

Original Research Article

Medical hypnosis on depression and interleukin-6 levels in lung cancer patients

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ABSTRACT

Background: Lung cancer patients are at high risk for depression, which is associated with poor treatment adherence. Medical hypnosis can improve symptoms of depression and affect interleukin-6 levels. This study aims to determine the effectiveness of medical hypnosis in improving depression and reducing IL-6 levels in lung cancer patients.

Methods: This study is a quasi-experimental study with a pretest and post-test control group design. It assessed depressive symptoms using BDI-II scores and serum IL-6 levels in an intervention group receiving medical hypnosis and standard therapy compared to a control group receiving standard therapy. Data analysis was conducted using univariate tests, followed by Pearson correlation tests and effect size measurement with Cohen's d test.

Results: The Wilcoxon test showed a decrease in IL-6 levels in the intervention group by 14.66 ± 19.45 ($p=0.008$) and a reduction in BDI-II scores by 8.26 ± 4.78 ($p=0.001$). Correlation tests indicated a significant relationship between IL-6 levels and BDI-II scores ($r=0.472$; $p=0.009$). Cohen's d test showed the effect size of medical hypnosis on IL-6 levels was 0.754 (moderate= $0.5 < ES < 0.8$).

Conclusions: Medical hypnosis is effective in improving depressive symptoms and reducing IL-6 levels in lung cancer patients.

Keywords: Medical hypnosis, Lung cancer patients, Depression, Interleukin-6 levels

INTRODUCTION

Lung cancer ranks third (8.8%) for new cancer cases in Indonesia.¹ Several studies indicate that cancer patients, especially those with lung cancer, are vulnerable to depression, which is associated with poor treatment adherence, thereby increasing the risk of mortality.^{2,3} The prevalence of depression in lung cancer patients is approximately 12-60%.⁴ Cancer patients experience repeated chronic stress due to treatment or the progression of cancer cells. Chronic stress can disrupt the immune system, particularly by increasing the production of pro-inflammatory cytokines (IL-6).^{5,6} Depression is also associated with elevated IL-6 levels.^{7,8} Several other

studies have shown that increased IL-6 can worsen prognosis and shorten the life expectancy of cancer patients.⁹

A meta-analysis study showed that single antidepressant treatment is no more effective than a placebo in managing depression in cancer patients,¹⁰ highlighting the need for a combined therapeutic approach with social interventions, such as lifestyle modification, physical activity, and cognitive therapy or psychotherapy.⁶ Medical hypnosis could be a viable option for managing depression in cancer patients.^{11,12} Research on the effects of medical hypnosis on depression in cancer patients related to IL-6 is still limited in Indonesia. This study

aims to determine the effectiveness of medical hypnosis on depressive symptoms and IL-6 levels in lung cancer patients.

METHODS

Study design

This study is quasi-experimental research with a pre-test and post-test control group design, involving lung cancer patients undergoing treatment at Dr. Moewardi General Hospital in Surakarta during July 2023 to August 2023.

Subject selection technique

Subjects were selected using purposive sampling. Inclusion criteria: lung cancer patients at stage 3A or higher; BDI-II (Beck's depression inventory-II) score ≥ 11 ; age 18-70 years; able to read and write; fluent in Indonesian; willing to participate in the study; compliance with listening to the medical hypnosis recordings $>80\%$. Exclusion criteria: suffering from other inflammatory or autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis); presence of organic brain disorders; experiencing hearing impairments.

Research procedure

Subjects who agreed to participate in the study were divided into intervention and control groups. Interviews were conducted to assess BDI-II scores, and venous blood samples were taken to measure IL-6 levels. Subjects in the intervention group listened to medical hypnosis recordings twice a day for 28 days at home, starting with one face-to-face hypnosis session and standard therapy (psychoeducation), while the control group received standard therapy only. The implementation of medical hypnosis at home was monitored daily via video call and reminders were sent through WhatsApp by the researchers. On the 28th day, BDI-II scores and IL-6 levels were reassessed.

Statistical analysis

All data were analyzed using SPSS version 25 and JASP version 0.18.0. Hypotheses were tested by comparing BDI-II scores and IL-6 levels between the two groups in pre and post-tests, as well as the post-pre difference. Pearson's correlation test was conducted to assess the relationship between variables. The effect size of independent variables on dependent variables was evaluated using Cohen's d test. Significance was considered if the $p < 0.05$ with a confidence interval (CI) of 95% or $\alpha = 5\%$.

