Effect of Extra-Virgin Olive Oil on Hand Foot Syndrome and hs-CRP in Patients Receiving Capecitabine: A Randomized Trial

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ABSTRACT

Background: *Hand Foot Syndrome (HFS) is a frequent adverse effect observed in patients undergoing capecitabine chemotherapy, often leading to treatment disruptions and dose adjustments. Elevated C-Reactive Protein (hs-CRP) levels have been associated with the development of HFS. This study aimed to assess the potential of unrefined Extra Virgin Olive Oil (EVOO) supplementation in mitigating HFS and hs-CRP elevation among individuals receiving capecitabine chemotherapy.* ***Methods:*** *Between November 2022 and May 2023, forty-five eligible participants were enrolled in this randomized trial. Patients with advanced colorectal or breast cancer were randomly allocated into three groups: an intervention group receiving unrefined EVOO supplementation (30 mL per day) alongside capecitabine, a placebo group receiving refined extra light olive oil (ELOO) supplementation (30 mL per day) alongside capecitabine, and a control group receiving capecitabine alone. The masking of both placebo and intervention groups was ensured through identical packaging and instructions, maintaining participant and physician blindness to the assigned treatments. Randomization, achieved via computer-generated sequences, ensured even distribution among the three groups.* ***Results:*** *HFS incidences were notably lower in the EVOO group (13.3%) compared to the placebo (66.7%) and control (80%) groups. Incidence of Grade 2 or more severe HFS were observed in 20% of placebo and 40% of control group patients. No cases of severe HFS were reported in the EVOO group. Moreover, EVOO supplementation led to a significant reduction in hs-CRP levels when contrasted with the placebo and control groups. These findings suggest that EVOO may serve as a preventive measure*

against HFS and exhibit anti-inflammatory effects in patients undergoing capecitabine chemotherapy. ***Conclusion:*** *This study demonstrates the potential benefits of incorporating unrefined EVOO into the regimen of patients undergoing capecitabine chemotherapy. EVOO supplementation was associated with lower incidences of HFS and a reduction in hs-CRP levels, indicating its possible role in preventing HFS development and mitigating inflammation.*

Keywords: *Hand Foot Syndrome, C-Reactive Protein, Extra Virgin Olive Oil, Capecitabine.*

INTRODUCTION

Hand Foot Syndrome (HFS), also known as palmar-plantar erythrodysesthesia, is a common and debilitating side effect in cancer patients taking capecitabine, an oral fluoropyrimidine chemotherapy agent. HFS symptoms include erythema, swelling, pain, tingling, and, in severe cases, blistering and ulceration, primarily affecting the palms of the hands and soles of the feet.[1] This syndrome can have a significant impact on patients' daily activities, resulting in reduced functional capacity and a lower quality of life.[2] Furthermore, HFS has been linked to treatment interruptions and dose reductions, potentially jeopardizing the efficacy of capecitabine-based chemotherapy regimens.[3]

C-Reactive Protein (CRP), an acute-phase reactant and marker of systemic inflammation, has been implicated in the pathogenesis of HFS.[4] CRP is synthesized by the liver in response to various inflammatory stimuli, and elevated levels of CRP have been observed in patients with severe HFS.[5] The presence of inflammation in HFS suggests a complex interplay between chemotherapy-induced tissue damage, inflammatory processes, and subsequent clinical manifestations.[6] Understanding the role of CRP in HFS could provide valuable insights into the underlying mechanisms and potential targets for therapeutic intervention.

Extra Virgin Olive Oil (EVOO) is a key component of the Mediterranean diet and has gained recognition for its numerous health benefits. It is derived from the pressing of olives without the use of heat or chemical treatments. EVOO is high in monounsaturated fatty acids like oleic acid, as well as bioactive compounds like oleocanthal, which have antioxidant and anti-inflammatory properties.[7] These properties have been linked to a variety of health benefits, including inflammatory pathway modulation.[8]

Despite EVOO's potential anti-inflammatory properties, its role in preventing HFS and modulating CRP levels in capecitabine-treated patients is largely unknown. The effect of EVOO supplementation on HFS and CRP levels in this patient population could provide important insights into the potential benefits of this dietary intervention in mitigating chemotherapy-induced side effects and reducing inflammation. Current study aims to evaluate the impact of EVOO supplementation on the incidence of HFS and high sensitivity CRP (hsCRP) levels in patients receiving capecitabine chemotherapy.

