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Effect of Lemon Scent on the Anxiety of Cancer Patients Undergoing Chemotherapy; a Clinical Trial

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ABSTRACT

Aims One of the cancer treatments is chemotherapy. Anxiety is one of the important symptoms of patients undergoing chemotherapy. Considering the effect of lemon aromatherapy on improving anxiety in patients without cancer, maybe it can also improve the anxiety of patients with cancer. This study aimed to determine the possible effect of lemon scent on the anxiety of patients undergoing chemotherapy.

Instruments & Methods This is a one-sided blind clinical trial study, which was carried out on 50 patients undergoing chemotherapy at Shahid Beheshti Hospital in Kashan, Iran in ––2021-2022. Patients were randomly divided into two test and control groups. During chemotherapy, three drops of lemon essential oil were used and in the control group, 3cc of water were poured on a paper napkin. The subjects were then asked to breathe normally. This method was used once a week for 4 weeks during chemotherapy. Data were analyzed using SPSS 16 software.

Findings The mean age of intervention and control groups were 52.20±9.63 and 51.48±12.29 years, respectively (p=0.81). The mean duration of the disease of intervention and control groups were 40.04±27.53 and 35.32±19.57 months, respectively (p=0.48). No significant differences were seen between two groups in the demographic characteristics; sex, marital status, education level, underlying disease, and cancer type. The ANOVA test with repeated measures showed no significant decrease in overt and covert anxiety of patients over time (p>0.05).

Conclusion Aromatherapy with lemon essence has no effect on the overt and covert anxiety of the cancer patients undergoing chemotherapy.

Keywords Aromatherapy; Chemotherapy; Anxiety; Lemon

CITATION LINKS

[1] Screening, evaluation, and management of cancer-related fatigue: Ready for implementation to practice? [2] "I go into crisis when …": Ethics of care and moral dilemmas in palliative care [3] Effects of Aromatherapy Using Sour Lemon on Nausea in Patients Undergoing Chemotherapy: A Quasi-Experimental Study [4] Depression and anxiety in patients with cancer [5] The effects of relaxation on reducing depression, anxiety and stress in women who underwent mastectomy for breast cancer [6] Story therapy effect on reducing anxiety and improvement habits sleep in children with cancer under chemotherapy [7] Preoperative anxiety in patients undergoing outpatient cancer surgery [8] Dhikr therapy for reducing anxiety in cancer patients [9] Guided imagery: Reducing anxiety, depression, and selected side effects associated with chemotherapy [10] Effect of Music Therapy on Chemotherapy-Induced Nausea and Vomiting among Patients with Gastrointestinal Cancers [11] Efficacy of complementary therapies in reduction of chemotherapy induced nausea and vomiting in breast cancer patients: Systematic review... [12] Effect of aromatherapy with lemon essential oil on anxiety after orthopedic surgery [13] Comparison of essential compounds of fruit peel in tangerine, sour lemon and orange [14] The effects of lemon balm (Melissa officinalis L.) on depression and anxiety in clinical trials: A systematic review and meta-analysis [15] The effect of aromatherapy with orange essential oils on anxiety in patients undergoing hemodialysis [16] The effect of aromatherapy with orange essential oils on anxiety in patients undergoing hemodialysis [17] Inhalation aromatherapy during radiotherapy: results of a placebo-controlled double-blind randomized trial [18] Effect of inhaled lemon essential oil on cognitive test anxiety among nursing students [19] The effects of Rosa damascene aromatherapy on anxiety and sleep quality in burn patients: A randomized clinical trial [20] The effect of educational video on anxiety before surgery of patients candidates for eye surgery by fico method [21] The effects of lavender aromatherapy on pain following needle insertion into a fistula in hemodialysis patients [22] Anxiolytic effect of aromatherapy massage in patients with breast cancer [23] Aromatherapy: The effect of lavender on anxiety and sleep quality in patients treated with chemotherapy [24] The Effect of Aromatherapy on Postoperative Nausea in Women Undergoing Surgical Procedures [25] A systematic review on the anxiolytic effects of aromatherapy in people with anxiety symptoms [26] The effect of lemon inhalation aromatherapy on nausea and vomiting of pregnancy: A double-blinded, randomized, controlled clinical trial

