Asian Journal of Health Psychology
2017, Vol. 1, No. 1, p. 19-28 (Spring and Summer)

Received: 2/3/2016
Accepted: 4/3/2016

The Effect of Coping Therapy on Immunological Indicators in Patients with Coronary Heart Disease

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Abstract

Objective: The studies since the second half of the 20th century have revealed the effect of stress on the heart and vessels with mediating neurological indicators and techniques of dysfunctional coping techniques. They also have shown that stress management and the improvement of coping techniques improve the indicators. The present study examined the appraisal of the effect of coping-therapy on cortisol, Interleukin 6 (IL-6) and Interleukin 1β (IL-1β) in comparison with the control group. **Method:** The study was a quasi-experimental research with pre-test andpost-test design conducted on 44 patients (randomly assigned into two experimental and control groups) suffering from coronary heart disease who were hospitalized in ShahidRajaei Heart Hospital in Tehran. The experimental group was treated with coping-therapy, and the immunological indicators of both groups were measured using ELISA at the beginning, the fourth,the eighth, (immediately after the end of treatment), the tenth, and the fourteenth weeks. The collected data were analyzed using repeated measures ANOVA by SPSS. The gender and education of the sample was controlled statistically. **Results:** The results revealed that coping-therapy could significantly decrease cortisol from 4.693 to 2.519, IL-6 from 8.315 to 4.226, IL-1β from 2.759 to 1.850 from the PreTest to the end of the fourteenth week (follow-up). **Conclusion:** Considering the cognitive limitations of the present study, one can conclude that coping-therapy may decrease the negative effects of stress on immunological indicators through improving dysfunctional techniques to effective ones, and in this way, reveal the positive effects on health.

Keywords: Coping-Therapy, Immunologic, Cortisol, Interleukin, Coronary Heart Disease

Introduction

Developing research in recent years reveal that stress and socio-mental tensions are the age and gender independent factors as well as other classic physical risk factors of heart diseases that increase the cardiovascular responses through psycho-neuro-physiological mechanisms and the activation of the neural system, specially the sympathetic section that results in or keeps on cardiovascular diseases (Atkinson RL, 2000; Schwartz AR, 2003). The data supporting this relationship has been developing since the second half of the 20th century (Brammer L.M., 1993; Glozier N, 2013; Rozanski A, 1999; Saner, 2005; Steptoe A, 2012). Some studies have also been conducted on the mechanisms of stress on the immunity system and have revealed that the function of the system might be affected by stress (Segerstrom, 2004). In fact, stress influences the

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cardiovascular system in two ways: increasing the secretion of catecholamine, and increasing the secretion of corticosteroids that in long term harms the heart and vessels (Brammer LM, 1993)

Studies show that cortisol, Interleukin 6 (IL-6), and Interleukin 1β (IL-1β)are among the most significant mediators of stress (Lakhan, 2006; Rozanski A, 1999) with their density after stress (H. M. Steptoe A, Chida Y, 2007; Yamakawa K, 2009). Rohleder et al. found that stress plays a significant role in increasing the density of interleukin1β plasma levels (Rohleder N, 2006). Brydonet al. have revealed the seminal role of cytokine interleukin1β in the emergence of cardiovascular diseases (Brydon L, 2005). Qureshi et al. have emphasized on the role of stress on serum levels of cortisol (Qureshi GM, 2009). Von Kanel et al. in a study on 21 subjects with the mean age of 46.7, revealed that cute stress could cause a significant increase in interleukin 6 plasma levels that might cause the worsening of heart Coronary Heart Disease (CHD) and finally arteriosclerosis (Von Känel, 2006).

The studies on the relationship between stress and coping therapy with cortisol, interleukin 6, and interleukin1β have indicated that dysfunctional coping with stress might increase the cortisol and interleukin1β plasma levels. However, effective coping might decrease the cortisol and interleukin1β plasma levels by decreasing stress (Bayer U, 2010; Damsa, 1988). Other studies have revealed that the patients suffering from coronary vessel disorders make more use of dysfunctional techniques of coping with stress in comparison with healthy persons (Chiou A, 1997; Sarafino, 2002). The application of effective and dysfunctional coping techniques might bring up different consequences in health(Sarafino, 2002).

