

Interleukin - 6 Relationship on Response of Effectiveness of Mindfulness Based Cognitive Therapy for Cancer in Cervical Cancer Patients

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ABSTRACT

Objectives: Analyzing IL-6 levels as a predictor of MBCT-Ca effectiveness response and the effect of MBCT-Ca effectiveness in reducing anxiety, depression and improving quality of life (QoL) in cervical cancer patients.

Material and Methods: Randomized controlled trial experimental research with design in the oncology-gynecology clinic with 32 patients from March-August 2019 hospital, Surakarta. The treatment group, besides the standard therapy, was also given Ca 8 times. Levels of IL-6, EORTC-QLQ-C30 scores and HADS scores were assessed treatment.

Results: The average of IL-6 levels in pre-treatment 6.11 ± 6.41 , and post-treatment was 7.36 ± 8.74 ($p=0.796$) while in the control group in the averaged pre-treatment group 8.85 ± 6.48 , and post-treatment of 15.61 ± 8.99 ($p=0.063$). The control group had increased levels of IL-6 5,525 higher than the increase in IL-6 in the treatment group. In the control group experienced an average increase in HADS scores of 2.00 ± 12.39 , the treatment group had a decrease in HADS score of -3.38 ± 9.72 ($p=0.043$). While the EORTC QLQ C30 score of the control group is increased by an average of 9.25 ± 34.16 , the treatment group is decreased by an average EORTC QLQ C30 score of -1.31 ± 19.14 ($p=0.167$).

Conclusion: There was no significant difference in IL-6 levels in cervical cancer patients who received MBCT-Ca. MBCT-Ca is effective in reducing anxiety and depression, no effect of improving the QoL in cervical cancer patients.

Keywords: Anxiety, Cervical Cancer, Depression, Interleukin-6, MBCT-Ca, Quality of Life.

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INTRODUCTION

Cervical cancer is the fourth most frequent malignancy in women. It is estimated that globally there were 570,000 new cases in 2018, which represented 6.6% of all female cancers.[1] About 90% of deaths from cervical cancer occur in low and middle-income countries.[2] Carcinogenesis in cervical cancer is a multi-stage process that results in various malignancy characteristics such as invasion, overgrowth, and immune system deviation.[1]

The Human Papilloma Virus, women who suffer from a decrease in the immune system or use drugs for the immune system, are very at risk for increasing cervical cancer.[3][4] Starting from the zone of cervical transformation, most often in squamous cells results from epithelial changes from cervical intraepithelial neoplasia (CIN). [5] Interleukin-6 (IL-6) is one of the cytokines associated with the progression of cervical cancer, it is a dissolved mediator that is produced quickly and temporarily in response to infections, immune reactions and oncogenesis. IL-6 expression increased significantly in neoplastic lesions compared to CIN and normal cervix.[5][6] These cytokine expressions have also been shown to act as growth factors in cervical carcinoma cell pathways. IL-6 also acts as a predictor of poor prognosis in cervical cancer.[7][6] The production of IL-6 also stimulates the production of Th17, which is one of the main mechanisms of pathogenesis and also increased circulation in carcinogenesis.[8] [9] The use of Mindfulness Based Therapy (MBT) in oncology cases is now gaining ground; there is some positive evidence supporting the use of MBT for cancer patients, and cancer survivors who have symptoms of anxiety and depression, Mindfulness-Based Cognitive Therapy (MBCT) can increase the effectiveness of mindfulness-based interventions.[10][11] MBCT is more focused on getting patients to use a decentered approach to

internal experiences rather than teaching clients to change their minds and to reduce the fear of recurrence of cancer and to improve spiritual well-being.[12]

OBJECTIVES

To study the response level of IL-6 as a predictor of the effectiveness of MBCT-Ca in cervical cancer patients and the effect on the effectiveness of MBCT-Ca to reduce symptoms of anxiety, depression and improve quality of life (QoL) in cervical cancer patients

