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ORIGINAL ARTICLE

The Influence of Fish Oil Supplementation on the Adverse Effects of Chemotherapy in Patients with Hepatocellular Carcinoma

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KEYWORDS

Chemotherapy; Fatty acids supplementation; Hepatocellular carcinoma; Pathology

ABSTRACT: Chemotherapy is among the most crucial therapeutic options for advanced hepatocellular cancer (HCC). There are side effects associated with chemotherapy drug use in cancer patients. It has been shown in animal models that the consumption of omega-3 fatty acids can be effective in reducing the side effects. The purpose of this study is to assess the impact of fish oil supplementation on the adverse effects of chemotherapy in HCC patients. The present research was conducted as a double-blind clinical trial in Erbil City, Kurdistan region, Iraq between May 12, 2020, and December 16, 2021. After an interview, 28 HCC patients who volunteered and were receiving chemotherapy were randomly assigned to the experimental group and another 28 to the control group. The control group was given a placebo for six weeks whereas the experimental group received 3 g of omega-3 fatty acids. Following the initial collection of information for both groups, data on the side effects of chemotherapy were gathered at the start, the fourth, and the sixth weeks following the intervention. The data were examined using the independent sample t-tests, descriptive statistics, chi-square, and Cochran's Q-test. According to the study's findings, the patients in the experimental group had less nausea with passing time, and this difference was statistically significant ($p<0.05$). It is possible to draw the conclusion that taking fish oil supplements while receiving chemotherapy for HCC may be advantageous because it may lessen some of the negative effects of the treatment.

INTRODUCTION

There are negative side effects from chemotherapy drug use in cancer patients [1]. The prevalence rate of nausea and vomiting, which are two unpleasant side effects and the most frequent side effects of chemotherapy in cancer patients, is 54–96% [2–4]. Chemobrain, the term for the cognitive abnormalities associated with chemotherapy, is thought to affect 15% to 70% of those who have received this treatment [5]. Injury to neurons, vascular abnormalities, inflammation, oxidative stress, and/or alterations in the autoimmune response are some of the hypotheses around the underlying processes of adverse cognitive effects following chemotherapy [6,7]. The

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activation of chemically sensitive brain regions, activation of the autonomic nervous system, and mental and psychological elements are the key contributors to these adverse effects of chemotherapy [8,9].

Chemotherapy-induced nausea and vomiting can affect a patient's functional level and quality of life in addition to causing physical issues like electrolyte imbalances, malnutrition, dehydration, esophageal injuries, and exhaustion [10]. The patient may find nausea to be so severe that it keeps him/her from receiving further treatment. Lack of control of nausea and vomiting leads to exorbitant costs, including direct and indirect costs [11]. Direct costs include increased hospitalization days and additional costs related to medical and nursing care, while indirect costs include the loss or reduction of income of patients, family members, or their caregivers [12]. Recently, various methods have been used to control nausea and vomiting, including drug therapy and complementary treatments (Figure 1) [13,14,18].

