 DOI: 10.21608/adjalexu.2023.201355.1361

EFFICACY OF TOPICAL OMEGA-3 EMULGEL IN PREVENTING RADIATION-INDUCED ORAL MUCOSITIS: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

INTRODUCTION: One of the most common debilitating side effects that head and neck cancer patients suffer from during radiation therapy is oral mucositis. This leads to severe oral mucosal inflammation and ulceration that hinder the patient's nutrition and affects his quality of life and overall survival. Recently, Omega-3 polyunsaturated fatty acids have captured special interest in managing oral diseases due to its superior anti-oxidant, anti-inflammatory and wound healing properties.

OBJECTIVES: The purpose of this study is to assess the efficacy of topical Omega-3 emulgel in prevention of radiation induced oral mucositis and its associated pain.

METHODOLOGY: This study was conducted on thirty-six head and neck cancer patients who were planned to receive radiotherapy. Patients were randomly divided into two groups: Group I: eighteen patients were given conventional preventive treatment and Group II: eighteen patients received topical Omega-3 emulgel. All patients were clinically evaluated at baseline and after three and six weeks from treatment using World Health Organization (WHO) grading system for oral mucositis severity and Visual Analogue Scale (VAS) for perceived pain severity.

RESULTS: There was a significant lowering of VAS scores as well as WHO mucositis grades after six weeks of treatment in test group treated with topical Omega-3 emulgel when compared to the control group receiving conventional preventive treatment.

CONCLUSIONS: Topical Omega-3 emulgel showed a promising beneficial effect in preventing radiation-induced oral mucositis and reducing its associated pain

SHORT RUNNING TITLE: Omega-3 efficacy in oral mucositis prevention

KEYWORDS: Oral Mucositis, prevention, Omega-3, emulgel

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INTRODUCTION

Oral mucositis (OM) is regarded as one of the most common serious complications that develops during radiotherapy treatment in head and neck cancer (HNC) patients (1). Radiation-induced oral mucositis (RIOM) occurs as a result of DNA damage and cell apoptosis happening in the form of inflammation or ulceration in the oral mucosa. It is encountered in almost all HNC patients that undergo radiation therapy (2,3). The affected patients usually complain of mild to severe pain, difficulty in swallowing and dehydration which interferes with the oral intake of food leading to malnutrition. It can also lead to alteration/reduction in the treatment dose or breaking the treatment regimen which consequently affects patients' quality of life (1,4,5).

OM development and resolution are characterized by five continuous and overlapping phases (1,6). This usually involves reactive oxygen species (ROS) regeneration, transcription factors like nuclear factor kappa B (NF-κB) activation in addition to upregulation of some pro-inflammatory cytokines that include interleukin-1 beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) (3,6,7). This further worsens tissue injury which results in development of multiple painful ulcerations that are subjected to microorganisms' colonization leading to secondary infections, which is regarded as the most significant stage in OM (7). To date, there is no definitive effective preventive or therapeutic approaches for OM or its associated pain, thus a large number of studies proposing OM management has been conducted (1,3).

Omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) are recognized among essential fatty acids that are known for their role in healthy development, disease prevention, and appropriate growth. (8,9). They constitute a group of fatty acids including: α-linolenic acid (ALA; 18:3 ω-3), docosapentaenoic acid (DPA; 22:5 ω-3), stearidonic acid (SDA; 18:4 ω-3), eicosapentaenoic acid (EPA; 20:5 ω-3) and docosahexaenoic acid (DHA; 22:6 ω-3) where the two most vital bioactive forms in mammals among them are eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6) (8,10). Despite the fact that EPA and DHA can be formed from the precursor fatty acid ALA, this requires complex chemical reactions making their conversion less efficient in humans. Thus consumption of food such as fish and fish oils or nutritional supplements rich in these two principal fatty acids is recommended (10).

A growing body of research, including both human and animal studies, has demonstrated the therapeutic benefits of Omega-3 PUFAs, particularly EPA and DHA, in a number of human diseases, including diabetes, cancer, cardiovascular problems, and autoimmune disorders (9,11). This may be related to their anti-inflammatory and antioxidant properties, and also their support for epithelial integrity and wound healing ability (12,13). It was discovered that Omega-3 PUFAs lower levels of pro-inflammatory cytokines that include (TNFα), (IL-6) and (IL-1β) in addition to inhibiting arachidonic acid metabolites production which can limit tissue damage and actively suppress inflammation (14). DHA has also been shown to increase the expression of genes related to detoxification and antioxidant defense, which lowers oxidative stress (12).