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Introduction

Cancer is the second cause of death in America [1] and the third cause of death in Iran [2]. One of the cancer treatments is chemotherapy, which is performed aimed to destroy cancer cells [1]. Chemotherapy is accompanied by many physical and mental side effects such as fatigue, nausea, vomiting, anemia, alopecia, insomnia, anxiety, and depression, which can have a negative effect on the quality of life [3].

Failure to control these complications imposes many costs on the patient. The most important physical and mental symptoms in patients undergoing chemotherapy are anxiety, nausea, and vomiting [4]. Anxiety is a response to a threat, and cancer is a threatening factor [3]. Therefore, many cancer patients are anxious. In 2015, it was stated that 77% of patients undergoing chemotherapy experienced anxiety [5]. This rate is higher (about 93%) in people whose cancer has just been diagnosed compared to patients who have been treated [5]. Anxiety is a diffuse, unpleasant, and vague feeling of fear and worry with an unknown origin that a person experiences and it includes uncertainty, helplessness, and physiological arousal [6]. Among the causes of anxiety in patients undergoing chemotherapy, death anxiety, anxiety caused by the onset of pain, anxiety caused by disfigurement, disability, anxiety related to the side effects of chemotherapy or radiotherapy, and disruption of social and family relationships can be mentioned [7].

Anxiety control in patients undergoing chemotherapy can be done with drug therapy and psychological approaches. However, only about 50%-65% of cancer patients benefit from antidepressants or cognitive behavioral therapy, and there are still many patients who experience anxiety even during treatment [8]. The results of recent research indicate that a high percentage of patients still have physical and mental side effects of chemotherapy despite drug treatment to control anxiety. Significant side effects of anti-anxiety drugs such as benzodiazepines include drowsiness, extrapyramidal side effects, hypotension, headache, diarrhea, and constipation, which has led to the limitation of their consumption [9]. Considering the limited effect and dangerous side effects caused by the consumption of these drugs, the trend towards non-chemical and non-industrial treatments such as medicinal plants has increased.

One of the basic and low-risk measures in this field is the use of herbal medicine as the most active part of complementary and alternative medicine, which has attracted a lot of attention during the past decade [10]. Several factors have increased the tendency of people to use this method which includes 1- being involved in deciding the type of treatment, 2- avoiding the toxicity of drugs, 3- lack of medical insurance, 4- the high cost of medicines, and 5- interest in using preventive measures [10, 11].

One of the medicinal plants is lemon. Lime is the ripe fruit of the citrus lemon plant, which contains volatile oil. Lemon essential oil is obtained by squeezing the outer part of fresh lemon peel and contains 95% of different terpenes. Its pleasant smell is related to citral, which is found in 4-7% [12]. Lemon contains large amounts of vitamin C, vitamin B6, magnesium, potassium, and phosphorus [13]. Ghazizadeh *et al*.'s study in 2021 showed that lemon essential oil has anti-anxiety and anti-depressant effects in patients [14]. In the study of Kanani *et al*., it was shown that aromatherapy with orange essential oil reduces the anxiety of hemodialysis patients [15]. The results of the study by Nakayama *et al*. showed that the use of aromatherapy with lemon essential oil is useful in reducing salivary gland damage following the use of radioactive iodine for the treatment of thyroid cancer [16]. Kamrani *et al*. showed that aromatherapy with lime is useful in reducing the anxiety of patients before surgery [12]. Graham *et al*. showed that aromatherapy with a combination of plants including lavender, lime, and bergamot did not affect the anxiety of patients undergoing radiotherapy [17]. Johnson *et al*. showed that the anxiety of nursing students who underwent aromatherapy with lemon essential oil was not significantly different from the control group, and it has been suggested to conduct further studies in this field [18].

