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Effect of *Melissa officinalis* on Chemotherapy-Induced Peripheral Neuropathy in Cancer Patients: A Randomized Trial

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a significant cancer treatment side effect that can influence both quality of life and treatment course. Melissa Officinalis (MO), due to its high content of flavonoids, has antioxidant, anti-inflammatory, and neuroprotective properties.

Materials and Methods: The cancer patients diagnosed with CIPN attended a referral center in Sari (Iran). The hydroalcoholic extract of MO leaves was extracted by the maceration method. The control group received a placebo along with gabapentin as the standard treatment, and the intervention group received 500 mg Melissa officinalis 2 times daily for 3 months plus gabapentin. Patients were evaluated at the baseline and 3 months later, according to Common Terminology Criteria for Adverse Effects (CTCAE) and EORTC QLQ-C30 (Integrated System for Quality of Life Assessment).

Results: A total of 40 patients were considered as group D (intervention group), and 35 patients completed the study. Out of 40 subjects in the placebo group (P), 3 patients could not tolerate the drug due to gastrointestinal disturbances. The final values of CTCAE showed a statistically significant difference (p=0.010). Indicators related to the quality of life in both groups showed a significant improvement. In the intervention group, the pain perception and diarrhea experience were significantly reduced.

Conclusion: Quality of life indicators were improved by prescribing gabapentin with and without Melissa officinalis. The addition *of Melissa officinalis to* the chemotherapy regimen may improve diarrhea and pain perception.

Keywords: Cancer; Chemotherapy; Neuropathy; Lemon balm; Melissa officinalis

INTRODUCTION

Cancer has emerged as a serious global health issue especially in developing countries[1]. With the introduction of antineoplastic agents and targeted treatments, cancer management has experienced remarkable advancement, which fortunately resulted in better patient survival[2]. As most of these drugs act non-selectively on both normal and cancer

cells, side effects are inevitable so that in more than 80% of patients, there is at least one reported case of complications[3]. Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect experienced by cancer patients receiving a various class of antineoplastic drugs including taxanes, vinca alkaloids, platins and bortezomib [4].

Nerve damage triggers symptoms that can present as both sensory and motor weakness[5]. The prevalence is higher in the beginning and decreases within a few months following treatment course [6]. As different anticancer agents are used and based on follow-up length, the reported prevalence varies among studies from 96% for all neurotoxicity grades[7] to 3% for grade 3[8]. Pain, parathesia, allodynia and hyperalgesia, weakness are among reported symptoms[9]. Various treatment options are utilized by clinicians to manage CIPN including antidepressants, anticonvulsants, anti-inflammatory drugs and antioxidants[10]. The use of traditional medicine to treat diseases has an age-old history, especially in eastern countries, and Iran is one of the countries which medicinal plants have been mentioned in many scientific sources[11]. Melissa officinalis L (MO) or lemon balm is a therapeutic plant containing volatile compounds and flavonoids with many healing properties[12]. Thanks to its rich antioxidant and neuroprotective capacities, MO has gained much attention in neurological setting such as depression, anxiety, insomnia and pain[13].

Although the underlying mechanisms leading to CIPN are still to be understood, damage to DNA and inflammation has been suggested as responsible events[9,14]. Considering unique properties of MO on the one hand and the growing interest in using medicinal plants on the other hand, the present study aimed to investigate possible benefit of adding MO to standard regimen of CIPN in a sample of Iranian cancer patients.

MATERIALS AND METHODS

This study is a randomized double blind clinical trial registered in national database (IRCT20201128049515N2) investigating the effectiveness and side effects of MO in the treatment of peripheral neuropathy caused by chemotherapy drugs. After obtaining the necessary ethical approvals (IR.MAZUMS.IMAMHOSPITAL.REC.1399.8621), cancer patients aged 18 to 75 years referring to a university hospital (Sari, Iran) during 2021-2022 who started the first neurotoxic chemotherapy using vinca alkaloids, platinum derivatives or taxanes having symptoms of neuropathy including numbness and tingling (grade ≥1 based of Common Terminology Criteria for Adverse Events version) were included [15]. Chief resident was responsible for explaining the complete objectives of the study and possible benefits / side effects to the patients. Subjects then were asked to sign an informed written consent if willing to participate in the project.

If there were other possible causes of neuropathy (i.e. diabetes, thyroid dysfunction, vitamin B12 deficiency or alcohol abuse), concomitant medications for neuropathy symptoms, taking any type of antioxidant supplement in the last two months, pregnancy and or breastfeeding, lack of consent to participate in the study, the patients were excluded.