When compared to systemic supplementations, animal studies have shown that locally given Omega-3 has superior impact on reducing inflammation, promoting re-epithelialization, and wound healing (13). Studies on both humans and animals have shown how Omega-3 PUFAs can help treat a variety of oral conditions including gingivitis, periodontitis, and recurrent aphthous stomatitis (RAS) (14,15). A recent clinical study also revealed that Omega-3 PUFAs may have a therapeutic effect against OM that develops in cancer patients receiving chemotherapy (16). However, the preventive effect of Omega-3 has not yet been studied on RIOM. Hence, the aim of this research was to test the preventive effect of oral Omega-3 emulgel on RIOM and its associated pain.

MATERIAL AND METHODS

A. Material

Study design

A randomized, parallel arm, controlled, clinical trial was carried out on 36 patients planned to receive radiotherapy for the head and neck region, from both sexes. Participants were selected from the Department of Clinical Oncology, Faculty of Medicine, Alexandria University, outpatient clinic. All participants were given a detailed explanation of the study and signed an informed consent. The study was carried out and completed following the CONSORT 2010 guidelines for reporting clinical trials and the modified Helsinki's code for human clinical studies (2013) (17). Ethical approval has been granted by the Research Ethics committee, Faculty of Dentistry, Alexandria University (IRB NO: 00010556-IORG0008839- 0290-09/2021), and has been registered at ClinicalTrials.gov (NCT05214495).

Sample size, randomization and allocation concealment

Sample size was calculated assuming 5% alpha error and 80% study power. Bakr et al.(2) reported no signs of oral mucositis (grade 0) after 6 weeks of topical oral vitamin oral D application in 60% of patients compared to 13.3% with conventional treatment. Topical Omega-3 emulgel is assumed to have a similar effect as vitamin D (18,19). Based on comparison of proportions, the minimum sample size was calculated to be 16 patients per group, increased to 18 to make up for attrition bias. The total required sample size required = number of groups × number per group= 2 x 18 = 36 patients (G*Power (Version 3.1.9.4)). (20)

A computer-aided random allocation software [Sealed Envelope] (21) was used for randomization. Using permuted block technique, participants were randomly allocated in blocks of four to one of the two study groups. Allocation sequence was sealed in opaque envelopes and the allocation was performed by an assistant who was not part of the trial. Blinding of patients was challenging as several therapeutic agents with various regimens and doses were used in the control group while the test group only received topical Omega-3 emulgel. On the other hand, it was ensured that both the outcome assessor and the statistician were blinded to the process of allocation. Outcome assessment was carried out by a single trained oral medicine specialist.

Topical Omega-3 emulgel preparation

Fish oil (Omega-3 fatty acids 70.4%; EPA 34.9% and DHA 24.2%) was kindly gifted by Safe pharmaceutical company, Alexandria, Egypt. Using direct emulsification, fish oil emulsion was prepared. In brief, the aqueous phase that contains Tween 80 (El Gomhouria Co. Alexandria, Egypt) was added to the oily phase which contains Fish oil and Span 80 (sigma Aldrich, UK))(22). The ratio of water: oil was 6:4 and the ratio of the used surfactant was 7:3 for Tween 80 and Span 80 respectively. The mixture was pre-emulsified for 5

min at 20,000 rpm using T25-digital Ultra-Turrax homogenizer (IKA Works, Inc., Wilmington, NC). The formed coarse emulsion was then ultrasonicated using Branson Digital Sonifier S-450D (Emerson Electric Co., St. Louis, MO at 60% ultrasonic amplitude for 5 min(23). For preparation of gel, Carbopol 940 (Alamreya Pharmaceuticals, Alexandria, Egypt) was dispersed in water then neutralized using triethanolamine using pH meter (Mettler Toledo, Switzerland)(24). Masking of fish oil taste was made by applying few drops of apple oil. The final concentration of Fish oil in the preparation was 35% w/w.

B. Methods

Participants and intervention:

Selected male and female participants were considered eligible if they were proven to have HNC malignancy and were scheduled to receive radiotherapy on the head and neck region either as postoperative or definitive therapy and were 18 years old or more (25). While patients were excluded from the study if they were taking anticoagulants such as heparin, or aspirin or if they were suffering from any uncontrolled systemic condition (such as liver or renal disfunction, cardiovascular disease, autoimmune disease or diabetes). Patients were also non eligible if they had any uncontrolled physical or intellectual problem that could interfere with the procedure, or were planned to receive chemotherapy simultaneously with radiotherapy (2,25).

Detailed medical as well as dental history was taken from participants prior to the study. All eligible patients received proper basic dental care including emergency treatment, scaling and root planning and removal of clinically or radiographically detected septic foci (2).