According to the limited studies on the effect of aromatherapy with lemon essential oil on the anxiety of patients undergoing chemotherapy, the presence of anxiety caused by the side effects of chemotherapy in these patients, and the presence of contradictory studies on this issue, we aimed to determine the effect of aromatherapy with lemon on the anxiety of patients undergoing chemotherapy.

Instrument and Methods

This randomized clinical trial with a control group that using a pre- and post-test design was performed in 2021-2022. Twenty cancer patients who had been referred to the chemotherapy department of Shahid Beheshti Hospital in Kashan, Iran, for chemotherapy were sampled according to Kamrani *et al*. [12]. The formula 1 (α=0.01 and β=0.1) was also used to calculate the minimum sample volume in each study group. Due to having more accuracy and considering the statistical decline, 25 samples were determined in each group.

$$n=\frac{(\sigma_1^2+\sigma_2^2)\left(Z_{\frac{\alpha}{2}}+Z_{1-\beta}\right)^2}{(\mu_1-\mu_2)^2} \quad (1)$$

The sampling was conducted by two-stage. At first, patients were selected by the available sampling method, and then they were divided into 5 groups of 10 people based on random block allocation. The eligible patients who were over 18 years old, in the first day of chemotherapy, chemotherapy treatment once a week, and with stage I or II breast, esophageal,

colon, and gastric cancer (due to the same nature of the medicine therapy), and had a healthy sense of smell (measured by smelling alcohol) were selected. The patients who had no history of asthma or chronic obstructive pulmonary disease, not being allergic to plant essential oils, and the use of complementary medicine methods to relieve anxiety were not selected.

The researcher explained the objectives of the research to the subjects and obtained written consent from them to participate in the study (two contact numbers were taken from each patient). Before the intervention, a demographic information questionnaire (age, gender, marital status, employment status of the patient and spouse, education level of the patient, history of specific underlying disease, cancer type, duration of cancer) and Spielberger's overt and covert anxiety questionnaire were filled out by the two studied groups. Each of these scales has 20 items, which were scored by a 4-point Likert scale. In responding to the overt anxiety scale, the subject expresses her/his feelings at the same moment, and in responding to the covert anxiety scale; the subject refers to her/his usual feelings most of the time. The items of the questionnaire scored by the scores between 1 to 4. The scores of each of the two scales can be in the range of 20-80. A score of 20 indicates the absence of anxiety, a score of 21-42 indicates mild anxiety, a score of 43-64 indicates moderate anxiety, and a score of 65-80 indicates severe anxiety. This questionnaire had high validity and reliability. In Mokhtari *et al*., the reliability of this questionnaire was found to be 0.81 by Cronbach's alpha coefficient [19]. In Sattar, the validity of the questionnaire was confirmed and its Cronbach's alpha coefficient was 0.91 [20]. In this study, Cronbach's alpha coefficient was calculated at 0.87.

Used lemon essential oil was prepared by Barich Essence Oil Company in Kashan. The lemon essential oil used in the laboratory of Kashan University of Medical Sciences was analyzed by a gas chromatography device (Agilent 7820A GC; USA) connected to a mass spectrometer using helium gas (Agilent 6890 Mass Spectrometer; China) to ensure the purity of the essential oil and determine its composition accurately. The results of the device analysis showed that limonene (68.2%), beta-pinene (12.8%), gamma-terpinene (8.8%), and alpha-pinene (2.2%) were the main components of lemon essential oil.

