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Research Article

Correlation between MMP-9 and COMT in Breast Cancer-Related Pain Patients with Using Morphine

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Abstract

Background: In cancer cells, it was found that dopamine and dopamine receptor expressions were increased. This will cause the reuptake of norepinephrine and other epinephrine to decrease so that the stimulus to the adrenoreceptors is prolonged. This condition triggers the release of MMP-9 and COMT.

Method: The study was conducted in April-December 2020 using observational study designs aimed to correlation between MMP- 9 and COMT in breast cancer-related pain patients with using morphine. 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.

Results: The correlation of COMT enzyme levels with MMP-9, in breast cancer patients is shown in Table 2. There was a moderate positive correlation between COMT levels and MMP-9 levels in breast cancer patients and it was significant (r=0.545; P=0.016).

Conclusion: In conclusion, the novel findings of our study were that there is a correlation of MMP-9 and COMT, which increasing MMP-9 followed by a level of level COMT in pain associated with breast cancer.

Keywords

Cancer Pain, COMT, Thiamine, Morphine

1. Introduction

Cancer pain is described as total pain, which is the suffering that encompasses all aspects of a cancer patient's life, including physical, psychological (depression), social (withdrawing from the social environment), economic, and spiritual, so that all this can cause a decrease in the patient's quality of life [1,2]. Based on the type of cancer, there are 6 types of cancer that most often cause cancer-related pain: head and neck cancer, prostate cancer, uterine cancer, genitourinary system cancer, breast cancer, and pancreatic cancer. [3].

Cancer-related pain should be well resolved by referring to the guidelines for treating cancer-related pain issued by WHO since 1986 and were claimed to be able to control cancer pain by 70-90% [4]. But the fact in daily clinical practice is that there are still cancer patients experiencing pain because of their cancer. There are more than 50% of cancer patients suffering from cancer-related pain [5]. In the meta-analysis study (more than 100 studies) cancer-related pain was found in 39.3% after curative treatment, 55% in cancer patients who were undergoing anti-cancer treatment, meanwhile, in patients with advanced cancer it was found 66.4%. Moderate to severe pain degrees were found in 38% of all cancer pain patients [6]. From the data in the United States, out of 4526 cancer patients alive, there are 1648 (34.6%) people experiencing chronic cancer-related pain and 768 people (16.1%) who experience a decrease in quality of life due to this pain (Jiang et al., 2019).

In cancer cells, it was found that dopamine and dopamine receptor expressions were increased [7]. This will cause the reuptake of norepinephrine and other epinephrine to decrease so that the stimulus to the adrenoreceptors is prolonged. This condition triggers the release of MMP-9, MMP-2 and decreased tissue inhibitor of metalloproteinase (TIMP) (MMP inhibitor) [8,9].

The relationship between adrenoreceptors and MMP-9 can be seen from an experiment with cultured NPC (*Nasopharing Carcinoma*) tumor cells given norepinephrine and epinephrine. The result showed that MMP-9 was increased in these cells [10]. The same thing was seen in human colon adenocarcinoma HT-29 cells given norepinephrine and epinephrine [11].

MMP-9 has also been found to be "up-regulated" in cancer patients. This increase was found in Giant Cell Tumors of Bone (GCTB), Non-Small Cell Lung Cancer (NSCLC), cervical cancer, pancreatic cancer, osteosarcoma, breast cancer, papillary thyroid cancer, gastric cancer, and prostate cancer [12-14].

2. Methods

The study was conducted in April-December 2020 using observational study designs aimed to correlation between mmp-9 and comt in breast cancer-related pain patients with using morphine

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 MMP-9 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%).

The correlation of COMT enzyme levels with MMP-9, MMP-2, VAS scores in breast cancer patients is shown in Table 2. There was a moderate positive correlation between COMT levels and MMP-9 levels in breast cancer patients and it was significant ($r=0.545$; $P=0.016$). It means that the higher the COMT enzyme level, the greater the MMP-9 enzyme level. However, the correlation between COMT enzyme and MMP-2 levels showed a moderate and insignificant positive correlation. The results of this study also reported a correlation between COMT and VAS scores which also obtained a moderate, but not significant, correlation. Meanwhile, the correlation between the COMT enzyme and serum thiamine levels was negative and insignificant (Table 2).

4. Discussion

In cancer cells, it was found that dopamine and dopamine receptor expressions were increased [7]. This will cause the reuptake of norepinephrine and other epinephrine to decrease so that the stimulus to the adrenoreceptors is prolonged. This condition triggers the release of MMP-9, MMP-2 and decreased tissue inhibitor of metalloproteinase (TIMP) (MMP inhibitor) [8,9].

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The MMP-9 that appears will activate macroglia resulting in degradation of the extracellular matrix of nerve cells. This is the precursor to neuropathic pain in cancer patients. After degradation, nerve cells undergo upregulation of sodium channels, causing hyperpolarization of nerve cells and leading to peripheral sensitization, central sensitization, and nerve cell plasticity characterized by neuropathic symptoms of hyperalgesia and allodynia [15-17]. The events of peripheral sensitization, central sensitization, and plasticity processes are not only mediated by MMP-9 but also mediated by MMP-2 [9,18,19].

MMP-2 will appear in the final phase of nerve tissue damage. The results of 13 studies reviewed by Zhang et al. 2011 found that mean MMP-9 levels would increase after nerve injury at 12 to 24 hours. Then followed by MMP-2 levels which would increase on day 5 after nerve injury [20].

The excretion of MMP-9 and MMP-2 would cause activation of *prointerleukin* 1-β (inactive) to *interleukin* 1-β (active) and this will cause nerve cell hyperexcitability and this is the beginning of neuropathic pain [15].

From the information regarding MMP-9 and MMP-2, it can be concluded that MMP-9 and MMP-2 are important factors in the occurrence of pain symptoms that might be prevented by giving thiamine. According to the study on the animal, thiamine can prevent symptoms of neuropathic pain while increasing inhibition of TNF-α and IL-6 [21]. In addition, thiamine also has an anti-pain effect when used as a single drug even though its effect is still observed at the level of the experimental study on the animal, besides thiamine when combined with other painkillers such as NSAIDs and glucocorticoids, can increase the antinociceptive and anti-inflammatory action of these drugs so that the anti-pain effect of the drug will increase [22]. Meanwhile, thiamine administration will also increase the formation of ATP at the cellular level so that there is an increase in activity and COMT levels in the plasma [23,24]. The results of the literature review found that the use of single thiamine in clinical practice is only limited to case reports such as cases of fibromyalgia [25], and cluster headaches [26], even with varying doses. The use of thiamine for cancer pain has not been widely found, including the dosage, duration of use and side effects.

5. Conclusion

In conclusion, the novel findings of our study were that there is a correlation of MMP-9 and COMT, which increasing MMP-9 followed by a level of level COMT in pain associated with breast cancer.

6. Acknowledgement

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7. Conflict of Interest

The authors declare that there is no conflict of interest.

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: Levels of COMT and MMP-9 before morphine administration.

Characteristics	Serum Level (n=9)
COMT enzyme levels (ng/ml)	0,11 ± 0,04
MMP-9 enzyme levels (ng/ml)	2227,6±396,1

Table 3: The Relation between COM*T* Enzyme Levels and MMP-9 in Breast Cancer Patients.

COMT	Breast Cancer Patients (n=19)	
	r	P
MMP-9	0,545*	0,016

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