Dimesdale in a research on cognitive stress and its effect on cardiovascular diseases found that learning to control stress might decrease the risk of attacks and increase the function of ventricle muscles in coronary patients(Dimsdale, 2008). Linden, Melanie, and Leclerc in an analysis of 9856 heart patients came to the conclusion that psychotherapy can simultaneously decrease the death rate among the patients. They believe that psychological intervention is often a part of rehabilitation of heart patients(Linden, 2007). Using meta-analysis methodology, Shapiro in a study on explaining the correlation between the psychological reasons and the blockage of the coronary vessels, analyzed the results of 23 research done using random clinical trial. The results revealed the important role of stress in heart attacks. Also, the results from the comparison of 2024 heart patient group with the control group confirmed that psychological interventions and training to control stress significantly resulted in decrease of emotional disturbances, systolic hypertension, cardiac arrhythmia, and decrease of blood cholesterol in comparison with the patients who had not received such interventions. Patients under two years follow-up revealed that the rate of death among the persons who had not received psychological services had increased significantly (Shapiro, 2011). Aghayousefi et al. in a study examined the effect of coping-therapy on the hopelessness of infertile women. Their results revealed that coping-therapy decreased hopelessness, negative attitude toward the future, pessimism, lack of planning for the future, and failure expectancy in infertile women, but the results showed no significant effect on instability in thinking (Aghayousefi, A; Zare, H; Choobsaz, F & Motiei, G., 2011). In addition, Aghayousefi and Zare in a study on 100 female patients suffering from cardiovascular disorders, aged 35-55, examined the effect of coping-therapy on stress reduction of women suffering from cardiovascular disorders. The results indicated that the total scores of stress and stress originated in conflict and inner-family problems in the experimental group had decreased significantly. Their results showed that coping-therapy might, in long term, decrease the amount

of stress in worsening these disorders in women suffering from coronary diseases (Aghayousefi, A; Zare H, 2009).

Objective of the Study

Considering the effect of stress and dysfunctional coping on the immunity system and its effect on health and specially the cardiovascular system, the purpose of the present study is to examine the effect of a psychological technique founded on improving the dysfunctional coping methods on the decrease of the cortisol and interleukin1β plasma levels.

Method

Participants

The population of the study consisted of Coronary Heart Disease (CHD) patients hospitalized in ShahidRajaei Heart Hospital in Tehran. Forty four volunteer CHD patients in the women internal ward, men internal ward, and private wards, whose coronary artery blockage (at least 90 percent in one main artery) was confirmed by angiography, were selected for the study. There were equal men and women in the sample. They divided in two equal groups with equal male and female patients. The age of sample was 45 and above. The requirement for the patients to participate in the study was their content and having no critical disease but CHD. The public and private wards of the hospital paved the way for participants from different socio-economic status to take part in the study. Information such as the disease period, hospitalization period, the degree of the blockage of their arteries, and other information were extracted from their medicine profile. The sample size was selected based on previous studies (Brenner K, 2011; Rohleder N, 2006; Roy, 2004; Steptoe A, &Chida Y, 2007).

Ethical issues

To observe the ethical issues, patients' content, observation of their rights and freedom in the research, protecting against risks and dangers, confidentiality by the researchers, proper use of data, making patients aware of all tests conducted on them considering the dignity of patients, and the legal and ethical issues were considered in a written content letter. In addition, the researchers answered all questions by the patients and explained them that they might randomly be assigned into one of the experimental or control groups. After the end of the study, the intervention of experimental group was done for the volunteers in the control group. Furthermore, the performer of the intervention had passed the training sessions for coping-therapy and was qualified for the task.