MATERIAL AND METHODS

This study is experimental analytics Randomized Controlled Trial, (*pre and post-test design*). Subjects were 32 patients with advanced cervical cancer with International Federation of Gynecology and Obstetrics (FIGO) 2018, stage IIB-IV at Dr. Moewardi hospital, Surakarta. Sixteen patients of cervical cancer patients who were treated with MBCT-Ca and standard therapy and 16 cervical cancer patients who performed standard therapy which all met the inclusion criteria and exclusion. Independent variable of this study is MBCT-Ca, and the dependent variable was interleukin-6, anxiety and depression, which measuring variables with HADS and EORTC-QLQ-C30 score. Cervical cancer patients with stage II B and or more who are undergoing chemotherapy age group of 18–60, willing to be the subject of research and sign a letter of research consent and cooperative to follow MBCT-Ca was included in the study. As a control group, 16 age and chemotherapy matched. Subjects having a history of severe mental disorder with psychotic symptoms, manifestations of multiorgan disorders, severe comorbid disease and received mindfulness-based training before was excluded from the study. Data analysis was performed using SPSS 21 for Windows. In this study, the analysis is presented with frequency distribution, and

percentage continue with univariate analysis and bivariate analysis. Research ethics included informed consent, anonymity, confidentiality and ethical clearance. The eligibility in this study from the Ethics Committee, Dr. Moewardi Hospital with Ethic letter, number 948 / IV / HREC / 2019.

RESULTS

Research subjects were 32 cervical cancer patients in Dr. Moewardi Surakarta, which was divided into two groups: 16 patients of cervical cancer patients who were treated with MBCT-Ca and standard therapy and 16 controls of cervical cancer patients who performed standard therapy which all met the inclusion criteria and exclusion.

Table 1: Characteristics of cervical cancer patients

Characteristics	N	Average or Frequency
Age (years)	32	56 ± 8.68
Education	32	
Low		30 (93.75%)
High		2 (6.25%)
Employment status	32	
Work		15 (46.9%)
Housewife		17 (53.1%)
Marital status	32	
Married		25 (78.1%)
Other		7 (21.9%)
Income	32	
<1 million		21 (65.6%)
> 1 million - <5 million		11 (34.4%)

Table 1 shows the mean age of cervical cancer patients was 56 ± 8.68 years, 93.75% having low education, 53.1% not working, 78.1% of marital status married and 65.6% earning <1 million.

Before analyzing the data, it is a homogeneity test of data in both groups with the Levene test. To find out the differences in research subjects is shown in table 2.

Table 2: Characteristics of treatment and controls cervical cancer patients.

Group	Interleukin-6 levels		p-value
	Pre treatment	Post-treatment	
Treatment	6.11 ± 6.41	7.36 ± 8.74	0.796
Control	8.85 ± 6.48	15.61 ± 8.99	0.063

Characteristics	Group		OR	p
	Treatment	Control		
Age	55.94 ± 9.00	55.44 ± 8.63		0.765
Education			-	0.002
Low	14 (43.8%)	16 (50.0%)		
High	2 (6.2%)	-		
Employment status			1,286	0.629
Work	8 (25.0%)	7 (21.9%)		
Housewife	8 (25.0%)	9 (28.1%)		
Marital status			3,182	0.011
Married	13 (72.2%)	16 (88.9%)		
Other	5 (27.8%)	2 (11.1%)		
Income			4,333	0.004
<1 million	8 (44.4%)	15 (83.3%)		
> 1 million - <5 million	10 (55.6%)	3 (16.7%)		

Mean different test results of cervical cancer patients who were treated with MBCT-Ca and control groups who showed that there were no significant differences in patient age and occupational variables (p value> 0.05). The results of the Levene test showed there were no differences in variance.

There were significant differences in the variables of education, marital status and income (p <0.05) between groups.