The thirty-six assigned patients were randomly allocated to one of the study groups:

The control group comprised eighteen patients which received conventional preventive therapy that was begun one day before radiotherapy to six weeks after and was applied twice daily.(2,26). This preventive therapy included topical antifungal agent (Miconaz oral gel) (Manufactured at Medical Union Pharmaceuticals, 6th District-Nasr City- Cairo, Egypt.), anti-inflammatory mouthwash, sodium bicarbonate mouthwash (Alkamisr sachets) (Manufactured at Misr Co. For Pharm. Ind. S.A.E., Egypt.) Topical anesthetics agent as (Oracure gel) (Manufactured at Amoun Pharmaceutical Company El Obour city, Cairo, Egypt.), as well as systemic analgesics, were provided if needed.

The test group comprised 18 patients that were given topical Omega-3 emulgel which was formulated by the aid of the Pharmaceutics Department, Faculty of Pharmacy, Alexandria University, as previously described. One gram was applied by the patients twice daily, one day before starting radiotherapy to six weeks after (27,28).

Clinical evaluation

Patients were clinically-evaluated at baseline, three and six weeks after intervention by the following:

A) The severity and intensity of OM was measured by using the WHO grading system (29) That is explained as four different grades: grade 0 (none), grade I (mild mucositis: oral soreness and/or erythema), grade II (moderate mucositis: oral erythema, ulcers, and solid diet can be tolerated), grade III (severe mucositis: oral ulcers, but solid diet cannot be tolerated), and grade IV (life-threatening: oral alimentation is impossible).

B) Pain and discomfort were reported by patients using the Visual Analogue Scale (VAS) (30,31) where pain levels were rated on a scale from 0 (no pain) to 10 (intolerable pain).

Statistical Analysis

Data collected were analyzed by the aid of IBM SPSS for Windows (Version 23.0) and significance was set at p value <0.05. Descriptive statistics were calculated for all variables. Comparisons of mucositis scoring and VAS were done using Mann-Whitney U test. Age and gender were compared using independent samples t- and Chi-square tests, respectively. Intention-to-treat analysis was used in the data analysis of this trial.

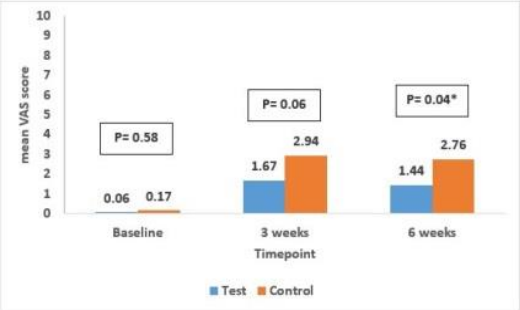
RESULTS

Table 1 shows the patients' demographic data and baseline characteristics. There were no statistically significant differences in the demographic characteristics between both groups. The mean ± SD age was 53.9 ± 13.8 and 58.9 ± 11.60 in the test and control groups. The majority of participants were males, and half of them presented with oral cancer.

Table 2 shows that all the included patients presented with grade 0 mucositis at baseline ($p=1.00$). There was a significant difference in the mucositis grades between both groups at both the three- and six-weeks follow-up appointments. More than 50% of the test group participants did not develop mucositis (score 0), and none of them showed grade 4 (severe) mucositis.

Figure 1 represents the perceived pain using VAS across time. There were no significant differences between both groups at baseline and after three weeks ($p >0.05$). However, the control group showed significantly higher VAS scores at six weeks ($p= 0.04$).

Figure 1. Perceived pain using VAS in the two study groups across time



*Statistically significant at p value <0.05

Table 1: Baseline characteristics

		Test (n=18)	Control (n=18)	P value
Age a	Mean (SD)	53.9 ± 13.8	58.9 ± 11.6	0.24 a
Gender: n (%)	Males	9 (50%)	14 (77.8%)	0.08 b
	Females	9 (50%)	4 (22.2%)	
Diagnosis: n (%)	Oral Cavity	9 (50%)	9 (50%)	1.00 b
	Other sites	9 (50%)	9 (50%)	

a: Independent samples t-test
b: Fisher exact test

Table 2 WHO mucositis grade

		Test (n=18)	Control (n=18)	P value
Baseline	Grade 0	18 (100%)	18 (100%)	1.00
	Grade 1	0 (0%)	0 (0%)	
	Grade 2	0 (0%)	0 (0%)	
	Grade 3	0 (0%)	0 (0%)	
	Grade 4	0 (0%)	0 (0%)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
3 weeks	Grade 0	11 (61.1%)	4 (22.2%)	0.03*
	Grade 1	4 (22.2%)	2 (11.1%)	
	Grade 2	0 (0%)	5 (27.8%)	
	Grade 3	3 (16.7%)	5 (27.8%)	
	Grade 4	0 (0%)	2 (11.1%)	
	Median (IQR)	0.00 (0.00, 1.00)	2.00 (0.75, 3.00)	
6 weeks	Grade 0	11 (61.1%)	2 (11.1%)	0.007*
	Grade 1	4 (22.2%)	7 (38.9%)	
	Grade 2	1 (5.6%)	5 (27.8%)	
	Grade 3	2 (11.1%)	3 (16.7%)	
	Grade 4	0 (0%)	1 (5.6%)	
	Median (IQR)	0.00 (0.00, 1.00)	2.00 (1.00, 2.50)	