Measures

Human IL-1βand IL-6 kits (made in Austria by Bender Med System) and cortisol (made in Germany by IBL manufacturing co.) with ELISA measuring technique that was used in other research (Bayer U, 2010) were applied in the present study. The method of measuring IL-1βand IL-6 were the use of Sandwich ELISA and the use of micro plates covered with monoclonal antibody against IL-1β and IL-6. To measure IL-1β, For example, first, 50 μL of the serum of each patient was added to each Cap with 50 ml sample diluents. Then from the standard, we made serial dilutions and added them to the related Caps. 50ml of monoclonal anti IL-1β that was conjugated with biotin was added to all Caps. After 2 hours incubation in the room temperature and on the rotator and 3 times washing, 100 ml streptavidin-HRP was added to all Caps. After 1 hour incubation in the room temperature and 4 times washing, 100 ml of the TMB substrate solution was poured into the Caps. After 10 minutes reaction with the solution, the stopping ceasedand the content of plates were read by ELISA reader in 450nm wave length. After drawing the normal curve, the density of IL-1β per pg/ml was calculated based on the curve. In this research, to increase the accuracy and to control the quality, each sample was repeated several times.

To measure the amount of blood serum

Table 1. Coping-therapy protocol

Session on intervention	Activity content	Homework
1	Definition of stress, its effect on health, introducing strategies to cope with stress and proper situations to use them in stressful contexts, discussion	Taking notes of the most stressful events in the last week and the actions done to reduce stress
2	Stating the experienced stress in the last week and reactions to these stress issues, more adaptable and effective coping methods that might be more useful	Using the practiced techniques in the session and rewriting of the stressful events in the week, appraisals and practice to use more effective methods and writing down for next session
3	Reporting the result of using new coping methods in appraisal of experienced stressful events during the week, the experiences emotions after the changes in behavior, more effective methods that might be used in the similar situations	Using the practiced methods in sessions and rewriting stressful events of the week, evaluating and practice for using effective coping methods and writing down for next session
4 to 8	Stating the stressful events of the last week, first and secondary appraisals, evaluating the degree of adaptability of new coping methods, emotions experienced, more effective coping methods that might have been used	Using the methods practiced in the session and rewriting of stressful events in the week, evaluating and practice to use effective methods and writing them down for next session

cortisol using ELISA in each of the Caps, ELISA streptavidin was coated. To the Caps, first, the patient's serum with the amount mentioned in the kit and then, monoclonal antibody against cortisol were added. In the case of existence of cortisol in serum, the cortisol makes a mixture that its antigen bonds with conjugated antibody and enzyme from one hand, and the antibody marked with biotin on the other hand. This combination through the biotin connected to the antibody links with the streptavidin in the bottom of the Cap. In the next phase, after finishing the incubation time and 3 times washing, substrate was added to the Caps. The substrate contains 2 A substrate that were tetramethylbenzidine and B substrate that is hydrogen peroxide (H2O2) both of which were mixed equally prior to consumption. The substrate was influenced by enzyme during the incubation period and produced a color that was read in 450 nm wave length.

Intervention methods

Coping-therapy technique is used as a method to modify effective coping skills. The technique has been founded by Aghayousefi (AghaYousefi, 2001) based on type and strength of stress and individual's coping methods using Lazarus-Folkman's(Lazarus, 1984) transactional stress theory. In this type of intervention, the therapy sessions can be individual or team-based. In the group sessions, the general principles of group therapy sessions should be observed. The time for individual sessions is 45 minutes in average, and for groups the time is 2-3 hours. These sessions are except interview and even pre- and post-test sessions(Aghayousefi, A; Zare H, 2009). In this study, the coping-therapy sessions were 8 individual sessions, one session per week, and each session 1 hour.

Research design and data analysis

Since the major sample was selected non-randomly and the subcategories were selected randomly, the study was a quasi-experimental one with pre and post-tests with control group. The biomarkers of cortisol and interleukin1β were measured at the beginning, the fourth session of intervention, the eighth session, the post-test session (2 weeks after the eighth session), and the follow-up session (four weeks after the post-test) following 12 hours fasting period.

To test the research hypothesis, repeated measures ANOVA was run using SPSS 17.

Results

In the following section, the results of repeated measures ANOVA regarding the effect of coping-therapy on immunologic biomarkers are presented.

Cortisol

To test the effect of coping-therapy on the cortisol level of patients' blood plasma in comparison with the control group, first the assumptions of repeated measures ANOVA were met and then the test was run. Table 2 displays the results.