METHODS

This controlled clinical trial employed a randomized, three-arm design to assess the effect of extra virgin olive oil (EVOO) supplementation on the incidence of Hand Foot Syndrome (HFS) and C-Reactive Protein (CRP) levels in patients receiving capecitabine chemotherapy. The study was conducted from November 2022 to May 2023. The study included patients diagnosed with advanced colorectal or advanced/metastatic breast cancer who were scheduled to undergo capecitabine-containing chemotherapy regimens. Each participant of the trial was asked the informed consent and was willing to participate voluntarily. Ethical considerations were carefully addressed throughout the study, and the trial was conducted in compliance with relevant ethical guidelines and regulations. The study protocol was approved by The Ethics Committee of the Mohammad Hoesin General Hospital (ID 06/ XVII.5.11/RSMH/2022).

Forty-five eligible participants were enrolled and randomly allocated into three groups: the intervention group receiving unrefined EVOO supplementation (30 mL per day) alongside capecitabine, the placebo group receiving refined extra light olive oil (ELOO) supplementation

(30 mL per day) alongside capecitabine, and the control group receiving capecitabine alone, with both the placebo and intervention groups being masked through the use of identical packaging and instructions to ensure participant's and physician's unawareness of the assigned treatment. Randomization was performed using a computer-generated randomization sequence, ensuring an equal distribution of participants among the three groups.

The follow-up period for each participant extended over two cycles of chemotherapy (six weeks). HFS incidence and severity were evaluated using the standardized National Cancer Institute (NCI) grading criteria as shown in table 1. The presence of HFS-related symptoms, such as erythema, swelling, pain, and blistering, were carefully assessed by board certified medical oncologists. The follow-up period was terminated shortly in participants whom severe HFS was developed and thus standard management was delivered. Additionally, high-sensitivity C-Reactive Protein (hsCRP) levels were measured as a marker of inflammation. Blood samples were collected at baseline and after two cycles of chemotherapy. The hsCRP levels were quantified using the enzyme-linked immunosorbent assay (ELISA) method. The hsCRP assay was conducted according to established protocols and quality control measures to ensure accurate and reliable results.

Data collected from the study participants were analysed using *SPSS for windows 26 version*. Descriptive statistics were used to summarize the characteristics of the participant groups, including demographic data, baseline HFS incidence, and hsCRP levels. Comparative analyses, such as chi-square tests and analysis of variance (ANOVA), were employed to evaluate the differences in HFS incidence and severity between the intervention groups (EVOO and ELOO) and the control group. Changes in hsCRP levels within and between the groups were assessed using *Wilcoxon-tests* and *Mann-Whitney tests*, respectively.

RESULTS

Between November 2022 and May 2023, a total of 45 participants were enrolled in the study, and they were evenly distributed into three groups: EVOO, ELOO, and the control group, with 15 participants in each group. These participants constituted the full analysis set. The baseline demographic characteristics of the participants were found to be well balanced, as shown in Table 2. The median age of the participants was 55, 52, and 54 years in the groups with and without pyridoxine, respectively. Approximately half of the participants in each group had not received any previous chemotherapy for advanced or metastatic colorectal/breast cancer, while about one-third of the participants in each group had received first-line chemotherapy.

The incidence of Hand Foot Syndrome (HFS) was evaluated among the three groups, revealing distinct differences. In the EVOO supplementation group, HFS developed in 2 out of 15 participants (13.3%), demonstrating a significantly lower occurrence compared to the placebo group receiving olive oil (ELOO) supplementation, where HFS was observed in 11 out of 15 participants (73.3%), and the control group receiving capecitabine alone, where HFS occurred in 12 out of 15 participants (80%). Moreover, Grade 2 or worse HFS was seen in 3 participants (20%) in the ELOO group, while 6 participants (40%) in the control group experienced the same severity level. Notably, none of the participants in the EVOO group developed severe HFS.

Table 1. National Cancer Institute Grading Criteria of Hand Foot Syndrome[9]

Severity	Grade	Clinical Domain
Mild/Moderate	1	Dermatitis-related skin changes (e.g., erythema, peeling) with altered sensations (e.g., tingling, numbness, burning) that are unrelated to interruption in daily tasks.
	2	Skin alterations presented with mild pain that has minimal impact on daily activities, and the skin surface remains undamaged.
Severe	3	Ulcerative dermatitis or skin changes characterized by severe pain that significantly hinders daily activities; visible tissue breakdown is evident, such as peeling, blisters, bleeding, and oedema.

