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The Value of Comprehensive Nursing Intervention on Anxiety in Patients with Acute Heart Failure and Diabetes via Expression of Stress-related Genes

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ABSTRACT

Many patients with acute heart failure and diabetes experience varying degrees of anxiety upon entering the cardiac intensive care unit, which has adverse effects on the recovery process of these patients. Anxiety syndrome in these patients increases the risk of death up to three times. This study aimed to determine the effect of comprehensive nursing intervention on anxiety in patients with acute heart failure and diabetes by evaluating the expression of stress-related genes, i.e. COMT and BDNF genes. In this clinical trial study, 74 patients with acute heart failure and diabetes hospitalized in the cardiac intensive care unit were selected by convenience sampling method and randomly assigned to intervention and control groups. The control group received routine ward care, and the intervention group received nursing support program-based interventions in three informational, emotional, and physical dimensions in addition to regular care. Beck Anxiety Inventory was completed before and after the intervention in both groups. The expression of COMT and BDNF genes was evaluated by the qRT-PCR technique. Data were analyzed by Mann-Whitney U and independent T-test in SPSS software version 16. Before the intervention, no significant difference was observed between patients' anxiety scores in the intervention and control groups ($p = 0.162$). While, after the intervention, the anxiety score of the intervention group was lower than the control group ($p = 0.02$). The expression of COMT gene results showed that this gene expression was no statistical difference between the control group and intervention group, before intervention ($p = 0.83$). But, after the intervention, the expression of this gene was statistically decreased in the intervention group in comparison with the control group ($p = 0.006$). The BDNF gene expression results demonstrated that there was no difference between the two groups, before intervention ($p = 0.46$). After intervention, statistical increase was observed in control group ($p = 0.042$) and intervention group ($p = 0.007$). According to the results of this study, the comprehensive nursing intervention reduced patients' anxiety in the intervention group compared to the control group. This result was also confirmed by evaluating the expression of stress-related genes. Therefore, it is suggested that this intervention method be used to reduce anxiety in these patients.

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Introduction

Diabetes is a disease that can increase coronary artery disease, heart failure, and acute myocardial infarction and lead to hospitalization of these patients (1). Acute heart failure and deterioration in the intensive care unit cause psychological reactions such as denial, anger, frustration, guilt, stress, anxiety, and depression in patients (2). Hospitalization in a stressful environment due to the presence of complex and noisy devices, alienation of the environment, lack of knowledge about the disease process, fear of the future and problems that may occur in the future for the patient, resuscitation, mortality of other patients, dealing with nurses, sleep disturbances, etc. are all considered as stressors that play a role in creating patients' anxiety (3). Studies over 20 years have also shown that anxiety is a risk factor for fatal cardiovascular complications, such as sudden cardiac death (4).

Anxiety is an unpleasant condition that manifests itself with feelings of worry and stress, activation of the autonomic nervous system, and fatigue, muscle weakness, palpitations, chest pain, and headache, sweating and sweating (5). Increased activity of the sympathetic nerves following anxiety also increases the reactivity of the veins, increases heart rate and blood pressure, and ultimately causes intra-tissue damage and platelet aggregation (6). Therefore,

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relieving the patient's anxiety and fear as a nursing action reduces the sympathetic stress response. Decreased sympathetic stimulation reduces cardiac output and relieves the signs and symptoms of ischemia (7).

Establishing a safe and caring relationship with the patient seems to play a unique role in reducing anxiety (5). Effective therapeutic communication with the patient and the provision of support programs can be very effective (8). This program includes providing information to the patient and encouraging them to express their feelings, examining the patient's negative beliefs and fears, explaining group therapy members' responsibilities, answering the patient's questions, and providing physical care (9). Also, having support enables a person to deal with pain and sorrow. Increasing support improves physical condition, reduces anxiety, and improves adaptation and patients' adaptive behaviors (10).

In dealing with a patient with acute heart failure and diabetes, most physicians seek treatment and reduce patients' anxiety by using medications (11). However, side effects of anxiety medications include cardiac dysrhythmias, sudden death, and the risk of drug dependence. The high cost of the drug and the time it takes to start working also should add to these problems. At present, less attention is paid to nursing support in the treatment of patient anxiety (12).