The results in Table 2 reveal that the effect of time (from the pretest to the follow-up sessions),which indicates the within group changes across time from the pre-test to follow-up session, is not significant (p=.900, F=.027). However, the interactive effect of group in time,which shows the effect of the type of interventions in changes in the means of both groups, is significant (p=.001, F= 26.310). Also, the interactive effect of gender in time and also the education in time that have been analyzed as covariate is not significant (p=.724, F=.163; p=.560, F=.399). Analyzing the means reveal that the amount of cortisol as an immunological marker in the experimental group in five phases (pre-test, after the fourth session of coping-therapy, after the eighth session, post-test, and the follow-up sessions) decreased,while in the control group, it increased.

Interleukin 1b

To test the effect of coping-therapy on the Interleukin 1β level of patients' blood plasma in comparison with the control group, first the assumptions of repeated measures ANOVA were examined and then the test was run. Table 3 displays

Table 2. Results of repeated measures ANOVA (cortisol immunological marker)

Cortisol In Time (weeks)	Groups: Mean (SD)		Time effect	Time*group effect	Time*sex effect	Time*education effect
	Control	Coping-therapy	F(p value)	F(p value)	F(p value)	F(p value)
			0.03 (0.90)	26.31 (0.01)	0.16 (0.72)	0.40 (0.56)
Pre-test	4.51 (1.55)	4.69 (1.73)				
4th week of the start of treatment	6 (2.49)	3.6 (1.38)				
8th week (last session of treatment)	6.93 (3.83)	2.76 (1.41)				
Post-test (10th week)	7.12 (3.87)	2.62 (1.47)				
Follow up (14th week)	7.18 (3.91)	2.52 (1.45)				

Graph 1. Effects of Coping-Therapy on Cortisol from PreTest to Follow Up in comparison with control

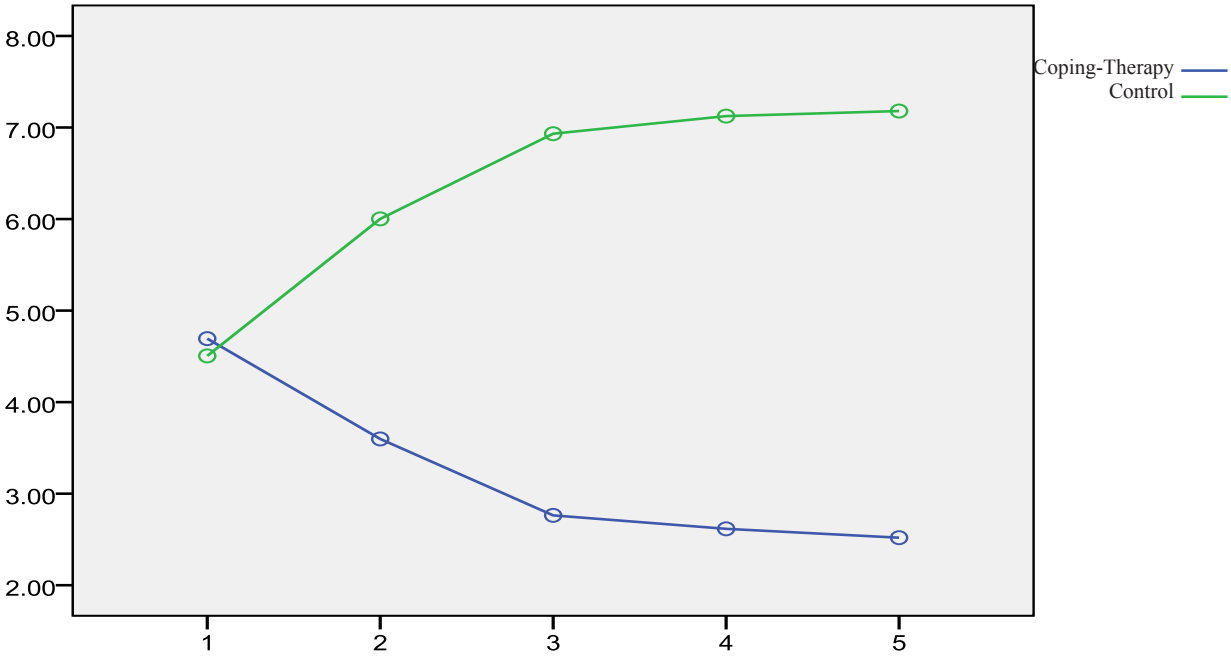


Table 3. .results of repeated measures ANOVA (Interleukin 1β)