Randomization

The stratified block randomization method was used for randomization. Patients were divided into classes in terms of drug use: a) platinum drugs (cisplatin or oxaliplatin), b) vincristine, c) bortezomib, and d) taxanes (taxol-taxotere).

Then, in each class based on a random sequence created online, patients were assigned into two intervention and control group. Four random chains of each group were used separately by the online randomization system. The grouping of patients and the type of intervention received were only at the disposal of the first project manager, and according to the considered codes, others (the patient, flow who was in charge of clinical evaluations, and the statistical analyst) did not know about the grouping of patients. MO and placebo drugs were placed in an envelope, according to the codes determined in advance and given to the participants based on randomization. Gabapentin was prescribed as a standard treatment for neuropathy and was purchased by the patient and was approved by the project manager.

Preparation of Melissa officinalis L. capsules

The plant sample (Melissa officinalis L.) was purchased from the medicinal plant production farm (Behshahr city) and after cleaning, it was kept in a drying machine at 45°C for one week. To prepare the plant sample for the extract First, they were converted into small pieces with a mechanical electric mill. Hydroalcoholic extract was extracted by maceration method. After extracting and drying 20 kg of aerial parts, 2860 grams of dry extract powder was obtained. The yield of the total extract was 14.3%. The amount of total phenol in the extract was calculated as 61.35 mg equivalents of Gallic acid per gram of extract.

Intervention

The placebo group (P): 300 mg of gabapentin daily and placebo every 12 hours for 3 months as the standard treatment for peripheral neuropathy.

The intervention group (D): In addition to the usual daily 300 mg gabapentin, received MO hydroalcoholic extract of the plant in the form of capsules (500 mg 2 times a day) for 3 months. All patients were advised to take the tablets after every meal.

Neuropathy assessment

The Common Terminology Criteria for Adverse Events (CTCAE) is a system developed for determining adverse events and their severity in cancer trials. Generally adverse events are graded to a 1 to 5 point including mild, moderate, severe, life threatening and death[16].

The EORTC QLQ-C30 is a system for assessing the quality of life (QoL) of cancer patients participating in clinical trials and other types of research that include patient-reported outcomes. Questions come in functional and symptom domain Reference Values, reliability and validity of Persian version questionnaire was confirmed by Montazeri et al[17].

Statistical analysis

SPSS version 20 was used for analysis with a P<0.05. Statistical tests used were Chi-square, t-test, Mann-Whitney and Wilcoxon Signed Rank Tests.

RESULTS

A total of 40 people were considered for the placebo group (P), of whom three could not tolerate the drug due to gastrointestinal side effects, and 37 patients completed the study. Out of 40 people considered as intervention group (D), 35 patients completed the study, three patients were excluded due to irregular consumption, and two patients were excluded due to gastrointestinal complications. The average age in the intervention group was 57.51 and in the placebo group was 56.48 years (P = 0.651).

In the placebo group (P), 22 patients were female (59.5%) and 15 patients were male (40.5%). In the intervention group (D), 22 patients were female (62.9%) and 13 patients were male (37.1%). In terms of gender distribution, there was no difference between the two groups (p=0.768).

The included patients had colorectal, breast, ovary, lymphoma, stomach, uterus and pancreas tumors. The most common types of cancer in both groups were colorectal tumors, followed by breast cancer.

Table 1: Frequency of cancer types

Type of cancer	Total	Intervention group	
		D	P
Breast	24	10	14
	33.3%	28.6%	37.8%
Ovary	5	1	4
	6.9%	2.9%	10.8%
Colorectal	37	19	18
	51.4%	54.3%	48.6%
Gastric	1	0	1
	1.4%	0%	2.7%
Lymphoma	3	3	0
	4.2%	8.6%	0%
Uterus	1	1	0
	1.4%	2.9%	0%
Pancreas	1	1	0
	1.4%	2.9%	0%
Total	72	35	37
	100%	100%	100%

Regimen frequency is presented in Table 2.

Table 2: Chemotherapy agents

Chemotherapy	Total	Intervention group	
		P	D
Taxan	24	14	10
	33.3%	37.8%	28.6%
Platin	38	18	20
	52.8%	48.6%	57.1%
Taxan+platin	7	5	2
	9.7%	13.5%	5.7%
Vincristine	3	0	3
	4.2%	0%	8.6%
Total	72	37	35
	100%	100%	100%

The baseline values of (CTCAE) in two groups have been shown and the patients did not have a significant difference at the beginning of the study (p=0.92). Both P and D group showed significant improvement in terms of reducing CTCAE grade (P=0.01).