Anxiety impacts the expression of stress-related genes (13). COMT (Catechol-O-Methyltransferase) and BDNF (Brain-Derived Neurotrophic Factor) genes are the most critical stress-related genes that their expression changes during anxiety and stress (14, 15). The COMT gene provides instructions for making an enzyme called catechol-O-methyltransferase (16). COMT is also associated with higher levels of cortisol dysfunction and the HPA axis (which is mainly responsible for the body's ability to calm itself and relieve stress) (14). BDNF is a member of the neurotrophin family that supports neurons' survival, growth, and differentiation by acting on major central and peripheral nervous systems. On the other hand, it has been found that there is a direct relationship between BDNF gene polymorphism and the risk of depression and even patients' response to treatment (17). BDNF protein levels in the hippocampus are reduced in people with depression. Also, researches showed that stress could reduce the BDNF levels (15).

According to above, this study aimed to evaluate the value of comprehensive nursing intervention on anxiety in patients with acute heart failure and diabetes via expression of stress-related genes.

Materials and methods

Study population

The present study is a clinical trial study. The statistical population of this study was patients with acute heart failure and diabetes admitted to the cardiac intensive care unit. The study sample was 74 patients referred to the cardiac intensive care unit selected using the convenience sampling method. The sample size was determined so that the study had the necessary power to detect a difference of at least five units of anxiety between the intervention and control groups. Using G-power software version 3.1, assuming the probability of the first type error is 5%. The likelihood of the second type error is 20%. The standard deviation was considered 8.06 for the intervention group and 5.31 for the control group. The sample size obtained 31 for each group with a 20% probability of falling; the sample size increased to 37 individuals.

$$n = \frac{(s_1^2 + s_2)^2 (z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2}{(\bar{x}_1 - \bar{x}_2)^2} =$$

$$n = \frac{(8.06^2 + 5.31^2)(1.96 + 0.86)^2}{(4.81)^2} = 32$$

$$n = 32$$

$$64 \times 0.15 = 9.6 \Rightarrow 64 + 9.6 \cong 74 \Rightarrow n_1 = n_2 = 37$$

Inclusion criteria included: willingness to participate in research, diagnosis of acute heart failure and diabetes based on clinical signs, ECG, and a cardiologist's opinion, age between 30-80 years, full consciousness, and ability to answer questions. Exclusion criteria: Severe changes in the level of consciousness, mental illness, severe physical disability, anemia, cancer, incurable diseases, communication problems, cardiopulmonary resuscitation. Exclusion criteria were also the cancellation of continuing to participate in the study for any reason, decreased level of consciousness, or the patient's death during the study.

The samples were randomly divided into control and intervention groups by permutation blocks (4 blocks). The four blocks were considered code 1 for the intervention group and code 2 for the control group. In each block, two codes, one and two codes two were placed non-repetitively. The blocks were randomly selected with their eyes closed, and each block was randomly selected after use, and the next block was re-selected. With each block, the order of entry of individuals into the intervention or control group was determined. Assuming block 1221, the first and fourth persons entered the intervention group and the second and third persons joined the control group.

Data collection tools

Data collection tools were a personal information questionnaire (including age, gender, education, occupation, place of residence, hospitalization history) and Beck Anxiety Inventory (BAI). The Beck Anxiety Inventory is a standard questionnaire used in multiple studies. In the present study, its reliability was confirmed with Cronbach's alpha coefficient of 0.88. First, based on the willingness to participate in the study and having the inclusion criteria, after obtaining written consent, the BAI was completed at the time of admission to the cardiac intensive care unit, and those with mild, moderate, and high anxiety (score >8) entered the study. The personal information questionnaire was also completed for both groups at the beginning of the study.

Comprehensive nursing intervention

Comprehensive nursing intervention for the intervention group begins at the beginning of hospitalization. In this way, the subjects in the intervention group received a supportive care program every morning (between 8 and 10 o'clock) in the first three days of hospitalization in addition to the usual care. The supportive care program was informational, emotional, and physical in three dimensions, including:

A. Information dimension: Introducing the caregiver to the patient and getting to know him/her, initial assessment of the patient's specific needs (diet, activity, return to work), answering the patient's possible questions at a later stage, explaining the responsibilities of the members of the treatment team and the support system in the hospital, provide simple educational materials about the CCU patient and the care he needs, and related safety tips.

B. Emotional dimension: Encouraging the patient to express feelings, examining the patient's negative beliefs and fears, supporting the patient to make decisions about treatment measures

C. Physical dimension: Physical care of patients such as proper intravenous administration, oxygen therapy, bladder emptying, fasting, sampling for tests, attention to the patient in terms of injuries

It should be noted that the support program was prepared based on patient needs assessment and its scientific content by reviewing reference and valid scientific texts. The duration of the support program according to the patient's needs was a maximum of one hour. The length of time spent in the intensive care unit was at least three days if there was no problem. The control group received only routine care.