Differences in levels of IL-6 in cervical cancer patients receiving MBCT-Ca

To find out the difference in IL-6 levels in cervical cancer patients who received MBCT-Ca between the treatment group with the pre-treatment and post-treatment control groups, a paired difference test was used. Before a different test is performed, it is necessary to know the normality of the data of this study. Based on the Shapiro Wilk test, for the pre-treatment and post-treatment paired test the Wilcoxon

test was used because the data did not meet the normality assumption ($p < 0.05$).

Before testing the hypothesis, the homogeneity test is a prerequisite. Homogeneity test was used to determine the level of variance similarity between the two group. Homogeneity test results with statistical Levene test obtained $p=0.931$, which means the data in this study have homogeneous variance.

Table 3: Differences in levels of IL-6 pre-treatment and post-treatment between groups of cervical cancer patients who received MBCT-Ca (treatment group) and cervical cancer patients with standard therapy (control group)

Variable	Effectiveness		c	p-value
	Treatment	Control		
Anxiety (HADS)	-3.38 ± 9.72	2.00 ± 12.39	-0.360	0.043
Quality of Life (EORTC QLQ C30)	-1.31 ± 19.14	9.25 ± 34.16	-0.251	0.167

Based on table 3, it is known that in cervical cancer patients the average treatment group of IL-6 levels 6.11 + 6.41, and post-treatment average IL-6 levels 7.36 ± 8.74. From the paired t-test results obtained $p= 0.796$, which means that there is no significant difference in levels of IL-6 between pre and post-treatment in the treatment group.

IL-6 levels of cervical cancer patients in the control group were pretreated 8.85 ± 6.48, and post-treatment average 15.61 ± 8.99. From the paired t-test, $p=0.063$, which means that there were no significant differences in the levels of IL-6 pre and post-treatment in the control group (Figure1). Based on the description, the MBCT-Ca therapy has not been able to reduce levels of IL-6 and even tends to increase levels of IL-6 although it is not statistically significant. In contrast, in the control group, it increased more than in the

treatment group even though it was not statistically significant.

IL-6 levels as a predictor of the effective response of MBCT-Ca in Cervical Cancer Patients

To find out the level of IL-6 as a predictor of the effectiveness response of MBCT-Ca in Cervical Cancer Patients by finding the difference in the IL-6 level in the unpaired group. Based on the normality test with Shapiro, the difference test of unpaired groups of difference between groups did not meet the normality consideration ($p < 0.05$).

The results of IL-6 levels as predictors of the effectiveness response of MBCT-Ca in cervical cancer patients are as follows.

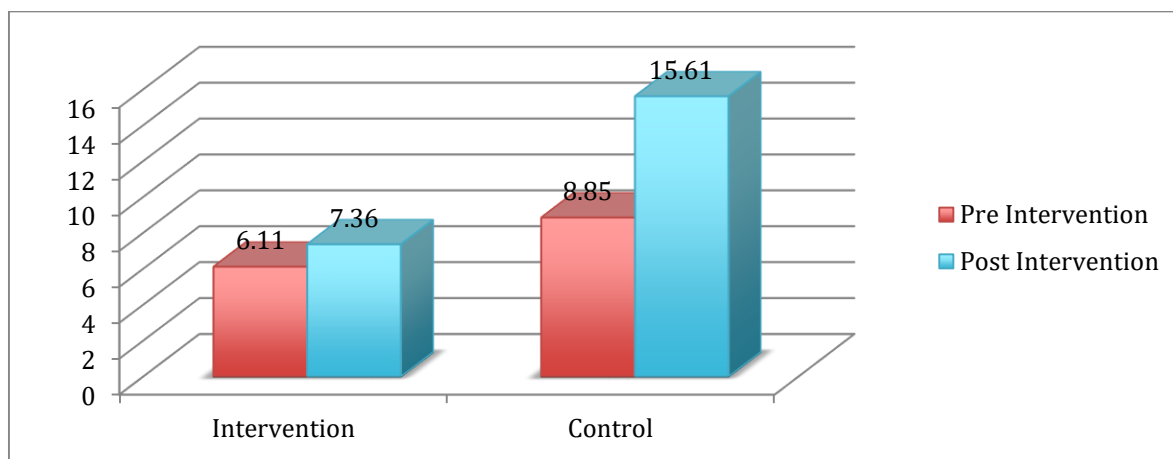


Figure 1: Levels of IL-6 pre-treatment and post-treatment between groups of cervical cancer patients who received MBCT-Ca (treatment group) and cervical cancer patients with standard therapy (control group)