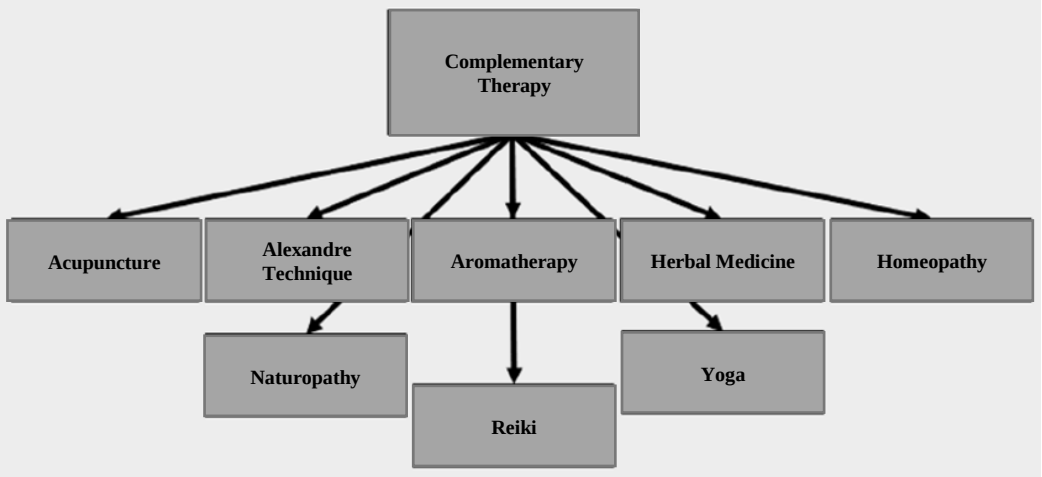

Figure 1. Some of the most popular types of complementary therapy methods.

The quality of life and performance of patients will be considerably improved, and their lives will be positively impacted, by selecting and providing the proper therapies, whether they involve drugs or non-drugs [15]. Therefore, major efforts should be made to develop new strategies for managing and treating nausea associated with cancer. The proper and main way to reduce nausea and vomiting is to use anti-nausea drugs, but these drugs are not effective for all patients and often cause unpleasant side effects. In some cases, a combination of drug and non-drug treatments is usually used [16–18].

To treat the nausea and vomiting brought on by chemotherapy, medical approaches with various effect mechanisms have been employed, but sadly, their claimed success rates range from 6-72% [19]. Although anti-nausea and vomiting drugs have expanded significantly in recent years, they have only been able to reduce the amount of vomiting and often do not have much effect on the feeling of nausea [20]. Despite the fact that the market for anti-nausea and anti-vomiting medications has grown dramatically recently, these medications frequently simply reduce the amount of vomiting while doing little to alleviate nausea [21]. In addition, the use of these drugs has side effects and doubles the side effects of chemotherapy.

The findings of several research suggest that supplementation with some omega-3 fatty acids, such as docosahexaenoic acid, can raise the blood level of this fatty acid during chemotherapy [22,23]. Additionally, it enhances cancer patient survival, cancer metastatic status, and chemotherapeutic tolerability [24]. Another study shows that taking nutritional supplements can reduce nausea during chemotherapy [25]. On the other hand, severe chemotherapeutic side effects in cancer patients can hinder the effectiveness of anticancer medications [26].

The second most frequent cause of cancer-related death worldwide is hepatocellular carcinoma (HCC), which is the sixth most prevalent malignancy overall [5]. It is the fifth leading cause of cancer-related death in Iraq [27]. Chemotherapy is one of the most crucial treatment modalities for advanced HCC, despite the fact that a

wide range of therapeutic choices are available for HCC. The purpose of this study is to examine the impact of supplemental omega-3 fatty acids on chemotherapy-related side symptoms like diarrhea, nausea, vomiting, abdominal cramps, and hair loss in HCC patients receiving chemotherapy medications.

MATERIAL AND METHODS

The current study was carried out as a double-blind clinical experiment at Erbil international hospital and PAR private hospital in Erbil city between May 12, 2020, and December 16, 2021. After receiving approval from the nutrition research center of the college of health sciences at Hawler Medical University (HMU) for accordance with ethical principles, this research was accepted by the Human Research Ethics Committee of the HMU.

The inclusion and exclusion criteria were used to choose 76 patients with HCC whose cancer was identified through MRI scan and pathology. In order to take part in the study, a face-to-face interview, an explanation of the research objectives, and obtaining written informed consent were all required steps. Finally, 56 patients gave their consent after completing all of these steps. Then they were randomly selected into an experimental group (n=28) and a control group (n=28). Following sample selection, the patients from the two study groups were matched for age, sex, and chemotherapy medication type. The inclusion criteria for the study included adults over 30 years of age with HCC undergoing chemotherapy, referring to Erbil international hospital and PAR private hospital in Erbil city, who gave their consent for the project. Exclusion criteria included suffering from other cachexia-inducing diseases such as cardiovascular diseases, pulmonary diseases, AIDS, kidney failure, acute leukemia, people with diabetes and multiple myeloma. The study excluded participants who did not correctly administer the prescribed medications during the study period.

