the Amsterdam Preoperative Anxiety Information Scale (APAIS) of 64 patients. The research was carried out at the Adam Malik Hajj General Hospital and the Regional General Hospital dr. Pirngadi Medan, and Integrated Laboratory of the Faculty of Medicine, University of North Sumatra. After obtaining permission from the USU / RSUP FK Ethics Research Committee. H. Adam Malik Medan, Head of Section / SMF Anesthesia and Intensive Therapy, FK USU / RSUP. H. Adam Malik Medan, Integrated Laboratory of USU's FK, and Regional General Hospital Pirngadi Medan conducted protocol preparations, filled out research forms and APAIS examinations to assess preoperative anxiety, tools and COMT serum examination materials. The sampling technique used is non probability sampling with consecutive sampling. Consecutive sampling is a sample selection technique by which all subjects who come and meet the selection criteria are included in the study until the number of required subjects is met.

Patients aged 19-60 years, surgery is planned under general anesthesia, APAIS SUM C score ≥11, ASA 1 and 2 physical status patients and patients willing to participate in the

study were included as the study inclusion criteria. Exclusion Criteria were Patients with mental problems and psychological, Ever consumed psychopharmaceutical, Alcohol consumption, History of head injury, Patients unable to communicate and fill out questionnaires independently, Patients with impaired kidney function, Patients with impaired liver and Patients with pregnancy and breastfeeding.

This study was approved by the ethics research committee in the field of health, Faculty of Medicine, University of North Sumatra with No. 619 / TGL / KEPK FK USU-RSUSU HAM / 2019, research permit for Medan Haji Adam Malik Hospital with No. LB.02.03 / .II.4 / 1770/2019, Pirngadi Regional General Hospital with No. 341 / B.LitBang / 2019, Mitra Medika General Hospital and Grand Medistra General Hospital and have received the patient's family's approval by signing an informed consent sheet.

2.1. Procedure

2.1.1. Preparation

After obtaining permission from the USU / RSUP FK Ethics Research Committee. H. Adam Malik Medan, Head of Section / SMF Anesthesia and Intensive Therapy, FK USU / RSUP. H. Adam Malik Medan, Integrated Laboratory of USU FK, and Pirngadi Regional General Hospital Medan, Mitra Medika General Hospital and Grand Medistra General Hospital conducted protocol preparations, filled in the research forms and examined APAIS SUM C and SUM I to assess preoperative anxieties and information needs, tools and materials for COMT serum examination.

2.1.2. Implementation

Patients registered for elective surgery under general anesthesia, who met the inclusion criteria, were asked to be subjects of the study. Patients were given an explanation of the study procedure and were asked to sign an agreement for participation in the study, three days before the operating schedule. Three days before the scheduled surgery in outpatient, patients were examined for anxiety using APAIS SUM C and SUM I APA scores, as well as blood collection for the COMT examination. Conduct data collection and analyze data with the help of software on the computer.

2.1.3. Statistic analysis

After all the necessary data has been collected, the data is then checked again for completeness before tabulation and processing. After that coding is given to the data to facilitate tabulation. Data is tabulated into the master table using computer software. Numerical data are displayed in mean values + SD (standard deviation) and median (minimum-maximum), while categorical data are displayed in numbers (percentages). The normality test uses the Kolmogorov-Smirnov normality test. The research hypothesis was tested using an independent t-test, Mann-Whitney and a Spearman correlation test was performed to see the strength of correlation between variables. A 95% confidence interval with a p value <0.05 was considered significant.

3. RESULT AND DISCUSSION

3.1. Result Research

There were 64 samples involved in this research that fit the inclusion and exclusion criteria. Sample characteristics are shown in Table 1.

Table 1 Sample Characteristic

Characteristic	Thiamine	Control	Total	p- value
Gender, n (%)				
Male	4 (30,8)	2 (33,3)	6 (31,6)	0,966[a]
Female	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[b]
Economic Status, n (%)				
Poor	12 (92,3)	6 (100)	18 (94,7)	0,323[b]
Prosperous	1 (7,7)	0 (0)	1 (5,3)	
Education Level, n (%)				
Bachelor Degree	2 (15,4)	1 (16,7)	3 (15,8)	0,467[b]
Senior High School	6 (46,2)	4 (66,7)	10 (52,6)	
Junior High School	2 (15,4)	1 (16,7)	3 (15,8)	
Elementary School	3 (23,1)	0 (0)	3 (15,8)	
Surgery History, n (%)				
Available	2 (15,4)	1 (16,7)	3 (15,8)	0,988[b]
Not Available	11 (84,6)	5 (83,3)	16 (84,2)	