During the study, the patients were in separate rooms. In the intervention group, using the scent of lemon (test), in addition to the usual care (3mg granisetron, 8mg dexamethasone). The researcher put 3 drops of lemon essential oil on a paper napkin with a dropper and placed under the mask of the subjects during chemotherapy. This method was used in the intervention group once a week (during chemotherapy) for 4 weeks. The intervention was continued from 5 minutes before the start of chemotherapy to the end of chemotherapy. In the control group, in addition to the routine measures of the department (granisetron, 8mg of dexamethasone), 3cc of water (placebo) was poured on a paper napkin and attached under the patient's mask during chemotherapy.

The overt and hidden anxiety questionnaire was filled out by the patient at the end of each chemotherapy session in both groups and the anxiety of the two groups was compared before the intervention, at the end of the first, second, third, and fourth week.

Data were analyzed using Chi-square (gender), exact Chi-square (education level, underlying disease, cancer type), Fisher's exact (marital status), independent T (age, duration of the disease), and ANOVA repeated measures (interaction effect of time and overt anxiety intervention) tests in SPSS 22 software.

Findings

The mean age of intervention and control groups were 52.20±9.63 and 51.48±12.29 years, respectively (p=0.81). The mean duration of the disease of intervention and control groups were 40.04±27.53 and 35.32±19.57 months, respectively (p=0.48). No significant differences were seen between two groups in the demographic characteristics; sex, marital status, education level, underlying disease, and cancer type (Table 1).

Table 1. Frequency of demographic characteristics in the intervention and control groups (numbers in parentheses are percentage)

Parameter	Intervention	Control	p Value
Gender			
Female	13 (52)	11 (44)	Chi-square
Male	12 (48)	14 (56)	p=0.77
Education level			
High school	18 (72)	18 (72)	Exact Chi-square
Diploma	6 (24)	5 (20)	p=0.58
Academic education	1 (4)	2 (8)	
Marital status			
Married	21 (84)	21 (84)	Fisher's exact test
Single	4 (16)	4 (16)	p=0.99
Underlying disease			
Diabetes	5 (20.8)	6 (24)	Exact Chi-square
Blood pressure	7 (29.2)	7 (28)	p=0.73
Kidney disease	4 (16.7)	1 (4)	
Lung disease	2 (8.3)	3 (12)	
Other	7 (25)	8 (32)	
Cancer type			
Gastric	4 (16)	0 (0)	Exact Chi-square
Colon	8 (32)	7 (28)	p=0.16
Breast	12 (48)	15 (60)	
Lung	1 (4)	3 (12)	

The changes in the mean score of overt anxiety did not differ over time. Also, the interaction effect of group and time was not significant regarding the changes in the overt anxiety score. The effect of covert anxiety time was not significant in both groups; so, there was no significant difference

between the covert anxiety score in three-time points in each group. The ANOVA test with repeated measures showed no significant decrease in overt and covert anxiety of patients over time (p>0.05; Table 2).

Table 2. Comparison of the mean score of overt and covert anxiety in five time points between two intervention and control groups (independent T-test)

Parameter		Intervention	Control	p-Value
Overt anxiety	Early stage	60.48±8.95	55.88±6.88	p=0.47
	1 week later	59.44±6.47	55.72±11.47	p=0.16
	2 week later	57.72±8.18	58.24±8.13	p=0.82
	3 week later	58.68±8.98	57.96±10.98	p=0.80
	4 week later	57.88±10.89	55.76±10.93	p=0.49
Covert anxiety	Early stage	58.44±7.56	55.36±5.76	p=0.11
	1 week later	58.24±5.84	55.36±9.36	p=0.39
	2 week later	57.56±6.39	57.40±6.23	p=0.97
	3 week later	57.52±7.27	57.48±8.63	p=0.98
	4 week later	59.08±8.09	54.36±8.34	p=0.46

Discussion

This study aimed to determine the effect of aromatherapy with lemon on the anxiety of patients undergoing chemotherapy.