Table 4: The difference in levels of IL-6 Pre-treatment and Post-Treatment between patients receiving MBCT-CA (treatment group) and cervical cancer patients with standard therapy (control group)

	Group		Difference	p-value
	Treatment	Control		
IL-6 levels	1,245± 7,752	6,770± 10,196	5,525	.163

Based on table 4 the treatment group experienced an increase in the average level of IL-6 $1,245 \pm 7,752$ while the control group experienced an increase in the average level of IL-6 $6,770 \pm 10,196$. The results of the Mann-Whitney test $p=0.163$, which means that there is no significant difference in changes in the level of IL-6 after intervention MBCT-Ca. In this study, it can be explained that the control group experienced elevated levels of IL-6 higher than 5,525 COM p ared to increased levels of IL-6 in the treatment group. So it was concluded that the level of IL-6 was not able as a

predictor of the effective response of MBCT-Ca in cervical cancer patients.

The effectiveness of MBCT-Ca to reduce symptoms of anxiety, depression and improve QoL in cervical cancer patients

To determine the effect of anxiety symptoms in the treatment group with the control group in cervical cancer patients performed by the Spearman rank correlation test.

Table 5. Effect of the effectiveness of MBCT-Ca on reducing anxiety symptoms, depression and improving in cervical cancer patients

Variable	Effectiveness		c	p-value
	Treatment	Control		
Anxiety (HADS)	-3.38 ± 9.72	2.00 ± 12.39	-0.360	0.043
Quality of Life (EORTC QLQ C30)	-1.31 ± 19.14	9.25 ± 34.16	-0.251	0.167

Based on table 5, cervical cancer patients the control group increase in average HADS score 2.00 ± 12.39 , the treatment group had a decrease in the average HADS score of -3.38 ± 9.72 , and the results of the Spearman rank correlation test showed $p=0.043$. We found there is an effect on the effectiveness of MBCT-Ca in reducing anxiety symptoms in patients with cervical cancer. While the score EORTC QLQ

C30 the control group experienced an average increase 9.25 ± 34.16 , the treatment group decreased the average score of EORTC QLQ C30 -1.31 ± 19.14 , and the results of the Spearman rank correlation test showed $p=0.167$ ($p > 0.05$), which means there is no effect of the effectiveness of giving MBCT-Ca in improving QoL in cervical cancer patients.