Table 2. Characteristics of The Participants

	EVOO Group (n=15)	ELOO Group (n=15)	Control Group (n=15)
Median age (years) (range)	55 (29-62)	52 (31-67)	54 (30-70)
Sex, Male, n (%)	9 (60)	8 (55.7)	6 (40)
Cancer Diagnosis, n (%)			
Colorectal	12 (80)	12 (80)	13 (87)
Breast	3 (20)	3 (80)	2 (13)
Stage, n (%)			
III	3 (20)	3 (80)	2 (13)
IV	12 (80)	12 (80)	13 (87)
Chemotherapy Regimen, n (%)			
Monotherapy Capecitabine	4 (26.7)	3 (20)	3 (20)
Capecitabine + Other Drug(s)	10 (66.7)	11 (73.3)	12 (80)
Concomitant Radiotherapy	1 (6.7%)	1 (6.7%)	0
History of Previous Chemotherapy, n (%)			
Naïve	10 (66.7)	9 (60)	9 (60)
Previous Chemotherapy	5 (33.3)	6 (40)	6 (40)
ECOG Performance Scale, n (%)			
0	10 (66.7)	11 (73.3)	8 (53.3)
1	2 (13.3)	2 (13.3)	4 (26.7)
2	3 (20)	2 (13.3)	3 (20)
Comorbidities, n (%)			
Type 2 Diabetes	1 (6.7)	2 (13.3)	3(20)
Hypertension	2 (13.3)	2 (13.3)	2 (13.3)

Table 3. Difference in Incidence of Hand Foot Syndrome

Severity	Grade	EVOO (n=15), n (%)	ELOO (n=15), n (%)	Control (n=15), n (%)	p[1]	OR[2] (95%CI)	OR[3] (95%CI)
Mild/ Moderate	1	2 (13.3)	8 (53.3)	6 (40)	0.219	4.0 (0.72-22.04)	3.0 (0.51-17.31)
Severe	2/3	0	3 (20)	6 (40)	0.089	7.0 (0.33-147.17)	13 (0.67-251.22)
Total		2 (13.3)	11 (73.3)	12 (80)	0.042	5.5 (1.03-29.15)	6.0 (1.14-31.53)

[1]Chi Square Test, [2]EVOO compared to Control, [3]EVOO compared to ELOO

In addition to evaluating Hand Foot Syndrome (HFS) incidence, the study also assessed the levels of high sensitivity C-Reactive Protein (hsCRP) among the three groups. The results revealed significant differences in hsCRP changes. In the EVOO supplementation group, hsCRP levels were significantly decreased after the intervention, indicating a reduction in systemic inflammation. In contrast, the placebo group receiving olive oil (ELOO) supplementation & control group showed significant increase in hsCRP levels.

Table 4. hsCRP Before and After Intervention among Groups

hsCRP	EVOO (n=15)	ELOO (n=15)	Control (n=15)	p
Baseline (mg/L)	9.45 (0.20, 126.90)	8.80 (0.90, 115.20)	9.60 (1.30, 80.70)	0,850[1]
After Chemotherapy (mg/L)	2.75 (0.18, 8.60)	21.00 (3.00, 60.00)	44.10 (9.70, 118.00)	<0,0001[1]
p'	0.005[2]	0.0021[2]	0.001[2]	

[1]Kruskall Wallis Test, [2]Wilcoxon Test

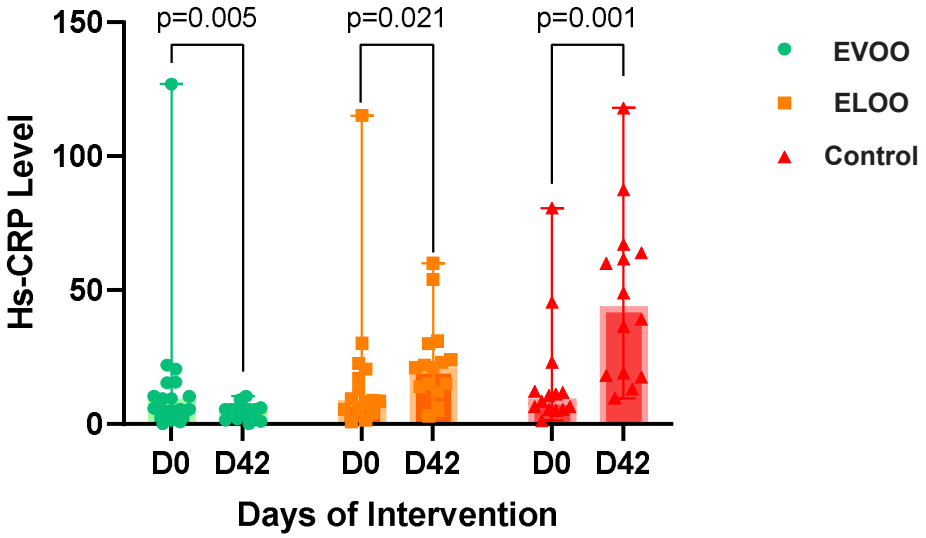

Figure 1. Bar Graph of serum Hs-CRP Level between intervention group.

