Nigella Sativa Oil for Oral Mucositis

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Abstract:

Oral mucositis (OM) is common treatment-induced toxicity in patients receiving chemoradiation for head and neck cancer (HNC). The present study aims to evaluate the efficacy and safety of Nigella sativa (NS) oil in chemoradiation-induced OM of HNC patients. From January 2017 to May 2018, 40 patients with HNC were randomly allocated into two groups each of 20 patients. The first group received NS oil mouthwash five times daily, while the second group received the routinely followed protocol (magic mouthwash) and served as a control. All patients received radiotherapy (RT) (60-70 Gy) in 30-35 fractions over 6-7 weeks with or without chemotherapy. Patients were evaluated weekly to estimate the onset and severity of OM and the patient's reported outcomes (pain, swallowing, and functional score). The majority of patients (70%) were men. The commonest primary tumor locations were the larynx (47.5), and pharynx (22.5%) mostly classified as stages III or IV. NS oil significantly reduces the RTOG of mucositis in the last 3 weeks of RT and improves the reported outcomes (pain and swallowing) during the next 6 weeks of RT compared with controls. The majority of patients in the NS group ingested either normal or soft food especially at the end of RT. In conclusion, NS oil decreases the duration and severity of OM with better patient-reported outcome and pain control compared with the routine treatment. NS oil can be considered as a feasible and affordable option for chemoradiation-induced OM in HNC patients.

Key words: Nigella sativa; oral mucositis; chemoradiation; head and neck cancer

أستخدام زيت حبة البركة كغسول للفم في علاج التهاب غشاء الفم الخاطي الناتج عن استخدام الأشعاع والأدوية لعلاج المرضى المصابين بسرطانات الرأس والرقبة

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الخلاصة:
يعتبرالتهاب غشاء الفم المخاطي من الأعراض الجانبية الناتجة عن العلاج في المرضى الذين يتلقون علاج اشعاعي وكيمياوي لسرطان الرأس والرقبة. تهدف هذه الدراسة إلى تقييم فعالية وسلامة زيت حبة البركة في علاج التهاب غشاء الفم المخاطي الناتج عن استخدام العلاج الأشعاعي والكيمياوي. منذ كانون الثاني ٢٠١٧ ولغاية أيار ٢٠١٨ أجريت دراسة على ٤٠ مريضا بسرطان الرأس والرقبة حيث تم تقسيمهم عشوائياً إلى مجموعتين من ٢٠ مريضا لكل مجموعة. تلقت المجموعة الأولى زيت حبة البركة كغسول فموي خمس مرات يوميا، في حين تلقت المجموعة الثانية البروتوكول العلاجي المتبع بشكل روتيني (غسول الفم السحري) واعتبرت مجموعة مقارنة. وتلقى جميع المرضى العلاج الإشعاعي لأكثر من ٦-٧ أسابيع مع أو بدون العلاج الكيميائي. تم تقييم المرضى أسبوعيا لتقدير البداية وشدة التهاب غشاء الفم المخاطي (الألم، ودرجة البلع، والوظيفية). غالبية المرضى (٧٠٪) كانوا من الرجال، وكانت مواقع الورم الرئيسي الأكثر شيوعاً في الحنجرة (٤٧,٥) والبلعوم (٢٢,٥٪) وتصنف معظمها ضمن المراحل الثالثة أو الرابعة. أدى استخدام زيت حبة البركة الى الحد من شدة التهاب غشاء الفم المخاطي في آخر ٣ أسابيع من التعرض للأشعاع وأدى أيضا الى تحسن النتائج المبلغ عنها من قبل المريض (الألم والبلع) خلال الأسابيع اللاحقة مقارنة مع مجموعة التحكم. الغالبية العظمى من المرضى في المجموعة الأولى تحسن استخدامها لوجبات الطعام الأعتيادية أو الناعمة خاصة في نهاية فترة العلاج بالأشعة والكيمياوي. يمكن الأستنتاج بأن زيت حبة البركة يقلل مدة وشدة التهاب غشاء الفم المخاطي مع نتائج أفضل في السيطرة على الألم بالمقارنة مع العلاج الروتيني. يمكن اعتبار زيت حبة البركة خياراً ممكناً وبأسعار معقولة للحد من التهاب غشاء الفم المخاطي الناتج عن استخدام الأشعاع والأدوية في علاج مرضى سرطان الرأس والرقبة.
الكلمات المفتاحية: حبة البركة، التهاب غشاء الفم المخاطي، العلاج الكيموشعاعي، سرطان الرأس والرقبة