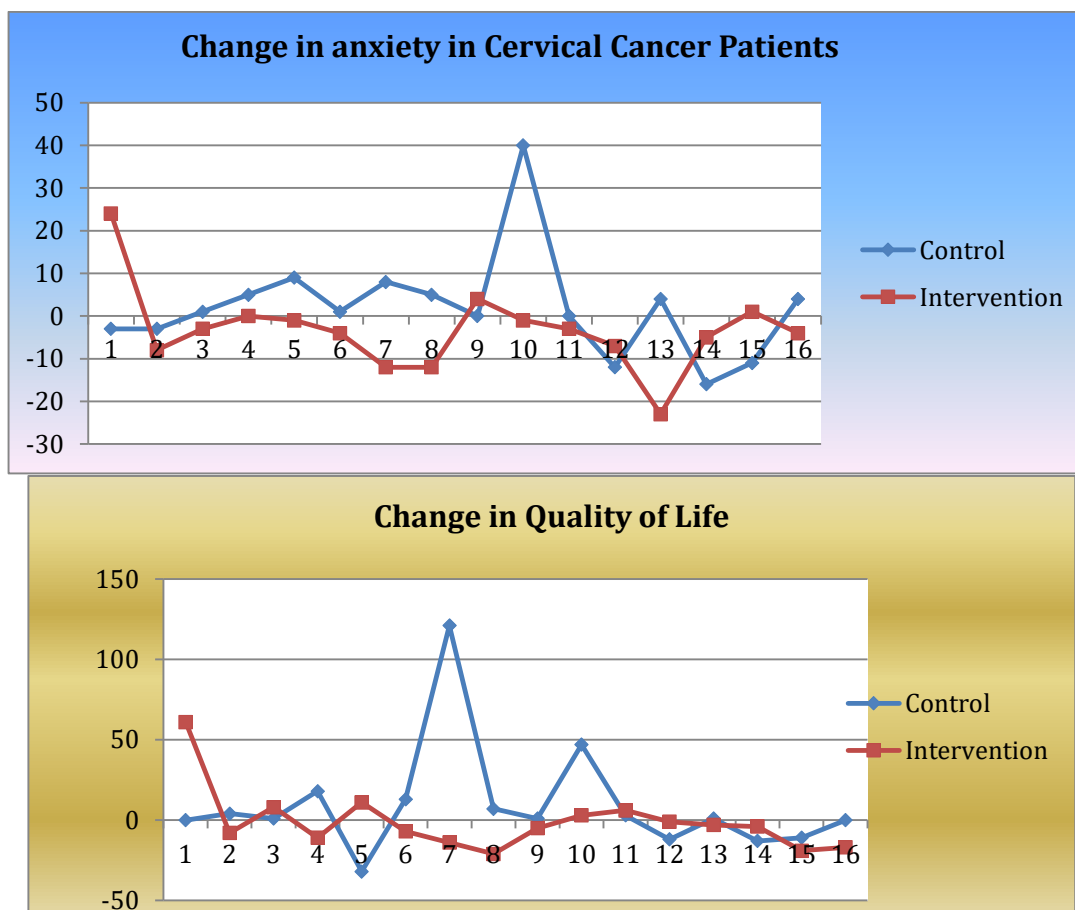


Figure 2,3: Graph of changes in anxiety and quality of life in cervical cancer patients who received (MBCT-Ca) (treatment group) and cervical cancer patients with standard therapy (control group).

MBCT-Ca psychological therapy provides a decrease in anxiety symptoms compared to the control group in cervical cancer patients. As for the EORTC QLQ C30, the treatment

group experienced a decrease even though it was not statistically significant.

DISCUSSION

The purpose of this study is to analyze and prove the difference in IL-6 levels in cervical cancer patients who are given MBCT-Ca on psychological, behavioral, and biological outcomes among diagnosed cervical cancer sufferers. The research findings show that the MBCT-Ca treatment program does not have a definite effect on cytokines, especially IL-6. Changes in IL-6 are inconsistent before and after each MBCT-Ca session; however, IL-6 as a whole tends to decrease in patients receiving MBCT-Ca compared to control patients. [13][14][15]

These results are in accordance with research conducted by that the level of IL-6 there was no significant change from the MBSR treatment. IL-6 is known as one of the earliest and more essential mediators of induction of acute-phase protein synthesis and is an essential regulator of CRP production by the liver. On the other hand, several studies have reported that IL-6 has a pro or anti-inflammatory effect, depending on the context of the cell or tissue. Therefore, it seems complicated to evaluate changes in IL-6 levels between before and after treatment. and is an essential regulator of CRP production by heart. Several studies have reported that IL-6 has a pro or anti-inflammatory effect, depending on the context of the cell or tissue. Therefore, it seems difficult to evaluate changes in IL-6 levels between before and after treatment. [16][17]

Exploratory analysis revealed that treatment group participants who received MBCT-Ca (including attending classes and practice at home) had lower IL-6 levels in post-treatment assessments, but was not statistically significant ($P > 0.05$). The IL-6 difference between the treatment and control groups became significant post-treatment MBCT-Ca. In a different study, "normalization" of cortisol levels was observed in a group of breast and prostate cancer patients after MBSR treatment, where high cortisol levels initially decreased post-MBSR and initially low cortisol levels increased post-MBSR. [18]