Interleukin 1b In Time (weeks)	Groups: Mean (SD)		Time effect	Time*group effect	Time*sex effect	Time*education effect
	Control	Coping-therapy	F(p value)	F(p value)	F(p value)	F(p value)
			0.09 (0.79)	48.04 (0.01)	0.221 (0.67)	0.217 (0.67)
Pre-test	2.76 (0.89)	2.54 (0.71)				
4th week of the start of treatment	2.75 (0.75)	2.36 (0.70)				
8th week (last session of treatment)	2.93 (0.79)	1.97 (0.60)				
Post-test (10th week)	3 (0.83)	1.92 (0.61)				
Follow up (14th week)	3.05 (0.81)	1.85 (0.62)				

the results.

Results of repeated measures ANOVA (Table 3) reveals that the effect of time that states within group changes across time from the pre-test to the follow-up session is not significant (p=.786, F=.094); however, the interactive effect of group in time, indicating the effect of type of intervention in mean changes of both group, is significant (p=.001, F=48.035). In addition, the interactive effects of gender in time and education in time that were considered as covariates in the analysis were not significant (p=.666, F=.221; p=.669, F=.217).

Examining the means reveal that the amount of interleukin1β in the experimental group in five stages (pre-test, after week 4, after week 8, post-test, and follow-up session) has decreased,while in the control group, it increased.

Figure 2 displays the mean changes in interleukin1β in both groups in five stages.

Interleukin 6

To test the effect of coping-therapy on the Interleukin 6 level of patients' blood plasma in comparison with the control group, first the assumptions of repeated measures ANOVA were met and then the test was run. Table 4 displays the results.

The results of repeated measures ANOVA

Graph2. Effects of Coping-Therapy on IL-1β from PreTest to Follow Up in comparison with control