The content validity method was employed to assess the scientific validity of the data collection tool. The reliability of the tool was assessed scientifically using the retest approach. Test-retest reliability was used to ascertain the scientific reliability of the tool. For this purpose, the questionnaires were filled out by 15 randomly selected cancer patients and after 10 days, the questionnaires were again given to the same patients to answer. The correlation coefficient between the two groups of data was then calculated, and a result of 0.97 was obtained, confirming the acceptable level of scientific confidence in the information-generating process. The sample size was estimated using the sample size formula [28].

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

where μ_1 is the mean of the outcome variable in group 1, μ_2 is the mean of the outcome variable in group 2, σ_1 is the standard deviation (SD) of the outcome variable in group 1, σ_2 is the SD of the outcome variable in group 2, and Z is the standard normal variate corresponding to desired values of α and β.

After identifying the patients and obtaining their personal consent, demographic information was collected and the changes related to side effects caused by chemotherapy (such as diarrhea, nausea, vomiting, abdominal cramps and hair loss) were calculated at the beginning, fourth and sixth weeks of the study.

During the course of this study, patients in the experimental group received 3000 mg/day omega-3 fatty acids in the form of 10 capsules that each contained 1200 mg of docosahexaenoic acid (DHA) and 1800 mg of eicosapentaenoic acid (EPA). The control group consumed a placebo of 2100 mg/day of medium chain triglyceride (MCT) oil in the form of 10 capsules.

All of the containers comprising omega-3 fatty acid supplements or placebos were coded as A and B before the trial began in order to prevent the researcher, the questionnaires, and the patients from knowing which kind of supplement each group had been given. This allowed the study to be double-blinded. Following the requisite research, individuals were randomly supplied 450 omega-3 capsules or a placebo, and instructed to take the pills with food at each of the three main meals (breakfast, lunch, and supper).

During the intervention period, telephone calls were made to the patients to ensure their supplement consumption while eliminating any issues. Nearly every 15 days, face-to-face meetings with the patients were conducted as part of the follow-up of the patients to keep

tabs on their supplement usage. Only 51 participants remained and were analyzed in this study (Figure 2). The patients were given enough medicines to last for one month and fifteen days, and they were urged to return any unused pills.