Although these findings are intriguing, the researchers cannot determine clinical relevance, and changes in IL-6 do not always indicate systemic changes. IL-6 is an inflammatory cytokine with pro and anti-inflammatory effects; high levels are associated with a poorer prognosis and invasive increases in the tumor microenvironment. Although the direct effect is to reduce IL-6 and cortisol at specific times showing a reduction in anxiety felt after treatment of MBCT-Ca, the long-term effects and clinical benefits of reducing cortisol and IL-6 have not been determined. Instead some studies also explain that blocking IL-6 or inhibiting associated signaling independently or in combination with conventional anticancer therapy can be a potential therapeutic strategy for cancer treatment through IL-6 dominated signals. Sample size too small to conclude definitive results. Further research is needed to clarify the importance of IL-6 levels and other contributing factors. [19][20]

The study contradicts showed that MBSR could have several beneficial effects on immune recovery. This is possible treatment characteristics, such as the number of sessions given is not the same or according to the standard specified at least six sessions. In this study, there was some leniency in attendance per session, but it was explained from the beginning of the program that it was very important to attend all sessions for eight weeks. However, due to the physical limitations of the participants, it was decided that the researcher would not treat the attendance too much, so the participants had the freedom to attend or not attend. The condition found in our study was that the MBCT-Ca training

dose received by participants was lower because the patient's arrival was less than optimal at each training session (the average arrival was 5 times). In addition, audio recordings for home exercise were not given as suggested by the MBCT-Ca gold standard due to technical issues during this study. [18]

Also, MBCT-Ca research findings affected anxiety reduction ($p < 0.05$). Research findings are in line with that MBSR can reduce symptoms of stress, depression post-treatment. Although the acute effect of attention on stress, depressive symptoms, and other results has been demonstrated in the cancer population, the persistence of this effect in the weeks and months post-treatment is less clear. Several awareness-based stress reduction trials for cancer sufferers have reported significant effects on depressive symptoms in post-treatment assessments, but not on follow-up assessments conducted between 24 months after treatment [21][22][23] MBSR has received significant attention over the past few years as a modality not only for reducing stress but also for improving chronic medical symptoms. The literature develops the physiological mechanism of MBSR and its potential efficacy in anxiety, depression, and pain. MBSR seems to have the potential to improve several health outcomes for specifically depression, anxiety, and mental health functions in general with marginal effects. [14][24][25]

This finding is in line with the goal of MBSR which is not to relieve pain but rather to reduce the pressure associated with pain or move closer to pain and work with it in meditation to have a different relationship with chronically uncomfortable sensations, which may not be detected with both in terms of pain intensity [24]

Regarding the QoL, MBCT-Ca did not improve all functional scale scores (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), and 6 single scales (shortness of breath, difficulty sleeping, loss of appetite, constipation, diarrhea and financial problems), the researchers themselves assume that cervical cancer patients who received MBCT-Ca therapy did not experience many changes in QoL. In this study, the QoL of patients was not affected by MBCT-Ca; this was possible because distress in the context of cancer diagnosis was a predictable response. However, the intensity and duration of distress varies according to the type of cancer, the social condition of the patient, the prognosis and morbidity associated with treatment. However, such insignificant results might be influenced by the small sample size. The findings of the treatment group had a worse initial score than the control group; this might be the reason why the treatment group still had a lower QoL than the control group. The study was not as expected; patients in the treatment group showed a decrease in quality of life, despite a decrease in anxiety and levels of IL-6. [26]

CONCLUSIONS

There was a decrease in levels in cervical cancer patients who received MBCT-Ca therapy and standard therapy compared to cervical cancer patients with standard therapy but not significantly significant. Interleukin-6 can not be used as a predictor for the successful response of MBCT-Ca in patients with cervical cancer. There is a significant effect on the effectiveness of MBCT-Ca in reducing anxiety and depression, but there is no effect on improving the QoL in cervical cancer patients.

CONFLICT OF INTEREST

There are no conflicts of interest.

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