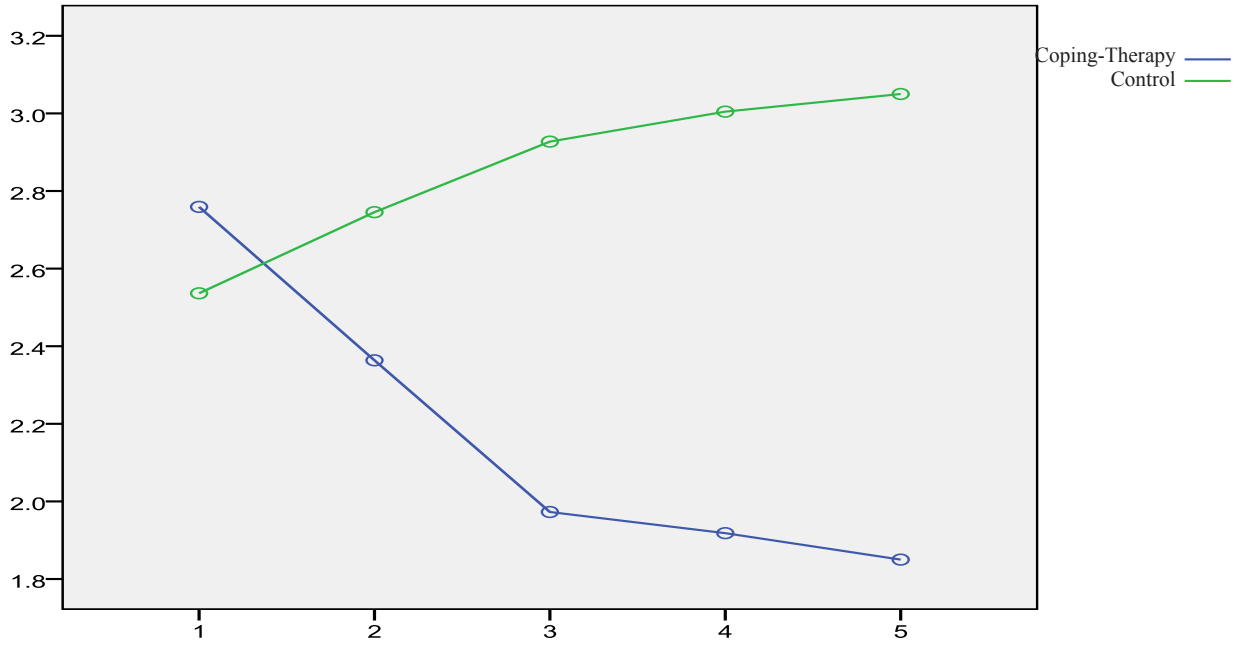
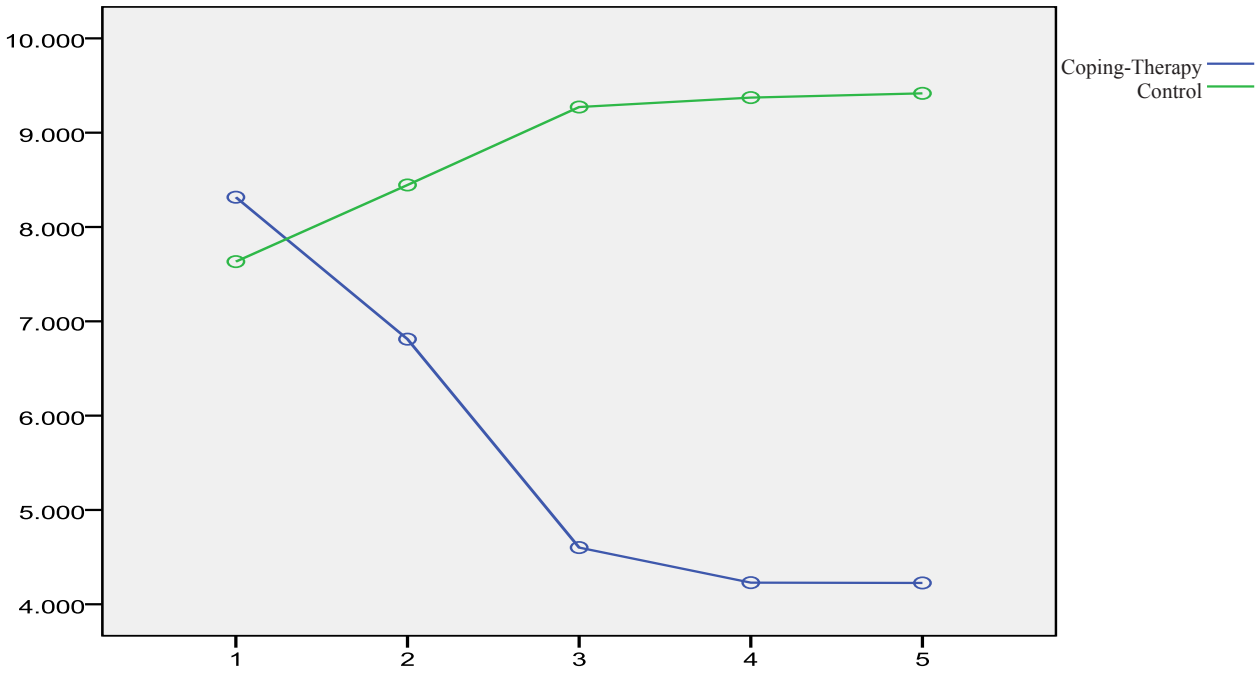


Table 4. Results of repeated measures ANOVA (interleukin 6)

Interleukin 6 In Time (weeks)	Groups: Mean (SD)		Time effect	Time*group effect	Time*sex effect	Time*education effect
	Control	Coping-therapy	F(p value)	F(p value)	F(p value)	F(p value)
			.24 (.65)	33.25 (.01)	1.69 (0.20)	0.11 (0.76)
Pre-test	7.63 (5.57)	8.32 (5.76)				
4th week of the start of treatment	8.45 (5.67)	6.81 (5)				
8th week (last session of treatment)	9.27 (6.07)	4.60 (3.66)				
Post-test (10th week)	9.37 (6.10)	4.23 (3.45)				
Follow up (14th week)	9.42 (6.05)	4.23 (3.45)				