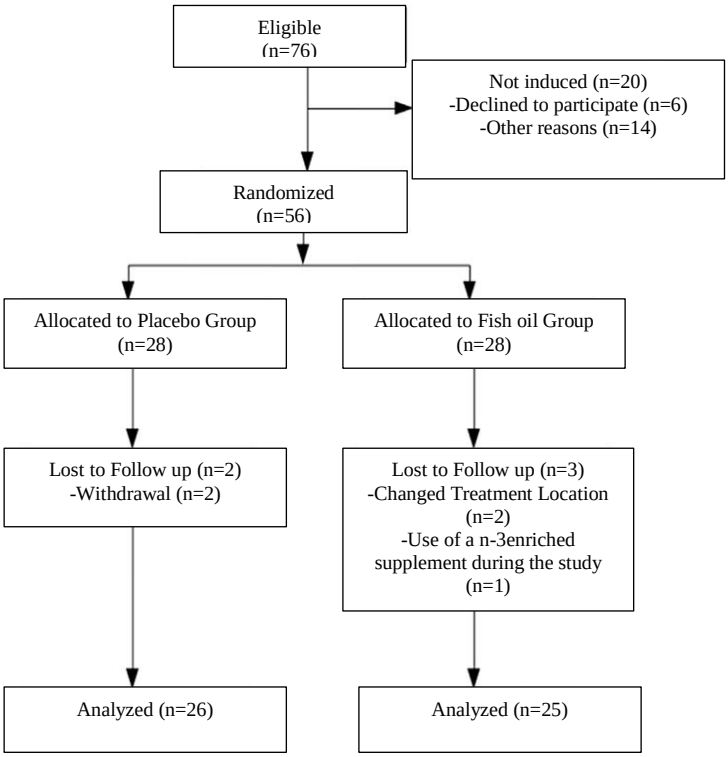

Figure 2. Flowchart of participants.

To achieve the goals of the research, descriptive statistics including frequency distribution tables and statistical indicators such as mean and SD were used and to answer the research questions, chi-square test was used to compare the side effects of chemotherapy in two groups. In the course of the study, the quantitative data were compared using an independent sample t-test, and the side effects of chemotherapy were compared using a Cochran's Q-test. The statistical significance level for all tests was considered to be 0.05. All information was presented as mean ± SD.

RESULTS

The present study was conducted on patients 5±2 months after the diagnosis of the disease and during chemotherapy. The demographic characteristics and some factors related to HCC patients were investigated. The data indicated that at the start of the investigation, there was no significant difference between the two study groups in terms of sex, disease stages, occupation, or literacy level when comparing the demographic features using the chi-square test. Also, the independent sample t-test did not reveal any differences between the two study groups in terms of study time, average height, weight, or age.

According to the chi-square test results, the experimental group experiences less nausea and cramping than the control group, and this difference between the two study groups became statistically significant six weeks following the intervention ($p<0.05$) (Tables 1 and 2).

Table 1. Comparison of the presence of nausea, vomiting and diarrhea in HCC patients undergoing chemotherapy in the studied groups.

Variable	Stages	Experimental group		Control group		p-value (Chi-Square)
		N	%	N	%	
Nausea	Initial	15	76.00	17	94.36	0.07
	Fourth week	16	82.33	18	95.00	0.21
	Sixth week	7	25.33	18	95.00	0.001
p-value (Cochran's Q-test)		0.001		0.381		
Vomiting	Initial	5	12.66	5	12.66	0.94
	Fourth week	5	12.66	5	12.66	0.43
	Sixth week	4	6.27	5	12.66	0.94
p-value (Cochran's Q-test		0.437		1		
Diarrhea	Initial	7	25.33	8	22.16	0.71
	Fourth week	6	19.00	7	25.33	0.58
	Sixth week	5	12.66	8	22.16	0.13
p-value (Cochran's Q-test)		0.351		0.814		

The results using Cochran's Q-test showed that in the experimental group, the occurrence of nausea in patients decreases with the increase in the duration of the study, and this difference was statistically significant ($p<0.05$). Although nausea in the control group increased with passing time, this difference was not statistically significant.

Table 2. Comparison of the presence of abdominal cramps and hair loss in HCC patients undergoing chemotherapy in the study groups.

Variable	Stages	Experimental group		Control group		p-value (Chi-Square)
		N	%	N	%	
Abdominal cramps	Initial	9	38.00	12	57.00	0.71
	Fourth week	9	38.00	11	50.66	0.58
	Sixth week	6	19.00	16	82.33	0.003
p-value (Cochran's Q-test)		0.204		0.081		
Hair loss	Initial	11	50.66	12	57.00	0.51
	Fourth week	11	50.66	12	57.00	0.39
	Sixth week	10	44.33	15	76.00	0.061
p-value (Cochran's Q-test		0.734		0.417		

In the control group, with the increase in the duration of the study there was no significant difference in the occurrence of abdominal cramps in patients ($p=0.081$). No significant difference was observed after the intervention in the rate of vomiting, diarrhea and hair loss between the two study groups. With passing time, Cochran's Q test demonstrated that hair loss, nausea, and diarrhea decreased in the experimental group; nevertheless, this difference was not statistically significant. In the control group, patients' hair loss, vomiting, and diarrhea did not differ significantly with time.