RESULTS

The research subjects consist of 30 individuals, divided into 15 individuals in the control group and 15

individuals in the intervention group. Based on demographic characteristics data, no statistically significant differences were found ($p > 0.05$), indicating homogeneity of the data (Table 1).

Table 1: Demographic characteristics of subjects.

Characteristics	Groups		P value*
	Intervention (n=15) frequency (%)	Control (n=15) frequency (%)	
Age (mean±SD)	56.33±7.34	56.47±9.99	0.51
Body weight (mean±SD)	53.4±8.68	47.56±11.04	0.18
Height (mean±SD)	159.27±10.96	155.27±8.049	0.31
BMI (mean±SD)	21.03±2.6	19.51±3.29	0.19
Sex			
Male	9 (60)	7 (46.7)	0.715
Female	6 (40)	8 (53.3)	
Residence			
Rural	9 (60)	7 (46.7)	0.715
Urban	6 (40)	8 (53.3)	
Education			
University	0	3 (20)	0.26
High school	4 (26.7)	4 (26.7)	
Middle school	6 (40)	3 (20)	
Elementary school	5 (33.3)	5 (33.3)	
Occupation			
Unemployed	3 (20)	5 (33.3)	0.416
Merchant	4 (26.7)	1 (6.7)	
Farmer	4 (26.7)	6 (40)	
Private sector	4 (26.7)	3 (20)	
Nutritional status			
Normal	13 (86.7)	9 (60)	0.215
Underweight	2 (1.3)	6 (40)	
Comorbidities			
None	10 (66.7)	13 (86.7)	0.39
Present	5 (33.3)	2 (13.3)	
Type of cancer			
Adenocarcinoma	11 (73.3)	12 (80)	1.00
Squamous cell	4 (26.7)	3 (20)	
Cancer stage			
IV A	3 (20)	4 (26.7)	1.00
IV B	12 (80)	11 (73.3)	
Duration of illness (years)			
<1	9 (60)	13 (86.7)	0.215
>1	6 (40)	2 (13.3)	
Depression			
Minimal	5 (33.3)	8 (53.3)	0.158
Mild	7 (46.7)	7 (46.7)	
Moderate	3 (20)	0	

*Comparison between unpaired groups of numeric data was conducted using the independent t-test/Mann-Whitney test.

Table 2: Difference in IL-6 levels before and after intervention between the intervention and control groups.

Group	IL-6 (mean±SD)		Difference	Levels before-after N (%)		P value*
	Before	After		Decreased	Increased	
Intervention	44.17±16.63	29.51±12.96	14.66±19.45	14 (93)	1 (7)	0.008
Control	57.36±49.79	33.87±13.07	23.49±48.69	9 (60)	6 (40)	0.191
P value	0.66	0.31	-			

*Comparison was conducted using the Mann-Whitney test, and the paired group comparison was conducted using the Wilcoxon test.

Table 3: Difference in BDI-II scores before and after intervention between the intervention and control groups.

Group	BDI II (mean±SD)		Difference	Levels before-after N (%)		P value*
	Before	After		Decreased	Increased	
Intervention	16.07±4.67	7.80±5.36	8.26±4.78	15 (100)	0	0.001
Control	13.53±1.99	12.53±4.01	1±2.77	9 (60)	6 (40)	0.299
P value	0.14	0.007	-	-	-	-

*Comparison was conducted using the Mann-Whitney test, and the paired group comparison was conducted using the Wilcoxon test.

The average IL-6 level in the intervention group before medical hypnosis was administered was 44.17±16.63, and after was 29.51±12.96.

The difference in IL-6 changes after and before intervention showed a statistically significant decrease in the mean of 14.66±19.45 with p=0.008 (p<0.05).

Table 4: Correlation test of body mass index (BMI), age, sex, residence, educational background, occupation, nutritional status, comorbidities, type of cancer, stage, type of chemotherapy, duration of illness, and BDI-II Scores with IL-6 levels.

Variables	R value	P value
BMI	-0.165	0.385
Age	-0.048	0.801
BDI-II	0.472*	0.009
Sex	0.199	0.198
Residence	-0.160	0.299
Educational background	-0.156	0.312
Occupation	-0.159	0.302
Nutritional status	0.116	0.453
Comorbidities	-0.374*	0.018
Type of cancer	0.004	0.980
Cancer stage	0.064	0.678
Type of chemotherapy	-0.034	0.825
Duration of illness	-0.470**	0.002

*p<0.05; **p<0.01

Meanwhile, the average IL-6 level in the control group at the initial data was 57.36±49.79, and after 28 days was 33.87±13.07. The difference in IL-6 change resulted in a mean decrease of 23.49±48.69, which was not statistically significant with p=0.191 (p>0.05).