Evaluation of COMT and BDNF genes expression

After providing 5ml of peripheral blood from all participants before and after the intervention, total mRNA was extracted by Rneasy FFPE Kit (50) (Cat. no: Q73504, Qiagen, Singapore). Prime Script RT Reagent Kit (Clontech, Takara) was used to synthesize cDNA. The instructions for this kit consisted of two steps. The first step was to add PrimeScriptTM RT Enzyme Mix I, Reaction buffer (5X), 100µl of Random Hexamer and the second step was incubation in a thermocycler at 37°C for 30 minutes, then at 85°C for 5 minutes. The product was then stored at -20°C. Primer design according to COMT and BDNF human cDNA sequences was performed using Gene runner software and National Center for Biotechnology Information (NCBI) site. The properties of primers are listed in Table 1. GAPDH was used as intra-standard control.

Gene expression levels were measured by qRT-PCR and Rotor-gene 6000 Thermocycler (Qiagen, Hilden, Germany). Reactions for COMT and BDNF genes in a volume of 10µl including 5µl of SYBR Premix Ex Taq II (Tli RNase H Plus)(2X)(Takara, Clontech), 0.2µl of forward primer, 0.2µl of reverse primer, 1µl cDNA, and 3.6µl Nuclease Free water. Temperatures were performed at the following:

Initial denaturation of 95°C for 5 minutes, 35 amplification cycles including denaturation at 95°C

for 40 s, binding at 60°C for 40 s and 40°C at 72°C for 40 s. Annealing and Melting were performed at 77-95°C. Relative quantification of expression was performed by the $2^{-\Delta\Delta CT}$ method.

Table 1. The properties of primers for COMT, BDNF, and GAPDH

Gene	Accession No.		Primer Sequence (5'-3')	Product Length	Annealing Temp.
COMT	L43122	Forward	GGATTTCGCTGGCGTGAAG	306bp	77°C
		Reverse	TCCACCACCTCCCTGTATTCC		
BDNF	EU 363494	Forward	GTTAGAGAGACTGGATTTAAG	170bP	95°C
		Reverse	TGGAACAGGCTGCTTTCAGTG		
GAPDH	NM_008084_2	Forward	ATTCAACGGCACAGTCAAGG	213bp	83°C
		Reverse	GCAGAAGGGGCGGAGATGA		

Statistical analysis

After completing and collecting the questionnaires, the data were analyzed by SPSS software version 16. In addition to descriptive statistics, including mean and standard deviation, T-test or Mann-Whitney U test were used depending on whether the distribution of variables was normal or not (Kolmogorov-Smirnov test). The significance level in this study was considered $p < 0.05$.

Results and discussion

The mean and standard deviation of age of the samples were 59.02±12.30 years in the intervention group and 59.02±11.08 in the control group. Independent t-test showed that the mean of the age variable was the same in the two groups of intervention and control ($p = 0.35$). The results also showed that the two groups in terms of gender variables ($p = 0.63$), education ($p = 0.55$), marital status ($p = 0.80$), employment status ($p = 0.47$), place of residence ($p = 0.83$), and hospitalization history ($p = 0.25$) were identical.

Regarding the main variable of the study, i.e. comparing the changes of anxiety score before and after the intervention in the two groups of intervention and control, the results of the Mann-Whitney U test showed that the anxiety score was not statistically different in both groups before and after the intervention ($p = 0.162$). However, the decrease in anxiety score after the intervention was statistically significant in the intervention group compared to the control group ($p = 0.023$) (Table 2).

To compare the level of anxiety after the intervention, linear regression was used to control the confounding variables and keep their effect constant. Post-intervention anxiety was studied in two groups with stable retention of disturbing variables (pre-intervention anxiety, education, occupation, location) (Table 3). The results of regression test analysis showed that despite keeping the effect of anxiety constant before the intervention and other confounding variables for the intervention, the amount of anxiety decreased by three units ($P = 0.039$).

Table 2. Median and Interquartile range of anxiety score for intervention and control groups

Anxiety	Intervention	Control	Mann-Whitney U Result
	Median ± IQR	Median ± IQR	P-value
Before Intervention	18.5 (10-32.5)	14 (7-26)	0.162
After Intervention	1 (0-5)	2 (0-8)	0.023

Table 3. Evaluation of the effectiveness of the intervention on anxiety: Multiple linear regression analysis

Anxiety	Assurance distance (95%)	Coefficients (β)	P-value
	-6.44 – 0.17	-3.30	0.039

The expression of COMT gene results showed that this gene expression was not statistically different between the control and intervention groups, before intervention ($p = 0.83$). But, after the intervention, the expression of this gene was statistically decreased in the intervention group in comparison with the control group ($p = 0.006$). The BDNF gene expression results demonstrated that there was no difference between the two groups, before intervention ($p = 0.46$). After intervention, statistical increase was observed in control group ($p = 0.042$) and intervention group ($p = 0.007$) (Figure 1).