*statistically significant at p value <0.05

DISCUSSION

Oral Mucosa is considered one of the highly susceptible areas that are adversely affected by head and neck ionizing radiation (32). One of the most commonly encountered life-threatening, toxic complications in HNC patients is RIOM since it is frequently associated with significant discomfort, pain and interference with solid and liquid food intake. This consequently affects patients adversely leading to malnutrition, prolonged hospitalization that negatively impacts the patient's quality of life and overall survival (3,33). In the past few decades, Omega-3 PUFAs health benefits have been outlined and escalated in multidisciplinary systemic diseases such as diabetes, cardiovascular diseases and cancer (8,9). They have also been shown to play critical roles in tissue homeostasis restoration and inflammation mitigation in a variety of oral diseases, that include oral mucositis (34). Thus, the main objective of this study was to evaluate the effect of Omega-3 topical emulgel on RIOM prevention in HNC patients treated by radiotherapy.

According to the present study's findings, a significant difference was demonstrated in VAS pain scores between the two study groups after six weeks, where pain scores were significantly lower in the test group compared to the control group. On the other hand, there was no significant difference in VAS scores between the two groups after three weeks, which could be explained by the short period of topical Omega-3 emulgel application at the first follow up time point. Our results also showed a notable decrease in OM in terms of both incidence and severity, at both evaluation dates in the test group. Moreover, in the test group, more than half of the patients showed no clinical signs of OM after six weeks, compared to just two patients in the control group. Hence, the effectiveness of topical Omega-3 emulgel in preventing OM and reducing its severity and accompanying pain was highlighted by these findings.

This is possibly explained by their strong anti-inflammatory and antioxidant effects illustrated earlier, as well as their capacity for rapid wound epithelialization. Additionally, studies have demonstrated that through cyclooxygenase and lipoxygenase pathways, Omega-3 PUFAs can successfully inhibit arachidonic acid metabolites production which can further limit tissue damage (14,35).

The findings of our study are consistent with those of Hashemipour et al., who noted a significant reduction in the severity and duration of OM in patients receiving Omega-3 systemic supplementation (16). Also, our outcomes are in line with those of El Khouli et al. who stated that using Omega-3 supplements significantly reduced the severity of RAS outbreaks and pain levels in his study (14). In spite of the difference in the

etiopathogenesis of RAS and RIOM, the study emphasises the role of Omega-3 consumption in mucosal healing and recovery (34). This may be connected to EPA and DHA's capacity to preserve cell barrier function and epithelial integrity at the cellular level by avoiding tight junction structure disruption and reducing cell necrosis (36). Moreover, the topical protective role of Omega-3 emulgel demonstrated in our results are comparable to the findings of Basha et al. who showed a significant enhancement in rats oral mucosal healing after being treated by topical Omega-3, compared to those treated by systemic administration (13). Similarly, the overall topical preventive effect of Omega-3 on OM is also aligned with Ferreira, P. et al who stated that vitamin E mouthwash lowered the incidence of symptomatic RIOM in oral and oropharyngeal cancer patients (37). In addition, Bakr et al also demonstrated a significantly positive effect of topically applied vitamin D in preventing RIOM, highlighting the promising role of topical preventive therapy (2).

The current study has some strengths, we believe that this is the first clinical trial to examine the effectiveness of topical Omega-3 emulgel in RIOM prevention. The study depended on clinical examination to estimate oral mucositis severity in addition to patients reporting different levels of associated pain using the (VAS). Thus, our study fills a knowledge gap by providing promising evidence about topical Omega-3 emulgel effect in prevention of RIOM.

On the other hand, the study had some limitations that includes short-term follow up, so further clinical trials with longer follow-ups and larger sample size are still needed. Trials contrasting the effectiveness of topical and systemic Omega-3 supplements on preventing oral mucositis are also required. Additionally, to determine and modify the precise dosage of Omega-3 emulgel in various oral disorders, more research is encouraged.

CONCLUSIONS

This study demonstrated a favourable effect of topical use of Omega-3 emulgel in RIOM prevention and decreasing the associated pain intensity owing to its potent anti-oxidant, anti-inflammatory properties and wound healing.

DECLARATIONS

Statement of conflict of interest

The authors declare that they do not have any conflict of interest

FUNDING

The authors did not receive funds for this study

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