The average BDI-II score in the intervention group before medical hypnosis therapy was 16.07±4.67, and after 28 days of therapy, it was 7.80±5.36. The difference in BDI-II change after and before intervention resulted in a mean decrease of 8.26±4.78. Statistically, it indicates a significant decrease with p=0.001 (p<0.05). The average BDI-II score in the control group at the initial data was 13.53±1.99, and after 28 days, it was 12.53±4.01. The difference in BDI-II change in the control group after 28 days compared to the beginning of the study resulted in a mean decrease of 1±2.77, which statistically indicates a non-significant decrease with p=0.299 (p>0.05).

Table 5: Correlation test of BMI, age, gender, domicile, education, occupation, nutritional status, comorbidity, cancer type, stage, chemotherapy type, duration of illness on BDI-II value.

Variables	R value	P value
BMI	-0.387*	0.035
Age	-0.194	0.305
Sex	0.099	0.532
Residence	0.207	0.189
Educational background	0.238	0.131
Occupation	-0.063	0.689
Nutritional status	0.374*	0.018
Comorbidities	-0.213	0.176
Type of cancer	-0.182	0.248
Cancer stage	0.106	0.499
Type of chemotherapy	-0.120	0.446
Duration of illness	-0.152	0.335

*p<0.05.

Table 4 shows a significant correlation between IL-6 levels and BDI-II scores (r=0.472; p=0.009) with a moderate strength of association (0.3<r<0.5) and positive

directionality. Significant correlations are also indicated for comorbid variables ($r=0.374$; $p=0.018$) with a moderate strength of association ($0.3 < r < 0.5$) and no directionality. Another variable showing a significant

correlation is duration of illness with IL-6 levels ($r=0.470$; $p=0.002$) with a moderate strength of association ($0.3 < r < 0.5$) and no directionality.

Table 6: Effect size of medical hypnosis on changes in BDI-II score and IL-6 level after intervention.

Parameter	T value	df	P value	Mean Difference	SE Difference	Cohen's d	SE Cohen's d
IL-6	2.918	14	0.011	14.657	5.023	0.754	0.381
BDI-II	6.687	14	<0.001	8.267	1.236	1.727	0.386

Based on the table above, a significant correlation is obtained between BMI and BDI-II scores ($r=0.387$; $p=0.035$) with a moderate strength of association ($0.3 < r < 0.5$) and no directionality. Significant correlation is also found between nutritional status variable ($r=0.374$; $p=0.018$) with a moderate strength of association and positive directionality.

Based on the table above, the effect size of medical hypnosis on changes in IL-6 levels after medical hypnosis is 0.754 (moderate= $0.5 < ES < 0.8$). This can be interpreted as medical hypnosis having a moderate effect on reducing IL-6 levels compared to the control. Meanwhile, the effect size of medical hypnosis on changes in BDI-II scores is 1.727 (large= $0.8 < ES$), which means medical hypnosis has a large effect on changes in BDI-II scores.

DISCUSSION

This study demonstrates that medical hypnosis can effectively reduce IL-6 levels and improve clinical symptoms of depression in lung cancer patients. The average BDI-II scores in the intervention group before and after medical hypnosis therapy for 28 days experienced a significant decrease. Based on other research, hypnosis has been associated with depression management because it can help patients increase positive expectations about treatment, reduce depressive symptoms (including insomnia and rumination), and shape/modify patterns of self-organization (cognitive, individual response, attention, and perception) that influence depressive thinking patterns and mood.^{17,18} Depression is one of the comorbidities experienced by lung cancer patients. The condition of depression in lung cancer patients is generally difficult to detect because its symptoms overlap with those of cancer, such as fatigue, inability to engage in activities, social withdrawal, and difficulty sleeping.¹⁹ This emerging depression can be influenced by tumor development, family support, treatment processes, socioeconomic factors, patient response to diagnosis, and the patient's psychological condition before cancer diagnosis.^{2,20} The condition of depression is also associated with treatment adherence and the risk of suicide.¹⁹