Bagheri *et al*., performed aromatherapy using 5% lavender essential oil and 3 drops for 20 minutes during four weeks in hemodialysis patients, and the results showed that aromatherapy does not affect their overt and covert anxiety [21]. Graham *et al*., found that aromatherapy with a combination of essential oils of lavender, bergamot, and a type of pine had no effect on reducing the anxiety of patients undergoing radiotherapy [17]. The findings by Graham *et al*. are similar to our study however the type of aromatherapy was a lemon scent in our study, and in the above studies it was aromatherapy with lavender or a combination with other scents. Imanishi *et al*. showed that aromatherapy massage with orange, lavender, and sandalwood essence in patients with breast cancer, twice a week for 4 weeks, reduced the anxiety of the patients under study [22]. Also, Azkaraman *et al*. found that aromatherapy with 3 drops of lavender essence during chemotherapy for one month reduced the overt and covert anxiety of patients undergoing chemotherapy [23]. In the above studies, although a different scent was used in aromatherapy, they were effective, while in this study, aromatherapy with lemon scent was not effective and the results of this study are not similar to the above studies. However, there is a difference of opinion about the effectiveness of aromatherapy to reduce anxiety, researchers believe that scent stimulates the limbic system by activating olfactory nerve cells to release neurotransmitters such as noradrenaline, serotonin, endorphin, and encephalin [24]. Kamrani *et al*. showed that inhaling three drops of lemon essence for 30 minutes can reduce the anxiety of patients after orthopedic surgery. They also showed that this effect continues up to 16 hours after surgery [12]. The results of the mentioned research are not consistent with this study. Perhaps, the reason for the difference between these two studies was the anxiety measurement tool, the Spielberger questionnaire was used in this study and the VAS tool was used in the study by Kamrani *et al*. Also, in this study, the intervention was carried out twice a week for 4 weeks but in Kamrani's study, the intervention was performed 30 minutes after the surgery. Lee *et al*., in a systematic study, reviewed all clinical trial studies from 1990 to 2010 that investigated the effect of aromatherapy on reducing anxiety. Lee *et al*. showed that aromatherapy is a treatment without complications, and in all studies, aromatherapy led to a reduction in anxiety [25]. The difference between the mentioned studies and this study may be due to the type of disease or the type of inhaled essence. In addition, considering that the above studies have investigated the effect of aromatherapy on anxiety in patients without cancer. Probably, the reason for not reducing anxiety in patients undergoing chemotherapy can be chronic diseases, side effects of chemotherapy, disruption of quality of life, and fear of death, so that the intervention could not reduce their anxiety. Another reason for not reducing the anxiety of the subjects may be that this research was conducted during Corona pandemic, and maybe the fear of Covid-19 disease as an intervener affected the results of our research. Yavari Kia *et al*. in a study showed the effect of aromatherapy with lemon on reducing nausea and vomiting in cancer patients undergoing chemotherapy [26]. In addition, Moghari *et al*. showed that aromatherapy with lemon essence reduced nausea and vomiting [3]. Therefore, considering the improvement of nausea and vomiting in the aforementioned study, it can be said that the lack of effect of chamomile aromatherapy on anxiety in the present study is probably not due to problems in the study design and maybe aromatherapy with lemon does not affect the anxiety of chemotherapy patients. Considering that anxiety is a mental concept that can only be evaluated by the individual, therefore, the researcher's trust in the correctness and accuracy of the answers given by the research units is one of the limitations of this study. Also, there were cultural, religious, social, economic and family differences between the patients, which can affect the results of the study. Considering the impact of aromatherapy on patients' anxiety in most studies, more research on a larger number of patients and with a higher dose and number of times is suggested in this matter.

Conclusion

Aromatherapy with lemon essence has no effect on the overt and covert anxiety of the cancer patients undergoing chemotherapy.

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Ethical Permissions: Ethical permission of this study was obtained from the Research Vice-Chancellor of Kashan University of Medical Sciences with a code of IR.KAUMS.NUHEPM.REC.1399.019. This study has been registered in the Clinical Trial Registration Center with the code IRCT20111210008348N45.

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