Graph 3. Effects of Coping-Therapy on IL-6 from PreTest to Follow Up in comparison with control



(Table 4) reveals that the effect of time indicating within groups changes across time from the pre-test to follow-up sessions is not significant (p=.648, F=.243); however, the interactive effect of group in time indicating the effect of type of intervention in both groups' mean changes is significant (p=.001, F=33.245). Also, the interactive effect of gender in time and education in time which were considered as covariates is not significant (p=.202, F= 1.686; p=.761, F=.114). Analyzing the means revealed that the amount of interleukin 6 in experimental group in five stages (pre-test, after week 4 intervention, week 8, post-test, and follow-up session) decreased, and in the control group, it increased.

Discussion and conclusion

The results of the present study revealed that the coping-therapy in treatment group compared to control group might decrease the immunologic indicators of cardiovascular patients including cortisol, interleukin 6, and interleukin 1b, and at least, up to six weeks after the last session of therapy, keeps it low. The findings of the study are in agreement with the results obtained by Dimsdale(Dimsdale, 2008), Linden, Melanie, and Leclerc(Linden, 2007), Shapiro(Shapiro, 2011), Aghayousefi et al.(Aghayousefi, A; Zare, H; Choobsaz, F & Motiei, G. , 2011), and Aghayousefi and Zare (Aghayousefi, H, 2009).

As observed, the coping-therapy within 8 treatment sessions revealed considerable changes in the amount of immunological biomarkers in CHD patients. It might be stated that although some studies revealed the effect of stress on health through biomarkers including cortisol, interleukin 6, and also interleukin 1β (Atkinson RL, 2000; Brammer LM, 1993; Glozier N, 2013; Lakhan, 2006; Qureshi GM, 2009; Rohleder N, 2006; Rozanski A, 1999; Saner, 2005; Schwartz AR, 2003; Segerstrom SC, 2004; H. M. Steptoe A, Chida Y, 2007; K. M. Steptoe A, 2012; Von Känel, 2006; Yamakawa K, 2009) that results in CHD(Brammer LM, 1993; Brydon L, 2005), other studies revealed the effect of using effective stress coping techniques in the decrease

of these immunologic indicators(Bayer U, 2010; Chiou A, 1997; Damsa, 1988; Roy, 2004; Sarafino, 2002).Coping-therapy through directing the person to concentrate on initial and secondary appraisals of stressful events and efficiency of coping methods, and also avoiding one specific coping technique in life and using different techniques based on each stressful context, reduce the effect of stressful situations and consequently shows its useful effects on immunologic indicators. The patient in therapy sessions learns, when facing a stressful event, to do, first an initial appraisal and if threatening, considering the context and possibilities, takes advantage of the most appropriate coping technique and follows the secondary appraisals accordingly.

Despite merits of the present study, like any other studies in the literature, the limitations of the study should also be taken into account and avoid overgeneralization of the research findings. Although the previous studies revealed the positive effect of modifying dysfunctional coping techniques in improving the biomarkers of cardiovascular patients, it must be considered that the present study was done using coping-therapy technique with few clinical trials and needs replications. The sample size was not sufficientenough to be generalized; in addition, the study was conducted on a country with its specific cultural context.

Implication for health policy/practice/research/ medical education

In order to reduce undesirable consequences and increase desirable medical outcomes in patients' CHD, coping-therapy is highly recommended.

Acknowledgment

We are deeply grateful to the authorities and staffs atShahidRajaei Heart Hospital in Terhran who helped us conduct the research project.

Footnotes

Author Contributions

AlirezaAghayousefi: original idea, study design, manuscript preparation and supervisionof the study,

Ahmad Alipour: advisor of the study,and

Nasim Sharif: execution of experiment, collection of data and statistical analysis.

Funding Support

We thank Payame Noor University to give us financial support of the study.

Abbreviation

Micro Liter (ml)
Nano gram (ng)
Mili Liter (ml)
Pico gram (pg)
Nano meter (nm)
The Enzyme-linked immunosorbentassey (ELISA)
Horseradish Peroxidase (HRP)
Analysis of Variance (ANOVA)

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