Remarks : Mann-Whitney Test

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

3.1.1. COMT enzyme levels in patients with preoperative anxiety and not preoperative anxiety

Table 2 Effect of thiamine on COMT levels

COMT (ng/dl)	Anxiety	Not anxiety	p- value
Before			
Mean ± SD	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)	

Remarks : independent T-test; *Sig. α<0,05

Based on Table 2, it was found that COMT levels in the anxiety and control groups had differences with p values = 0.014. In addition, COMT levels in the preoperative anxiety group were lower when compared to those without a preoperative anxiety group, where in the anxiety group they had COMT enzyme levels of 0.14 ± 0.08 ng / dl, while in the control group they had a higher COMT value of 0, 96 ± 1.11 ng / dl. Figure 1 shows that patients who did not experience preoperative anxiety based on APAIS scores had higher COMT level values.

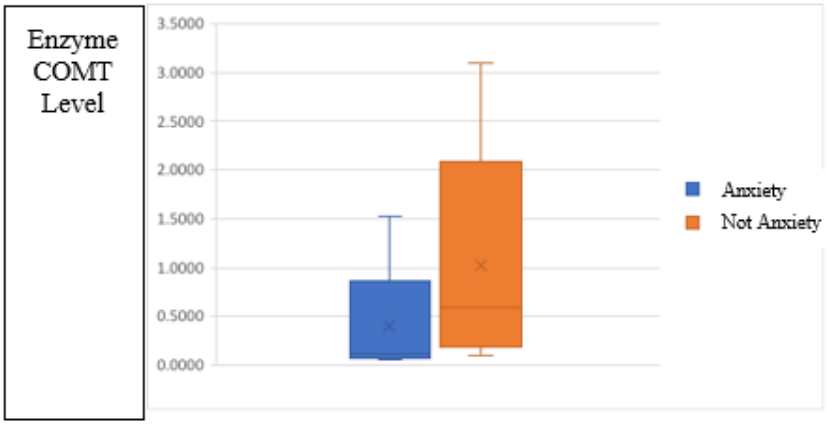

Figure 1 Comparison of COMT enzyme levels in patients with preoperative anxiety and not preoperative anxiety

3.2. Discussion

Based on the results of the study, it was concluded that COMT levels in the group with preoperative anxiety were lower compared to the group without preoperative anxiety. This shows that anxiety is caused by low COMT enzyme levels. In the research conducted by Lương and Nguyễn, it was found that patients with anxiety had very low levels of thiamine which was 25.06 nmol / L ± 6.0 nmol / L, so that it was thought to cause a decrease in APT production which could cause a decrease in COMT levels (Quoc Lu'o'ng & Nguyen, 2011). In the group with anxiety, sympatheticstimulation could occur. Excessive sympathetic stimulation can lead to the release of epinephrine and norepinephrine and hypothalamus simulation as a compensatory response through the activation of HPA axis regulation (Pearson et al., 2005; Pohjavaara et al., 2003). Thiamine works as a co-factor in all organ systems, especially nerve system cells. Decreased ATP production in the brain increases the production of toxic dopamine metabolism and decreases the work of COMT (Osiezagha et al., 2013). Barriers to COMT activity will result in disruption of HPA function and increase higher catecholeniergic activity, resulting in greater hypothalamic CRH release (Walder et al., 2010). From this explanation it is seen that decreased activity COMT also plays an important role in the emergence of preoperative anxiety. This was proven in this study, that patients with preoperative anxiety had very low levels of COMT (Vadhanan et al., 2017; Walder et al., 2010).

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 (Ruenwongsa & Pattanavibag, 1984). 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 catacolamine (Wilke & Hillard, 1994). High levels of ketecholamine in anxiety will result in an increase in autonomic nerve response. Thiamine actually plays a role in increasing levels of COMT responsible for the degradation

of ketololamin, which makes the inactive metabolite compounds, namely norepinephrine, methylated by COMT into normetanepinephrine, epinephrine to methanephrine, and dopamine to homovanilic acid through a combination of the actions of MAO and COMT (McGregor, 2014).

4. CONCLUSION

Patients with preoperative anxiety have lower COMT enzyme levels compared with patients without preoperative anxiety. Researchers suspect that the COMT enzyme plays a role in generating preoperative anxiety.

Conflict of Interest
The authors declare that there is no conflict of interest.

Source of Funding
This research is financed by independent financial from the researchers.