Table 3: CTCAE values at baseline and final

Neuropathy CTCAE Grades		Intervention group	
		P	D
1	Baseline	2	1
		5.4%	2.9%
2		20	21
		54.1%	60%
3		15	13
		40.5%	37.1%
1	Final	13	16
		35.1%	45.7%
2		22	10
		59.5%	28.6%
3		2	9
		5.4%	25.7%

Final items of QLQ-C30 after intervention are shown in Table 4a and 4b. Experience of Diarrhea along with nausea and vomiting improved in the group D.

Table 4 (a): QLQ-C30 single items after intervention

Intervention group		Dyspnoea	Insomnia	Appetite loss	Constipation	Diarrhoea	Financial difficulties
P	Mean	1.18	1.89	2.6	1.78	1.27	3.13
	SD	0.39	0.73	0.545	0.58	0.50	0.53
D	Mean	1.28	1.85	2.40	1.62	1.08	3.20
	SD	0.51	0.77	0.84	0.73	0.28	0.58
	P-value	0.45	0.82	0.20	0.160	0.071	0.59

Table 4 (b): QLQ-C30 single items after intervention

Intervention group		Physical function (items 1-5)	Role function (items 6 and 7)	Cognitive function (items 20 and 25)	Emotional function (items 21-24)	Social function (items 26 and 27)	Fatigue (items 10, 12, 18)	Nausea and vomiting (items 14 and 15)	Pain (items 9 and 19)	Global health status (items 29 and 30)
P	Mean	2.12	2.43	1.39	2.24	2.04	2.41	1.94	2.22	4.91
	Std.	0.49	0.64	0.48	0.59	0.56	0.48	0.56	0.641	0.79
D	Mean	2.24	2.72	1.27	2.08	2.22	2.49	1.68	2.25	4.78
	Std.	0.68	0.79	0.490	0.75	0.67	0.75	0.59	0.98	1.22
	P-value	0.60	0.15	0.22	0.11	0.309	0.87	0.053	0.82	0.95

The results of the Wilcoxon Signed Ranks test are shown in Table 5.
The data is defined as follows:
a. final < base
b. final > base
c. final = base
It can be concluded that both groups experienced improvement in different functions but, pain and diarrhea showed a significant decrease in MO intervention group.

Table 5 (a): Values of EORTC QLQ-C30 items in placebo group

Placebo group Final-base		Mean rank	Sum of ranks	P
Insomnia	Negative Ranks	6.05	60.50	0.008
	Positive Ranks	5.50	5.50	
Appetite loss	Negative Ranks	9.11	127.50	0.007
	Positive Ranks	8.50	25.50	
Constipation	Negative Ranks	6.50	65.00	0.021
	Positive Ranks	6.50	13.00	
Physical function	Negative Ranks	15.45	340.00	0.002
	Positive Ranks	11.00	66.00	
Role function	Negative Ranks	12.71	216.00	0.003
	Positive Ranks	7.40	37.00	
Emotional function	Negative Ranks	12.35	247.00	0.005
	Positive Ranks	13.25	53.00	
Role function	Negative Ranks	12.71	216.00	0.003
	Positive Ranks	7.40	37.00	
Emotional function	Negative Ranks	12.35	247.00	0.005
	Positive Ranks	13.25	53.00	
Social function	Negative Ranks	7.23	94.00	0.008
	Positive Ranks	11.00	11.00	
Fatigue	Negative Ranks	13.68	273.50	0.002
	Positive Ranks	10.30	51.50	
Nausea and vomiting	Negative Ranks	13.78	248.00	0.004
	Positive Ranks	8.67	52.00	
Pain	Negative Ranks	13.41	214.50	0.060
	Positive Ranks	10.69	85.50	
Global health status	Negative Ranks	5.75	11.50	0.00
	Positive Ranks	13.11	288.50	