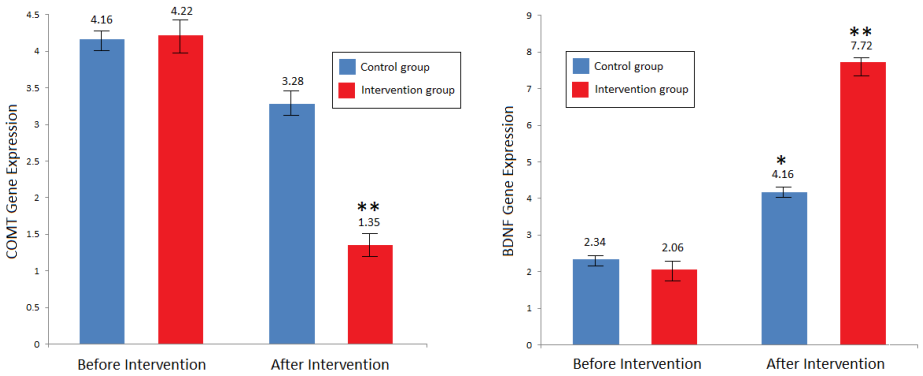

Figure 1. COMT and BDNF genes expression before and after of intervention in both control and intervention groups; *: p <0.05 and **: p <0.01

This study showed that after the comprehensive nursing intervention, a statistically significant difference was observed between patients' anxiety scores in the intervention and control groups. So that the score of the intervention group has decreased compared to the control group, this means that by providing this intervention to patients with acute heart failure and diabetes, the level of anxiety is reduced. Also, the expression of COMT and BDNF genes results proved it.

These results are consistent with the research of Ebrahimi *et al*. (18), who examined the effect of comprehensive nursing intervention on reducing the anxiety of patients receiving an electric shock. The program presented in their study, which is overlapped with the information and physical support of the present study, in addition to reducing physical complications, also has a practical effect on psychological difficulties and has reduced patients' anxiety. Also, Leung *et al.* (19) showed that the support program had a significant effect on reducing the psychological symptoms of the elderly. Their research demonstrated that emotional support is more important than instrumental support for reducing psychological symptoms.

A study by Rezaei *et al*. (20), which examined the effects of a comprehensive nursing intervention on anxiety and stress of family members of patients undergoing cardiac surgery in intensive care, showed that intervention was effective on the intervention group than the control group. The level of anxiety in both groups decreased after the intervention, and only a statistically significant difference between the two groups was observed two hours after admission to the intensive care unit. There was no statistically significant difference between the two groups on the second day of hospitalization and the third day of hospitalization. These differences can be due to the nature of the disease, receiving regular information from the control group, not having a phone call during the hours required by caregivers, not maintaining constant contact with family, and even measuring anxiety.

A study by Jahangirpour *et al*. (21) examined the effect of mindfulness training on reducing depression, hostility, and anxiety in people with coronary heart disease showed that there was anxiety between the two groups in the post-test anxiety scores. This study is also consistent with the present study, which in the informational dimension, gives teachings to patients to express emotions, examine and control negative beliefs and fears. Coinciding with the present study, the findings of Kumakech *et al* study (22)showed that comprehensive nursing intervention reduces social and psychological distress, especially the symptoms of depression, stress, anxiety, and anger in the affected group. This study also suggests the use of a support program for the mental and physical symptoms of other patients.

The results of Mohr *et al*.'s study (23) showed that the comprehensive nursing intervention did not increase the physical and mental health of patients with multiple sclerosis, which does not agree with the present study results. In the study of Watkins *et al*. (24), Anxiety has also been mentioned as an essential factor in the death of cardiovascular patients. Therefore, by cutting this ring, a big step can be taken towards the faster recovery of heart patients and reducing mortality in these patients.

Considering the effect of comprehensive nursing intervention on reducing anxiety in patients with acute heart failure and diabetes, developing a supportive care plan is necessary. Since nurses spend more time with patients in the intensive care unit, with proper planning and appropriate and standard support, they can play an essential role in meeting the needs of these patients in the information, physical and physical dimensions. Officials can also provide training and care for patients with acute heart failure and diabetes by providing training courses for nursing staff.

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Interest conflict

None.

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