DISCUSSION

The results of this clinical trial provide compelling evidence regarding the efficacy of extra virgin olive oil (EVOO) supplementation in reducing the risk of Hand Foot Syndrome (HFS) and modulating C-Reactive Protein (CRP) levels in patients receiving capecitabine chemotherapy. These findings contribute to our understanding of the potential benefits of EVOO as a dietary intervention in mitigating chemotherapy-induced side effects and inflammation.

The significant reduction in HFS incidence observed in the EVOO supplementation group compared to the refined olive oil (ELOO) supplementation group and the control group is noteworthy. HFS is a common and distressing adverse event associated with capecitabine, often leading to treatment interruptions and a decreased quality of life for patients.[10] Current study highlighted the potential preventive effect of EVOO supplementation on this side effect. Furthermore, the absence of severe HFS (Grade 2 or worse) in the EVOO group further supports the notion that EVOO may provide significant protection against the development of severe HFS.

The observed changes in CRP levels further reinforce the anti-inflammatory properties of EVOO. In the EVOO group, a significant decrease in hsCRP levels was observed after the intervention, indicating a reduction in systemic inflammation. In contrast, the ELOO group showed an insignificant increase in hsCRP levels, while the control group demonstrated a significant increase in hsCRP levels. The beneficial effects observed in the EVOO group can be attributed to the unique composition of EVOO, which is rich in monounsaturated fatty acids, particularly oleic acid, as well as bioactive compounds such as oleocanthal. Oleocanthal is a phenolic compound found in EVOO and is known for its potential health benefits.[11] It possesses strong anti-inflammatory properties and has been shown to exhibit similar effects to non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen.[12,13] Oleocanthal is believed to inhibit the activity of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, which are key enzymes involved in the production of inflammatory mediators called prostaglandins.[14,15] By blocking the activity of these enzymes, oleocanthal helps to reduce inflammation and alleviate related symptoms.

In the context of the present study, the potential presence of oleocanthal in the extra virgin olive oil used for supplementation could contri bute to the observed reduction in Hand Foot Syndrome (HFS) incidence and the modulation

of C-Reactive Protein (CRP) levels. However, more detailed investigations would be required to directly measure the levels of oleocanthal and its specific contribution to the outcomes of the trial. It is important to note that the ELOO supplementation group did not demonstrate significant benefits in preventing HFS or modulating CRP levels compared to the control group. This suggests that the specific components present in EVOO, such as oleocanthal, may play a crucial role in conferring the observed effects. The differences in outcomes between the EVOO and ELOO groups highlight the importance of using high-quality, unprocessed EVOO rather than other forms of olive oil in clinical interventions.

Despite the significant findings, several limitations should be considered. First, the sample size of this study was relatively small, which may limit the generalizability of the results. Further research with larger cohorts is needed to confirm the findings and assess the long-term effects of EVOO supplementation. Secondly, the mechanisms underlying the protective effects of EVOO on HFS and inflammation were not directly explored in this study. Further investigations are warranted to elucidate the specific pathways involved and to explore potential synergistic effects with capecitabine.

CONCLUSION

The study demonstrates that EVOO supplementation significantly reduces the incidence of HFS and decreases hs-CRP levels in patients receiving capecitabine chemotherapy.

CONTRIBUTION TO THE LITERATURE

This article significantly contributes to the current literature by being the first investigating the impact of non-refined Extra Virgin Olive Oil (EVOO) supplementation on Hand Foot Syndrome (HFS) and C-Reactive Protein (hs-CRP) levels in patients receiving capecitabine chemotherapy. The uniqueness lies in the focus on EVOO's potential preventive effect on HFS, a common and distressing side effect of capecitabine. Moreover, the study employs a randomized controlled clinical trial design, providing robust evidence for the potential benefits of EVOO supplementation. The observed reduction in hs-CRP levels further underscores EVOO's anti-inflammatory properties, which are crucial in the context of capecitabine-induced inflammation. Overall, this work enhances scholarship by offering valuable insights into a novel intervention that may improve patients' quality of life and treatment tolerability in the context of capecitabine chemotherapy.

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