The mechanism of medical hypnosis in improving depressive symptoms involves medical hypnosis being

able to provide cognitive signals through the sensory cortex in the brain, which then proceed to the transitional cortex and hippocampus. These cognitive signals are then transmitted to the amygdala, which, according to theory, can organize emergency signals that lead to cortisol improvement in the HPA axis pathway.²¹ Low cortisol levels will increase serotonin and dopamine production, thus reducing feelings of depression.²² McCann & Landes' study in 2010 also showed that positive emotion induction in hypnosis is known to reduce negative experiences, increase norepinephrine production, increase tryptophan levels, and increase serotonin receptors, thus improving depressive symptoms.¹⁷ The results of this study also revealed a statistically significant decrease in the average IL-6 levels of the intervention group subjects by 14.66 ± 19.45 , with $p=0.008$ ($p < 0.05$). This finding is consistent with research by Schoen & Nowack, 2013, which stated that medical hypnosis can reduce IL-6 levels. Subjects in Schoen & Nowack's study who received medical hypnosis intervention through recordings for 12 weeks were associated with improved cognitive abilities towards stress, enabling subjects to reduce depressive feelings.¹⁶

The study by Liu et al 2018, indicates an increase in IL-6 levels in lung cancer patients. This may be due to dysregulation of the HPA axis, which subsequently leads to neurotransmitter disturbances and triggers depression.⁸ However, other studies also show that both depression and cancer cell development can lead to increased IL-6 levels. Therefore, improving depressive conditions in cancer patients will be more challenging due to this increase in proinflammatory cytokines.¹⁹ The change in IL-6 levels in this study may be due to changes in cognitive coping, which can reduce patients' pessimism induced by medical hypnosis focusing on stress reduction. According to Schoen & Nowack, 2013, patients who do not overreact to stress will decrease physiological reactivity and concurrent inflammatory processes. Improvement in IL-6 levels may also be caused by lifestyle changes and improvement in appetite or diet.²³ This is consistent with previous research findings that self-efficacy leads to improvements in lifestyle practices and health behaviours in adults.⁸ Self-reported changes in health habits may reflect hypnotic suggestions aimed at addressing skills, self-esteem, and self-efficacy, which in turn facilitate improvements in

health behaviours such as healthy and nutritious eating. This is consistent with previous research findings that self-efficacy leads to improvements in lifestyle practices and health behaviours in adults.²⁴

This study also demonstrates that medical hypnosis provides a large effect size for changes in BDI-II scores and a moderate effect size for changes in IL-6 levels. The study by Milling et al also states that medical hypnosis is one of the effective interventions for improving depressive symptoms and provides a moderate effect size. According to Milling, the effect size of medical hypnosis is mainly influenced by individual hypnotizability. Individuals with high hypnotizability will show high effect sizes.²⁴ Conditions that may result in medical hypnosis not providing a large effect size on IL-6 after intervention include the presence of chronic stressors and/or tumor cell development that produce proinflammatory cytokines.²⁵ The duration of cancer illness becomes a variable correlated with IL-6 levels. Other studies indicate that patients who have been suffering from cancer for a longer period have passed the denial phase of their pain, so they have come to terms with the reality and are consequently more cooperative in therapy.²⁶ The length of illness in cancer patients will affect their attitude towards their condition. Patients will feel the need to make peace with their condition and hope for a "miracle" someday.²⁷ This feeling of reconciliation will make cancer patients more compliant with treatment and induce positive emotions, thereby increasing self-efficacy, leading to a decrease in IL-6 levels or improvement in depressive symptoms.^{24,27,28} The researchers did not take into account the type or name of chemotherapy drugs used. The type of chemotherapy did not show a significant correlation with either IL-6 levels or BDI-II scores. This contrasts with previous research indicating that chemotherapy side effects can affect compliance levels and increase the risk of depression. Additionally, the administration of chemotherapy drugs that modulate interferon may increase the risk of depression in lung cancer patients.^{19,25} The subjects in this study mostly fell into stage IV B, with 11 individuals (73.3%) in the intervention group and 13 individuals (86.7%) in the control group, while the remainder were in stage IV A. The cancer stage in this study did not show a statistically significant correlation with IL-6 levels and BDI-II scores. However, it was found that the higher the stage, the higher the IL-6 levels and BDI-II scores. This is consistent with Hansen's study in 2002, which found that lung cancer is typically detected at an advanced stage due to clear clinical symptoms. Other research also indicates that advanced cancer stages pose a higher risk of depression but cannot be used to determine cancer prognosis.³⁰

Limitations

The limitations of this study are as follows: The long-term effects of medical hypnosis on lung cancer patients are unknown. This study did not account for any potential

window effect between the subjects in the control and intervention groups. The administration of medical hypnosis treatment was conducted by the researcher without involving other parties or using blinding methods. This may pose a risk of intervention bias. The researcher may experience fatigue during the first session of administering medical hypnosis.

CONCLUSION

Medical hypnosis is effective in improving depressive symptoms and reducing IL-6 levels in lung cancer patients.

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