Table 5 (b): Values of EORTC QLQ-C30 items in intervention group

Intervention group Final-base		Mean Rank	Sum of Ranks	P
Insomnia	Negative Ranks	10.40	156.00	0.008
	Positive Ranks	8.50	34.00	
Appetite loss	Negative Ranks	12.17	219.00	0.002
	Positive Ranks	8.50	34.00	
Constipation	Negative Ranks	7.58	98.50	0.018
	Positive Ranks	10.75	21.50	
Diarrhoea	Negative Ranks	4.00	28.00	0.011
	Positive Ranks	0.00	0.00	
Physical function	Negative Ranks	14.72	338.50	0.002
	Positive Ranks	13.50	67.50	
Role function	Negative Ranks	12.82	243.50	0.001
	Positive Ranks	8.13	32.50	
Emotional function	Negative Ranks	15.74	393.50	0.000
	Positive Ranks	10.38	41.50	
Social function	Negative Ranks	7.95	87.50	0.024
	Positive Ranks	5.83	17.50	
Fatigue	Negative Ranks	13.28	305.50	0.001
	Positive Ranks	15.17	45.50	
Nausea and vomiting	Negative Ranks	14.07	309.50	0.000
	Positive Ranks	10.38	41.50	
Pain	Negative Ranks	13.36	294.00	0.002
	Positive Ranks	14.25	57.00	
Global health status	Negative Ranks	23.00	23.00	0.000
	Positive Ranks	11.50	253.00	

DISCUSSION

CIPN is a common and challenging complication arising from treatment with many common anti-neoplastic agents. As the incidence of cancer has raised globally and patients experience an improved survival, CIPN is showing an elevated trend. A key issue that deserves attention is the reduction or discontinuation of therapeutic doses due to CIPN complications, which can ultimately shorten the patient's survival [18].

According to our knowledge, this is the first study that has investigated the possible benefits of adding Melissa officinalis extract to standard treatment of chemotherapy-induced neuropathy. Both placebo and intervention groups showed significant improvement in quality of life components. However, intervention was more effective in reducing diarrhea and pain.

People have been using medicinal plants to treat diseases since ancient times [19]. Melissa officinalis is a popular medicinal herb with various application as antimicrobial agent, in pain management and neurologic disorders[20]. Activation of oxidative pathways and immune system effector cells can lead to a key compartment in CIPN; neuroinflammation[21,22] . MO has promising potential to neutralize free radicals and its anti-inflammatory properties can be even equal to NSAID drug [23].

Studies on animals have shown that the ethanolic extract of this plant is effective in controlling both neurogenic and inflammatory pain which can be attributed to its rosmarinic acid contents[24].

In another experimental research, the effectiveness of oral administration of MO essential oil on hyperalgesia was investigated using formalin test in diabetic rats. According to the results, the intervention successfully controlled hyperalgesia and resulted in lower pain-related behaviors [25].

When murine microglial cells were stimulated by Lipopolysaccharides, rosmarinic acid derived from MO downregulated proinflammatory factors in medium which highlights its neuroprotective characteristics[26]. In a study by Mirabi et al. (2017), girls with dysmenorrhea were randomly divided into two MO and placebo groups, and the pain intensity was evaluated with Visual Analogue Scale (VAS). The intensity of pain decreased in both groups after the intervention, but in the MO group, the reduction was significantly higher also it was well-tolerated and safe [27].

Another finding of the present study is related to the reduction of the experience of diarrhea associated with the consumption of MO supplement. Cancer treatment by affecting cells in the gastrointestinal tract (GI), can lead to a variety of symptoms including nausea, vomiting and diarrhea[28]. Chemotherapy-induced diarrhea, also known as (CRD), is a common and deliberating problem in cancer patients. Some of CRD behind mechanism are apoptosis of GI tract cells, secretion of pro-inflammatory cytokines and disruption of intestinal microbiota [28].

Various treatment options, such as antimotility agents (loperamide, atropine-diphenoxylate), antibiotics, and anti-inflammatory agents have been considered. Green tea contains relatively large amounts of catechin (a subgroup of the flavonoid family) and has various therapeutic activities, including antioxidant, anti-inflammatory and antibacterial activities. In the study of Emami et al., daily green tea (450 mg) prescription in patients receiving pelvic radiotherapy resulted in the reduced frequency and severity of diarrhea[29]. In an experimental model of colitis irritable bowel syndrome, MO significantly reduced rectal hypersensitivity and stool frequency. In addition, a significant decrease in TNF-α and an increase in antioxidant capacity were observed [30].

CONCLUSION

Finally, it seems that the MO supplement has few side effects, is well tolerated, and is useful in reducing pain and diarrhea in patients experiencing CIPN. More studies in this field can be helpful.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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