DISCUSSION

The results of the present study showed that taking fish oil supplements in HCC patients undergoing chemotherapy significantly reduced nausea and abdominal cramps. Symptoms such as heartburn, abdominal bloating, vomiting and nausea are seen in patients with HCC. According to [29] and [30], the prevalence rate of HCC nausea and vomiting is 49% and 51%, respectively. These numbers are consistent with the results of the current study. The rate of nausea and vomiting in the current study was 50.66% prior to chemotherapy. Numerous studies have demonstrated that the use of chemotherapy medications worsens nausea and vomiting in cancer patients, as well as causing

diarrhea, changes in taste and smell, anorexia, and ultimately cachexia [31–35]. The stimulation of chemically sensitive brain regions, the activation of the autonomic nervous system, and psychological factors are the key contributors to chemotherapy side effects in cancer patients [7]. Recently, a variety of ways have been employed to control nausea and vomiting since the absence of management of these conditions results in astronomical expenses, including an increase in the number of days spent in the hospital and additional costs for medical and nursing care [15,36]. Drug therapy and complementary therapies can be listed among them. Choosing and prescribing appropriate treatments, drug or non-drug treatment, will significantly improve the quality of life and performance of patients and will have favorable effects on their lives [37]. Many supplements have been used to control side effects caused by chemotherapy. For example, the effect of reducing nausea caused by chemotherapy drugs after taking ginger supplement has been studied [38]. Another used supplement is omega-3 fatty acids. Exacerbation of side effects following the use of chemotherapy drugs with the use of omega-3 fatty acids has not been reported. In contrast to the findings of the current study, it was demonstrated that daily ingestion of fish oil supplements containing 1.2 grams of DHA and 1.8 grams of EPA for two weeks had no effect on nausea in cancer patients [39]. The reason for the discrepancy in the results may be related to the duration of the study. The results of the present study's treatment with omega-3 fatty acids were consistent with other of researches, which found that omega-3 fatty acid supplementation lessens the negative effects of chemotherapy [22,37]. High consumption of omega-3 fatty acids may be non-toxic [40]. Because some research suggests that consuming omega-3 fatty acids while undergoing chemotherapy for breast cancer has no negative side effects and may even enhance the therapeutic effects of the medications [41,42]. As a result, substantial amounts of these fatty acids can be consumed by cancer patients with advanced disease with little negative impact. On the other hand, it has been suggested that omega-3 fatty acids can be used as a dietary supplement in cancer patients for a long time with minimal digestive complications [41]. Additionally, some fatty acid supplements, like DHA, have been said to enhance the efficacy of anti-cancer medications in patients and are natural supplements free of adverse effects [37]. The present study showed that taking omega-3 fatty acids supplements significantly reduces some side effects of chemotherapy such as nausea and abdominal cramps. Although the number of people suffering from hair loss, diarrhea and vomiting decreased in the experimental group at the end of the study, this decrease was not statistically significant.

CONCLUSIONS

Although none of the statistical tests in the current study revealed a significant difference between the two groups consuming omega-3 fatty acids and placebo, the quantity of nausea and abdominal cramps following the intervention revealed a substantial decrease in the experimental group. Additionally, there was no real change in other chemotherapy adverse effects such hair loss, diarrhea, or vomiting. The use of omega-3 fatty acids as a safe supplement in conjunction with chemotherapy for cancer patients can be recommended based on the results of this study and numerous other investigations. In this study, the failure to achieve the expected results can be attributed to factors such as the small number of samples available or the duration of the study. In order to conduct further research, it is advised to extend the time that omega-3 fatty acid supplements are used in conjunction with chemotherapy and to keep track of other variables that may influence these side effects.

Conflict of interests

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

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