Ethical Clearance

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

REFERENCES

Biddiss, E., Knibbe, T. J., & McPherson, A. (2014). The effectiveness of interventions aimed at reducing anxiety in health care waiting spaces: a systematic review of randomized and nonrandomized trials. *Anesthesia & Analgesia*, *119*(2), 433–448.

Celik, F., & Edipoglu, I. S. (2018). Evaluation of preoperative anxiety and fear of anesthesia using APAIS score. *European Journal of Medical Research*, *23*(1), 1–10.

Desbonnet, L., Tighe, O., Karayiorgou, M., Gogos, J. A., Waddington, J. L., & O'Tuathaigh, C. M. P. (2012). Physiological and behavioural responsivity to stress and anxiogenic stimuli in COMT-deficient mice. *Behavioural Brain Research*, *228*(2), 351–358.

Dhir, S., Tarasenko, M., Napoli, E., & Giulivi, C. (2019). Neurological, psychiatric, and biochemical aspects of thiamine deficiency in children and adults. *Frontiers in Psychiatry*, *10*, 207.

Mathew, R. J., Ho, B. T., Kralik, P., Taylor, D., Semchuk, K., Weinman, M., & Claghorn, J. L. (1980). Catechol-O-methyltransferase and catecholamines in anxiety and relaxation. *Psychiatry Research*, *3*(1), 85–91.

McGregor, N. R. (2014). Catechol O-methyltransferase: a review of the gene and enzyme. *J Dent Clin Res*, *1*(007).

Mitchell, M. (2013). Anaesthesia type, gender and anxiety. *Journal of Perioperative Practice*, *23*(3), 41–47.

Osiezagha, K., Ali, S., Freeman, C., Barker, N. C., Jabeen, S., Maitra, S., Olagbemiro, Y., Richie, W., & Bailey, R. K. (2013). Thiamine deficiency and delirium. *Innovations in Clinical Neuroscience*, *10*(4), 26.

Pearson, S., Maddern, G. J., & Fitridge, R. (2005). The role of pre-operative state-anxiety in the determination of intra-operative neuroendocrine responses and recovery. *British Journal of Health Psychology*, *10*(2), 299–310.

Pittman, S., & Kridli, S. (2011). Music intervention and preoperative anxiety: an integrative review. *International Nursing Review*, *58*(2), 157–163.

Pohjavaara, P., Telaranta, T., & Väisänen, E. (2003). The role of the sympathetic nervous system in anxiety: is it possible to relieve anxiety with endoscopic sympathetic block? *Nordic Journal of Psychiatry*, *57*(1), 55–60.

Quoc Lu'o'ng, K. V., & Nguyen, L. T. H. (2011). The impact of thiamine treatment on generalized anxiety disorder. *International Journal of Clinical Medicine*, *2*(4), 439.

Ruenwongsa, P., & Pattanavibag, S. (1984). Impairment of acetylcholine synthesis in thiamine deficient rats developed by prolonged tea consumption. *Life Sciences*, *34*(4), 365–370.

Tinambunan, P. M., Nasution, A. H., & Tanjung, Q. F. (2019). Effects of Preoperative Visits on Anxiety Incidence among Elective Surgery Patients. *Int J Innov Sci Res Technol*, *4*, 60–64.

Tunbridge, E. M. (2010). The Catechol-O-Methyltransferase Gene. *In: International Review of Neurobiology*, 7–27.

Ursini, G., Bollati, V., Fazio, L., Porcelli, A., Iacovelli, L., Catalani, A., Sinibaldi, L., Gelao, B., Romano, R., & Rampino, A. (2011). Stress-related methylation of the catechol-O-methyltransferase Val158 allele pπredicts human prefrontal cognition and activity. *Journal of Neuroscience*, *31*(18), 6692–6698.

Vadhanan, P., Tripaty, D. K., & Balakrishnan, K. (2017). Pre-operative anxiety amongst patients in a tertiary care hospital in India-a prevalence study. *Journal of Society of Anesthesiologists of Nepal*, *4*(1), 5–10.

Walder, D. J., Trotman, H. D., Cubells, J. F., Brasfield, J., Tang, Y., & Walker, E. F. (2010). Catechol-O-Methyltransferase (COMT) modulation of cortisol secretion in psychiatrically at-risk and healthy adolescents. *Psychiatric Genetics*, *20*(4), 166.

Wilke, R. A., & Hillard, C. J. (1994). Decreased adrenal medullary catecholamine release in spontaneously diabetic BB-Wistar rats: role of hypoglycemia. *Diabetes*, *43*(5), 724–729.