Introduction

Oral mucositis (OM) was considered as an acute inflammation induced by necrosis of the mucosal basal layer of the oral cavity [1]. It was one of the most well-known consequences of radiotherapy and/or chemotherapy-induced cytotoxicity in patients treated for head and neck cancer (HNC) [2,3]. Moreover, OM was correlated with the high rate of hospitalization and might interfere with the administration of programmed treatment strategies [4]. Despite its frequency and clinical impact, the risk factors for OM in HNC patients have not been well outlined to date. The incidence of mucosal injury has been recorded to vary with radiation intensity and protocol and the dose and schedule of the chemotherapeutic agents [5,6]. Although many agents have been used to manage OM, no well-defined standard guidelines or recommendations were established for the management of chemoradiation-induced OM in NHC patients. The use of topically installed formulations (e.g., mouthwashes) like 'magic' mouthwash is nowadays considered as a common practice for the care of chemoradiation-induced OM, for the claim that it benefits the relief of the associated symptoms like mouth pain, inflammation and ulceration [7]. Currently, the use of plants-derived products for the treatment of many diseases became a common clinical practice due to convenient access without prescription, low-cost, as well as the fewer adverse effects associated with the use of natural products. Among the medicinal plants, black seed (*Nigella sativa*) has a well-characterized broad range of medicinal properties and widely utilized for pharmaceutical, food and ornamental industries. Various types of chemical compounds that have different biological activities were isolated and identified from different NS species [8]. In addition to thymol, limonene, carvacrol, p-cymene, alpha-pinene, 4-terpineol, longifolene, and t-anethole benzene [9,10], the main constituent thymoquinone (TQ) has a variety of pharmacological properties [11,12]. The use of NS oil as a folklore medicine for therapeutic purposes has a long history in Indian and Arabic cultures. It has been traditionally used for the treatment of various pathological conditions including asthma, bronchitis, rheumatism, headaches, and dysentery in Southeast Asia, Northern Africa and the Middle East [13]. Moreover, it has been reported that NS oil promotes wound healing in domestic animals and the

enhancement of human gingival fibroblast proliferation with improved wound closure [14,15]. These effects were mostly correlated with the antimicrobial and anti-inflammatory activities of the NS constituents, specifically TQ [16,17]. Accordingly, the previously mentioned properties of NS oil encourage its use for the management of chemoradiation-induced OM in patients with HNC.

Methods

Study design and setting

The present prospective pilot open-label study was conducted from January 2017 to May 2018. Fifty-three patients of both sexes with ages above 18 years, diagnosed with squamous cell carcinoma of the head and neck, were evaluated at Hiwa Oncology Hospital, and Zhyanawa Radiation Center, Sulaimani, Iraq for eligibility. Only 40 patients who had a histopathologically confirmed squamous cell carcinoma of the head and neck meet the inclusion criteria were enrolled in the study and treated with radiation or chemoradiation (Figure 1). The study protocol was approved by the local Clinical Research Ethics Committee of the College of Medicine, University of Sulaimani (REC-45 in 13/2/2017) in accordance with the Helsinki declaration 2000, and signed informed consent was obtained from all the participants before enrolment in the study.

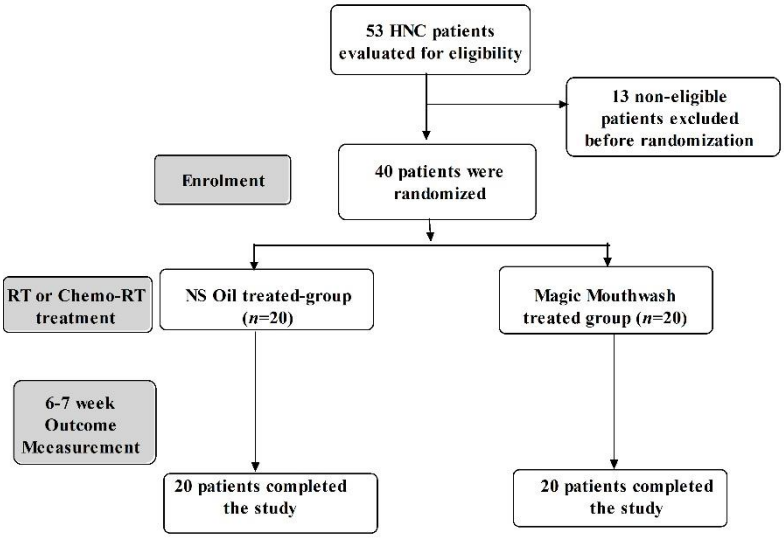

Figure (1): Flowchart displaying the HCN patient's screening, randomization, and intervention.

Inclusion and exclusion criteria

The inclusion criteria include histopathologically confirmed squamous cell carcinoma of the head and neck, primary tumor in stage T1, T2, T3 or T4, regional node of any status, distant metastases absent, age 18 years and above, Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 or 1, normal hematologic and biochemical parameters, willingness to fulfill the study requirements and providing a signed consent. The exclusion criteria include previous surgery in the head and neck, previous radiotherapy, uncontrolled systemic or widely disseminated disease, the presence of asynchronous double primary malignancy or simultaneous participation in another study.

Randomization and treatment

Utilizing a block randomization protocol, the eligible patient was randomly assigned by the clinician into two groups (20 patients in each group); the NS oil treatment group (group A) and the routinely followed treatment group (group B) utilized as a control. The patients in

group A received a topically administered NS oil as mouthwash (BARRY Int. PVT., LTD, Karachi, Pakistan), obtained from a local distributor (Voucher No.: 85-4-2017) and approved for quality assurance by the department of Pharmaceutics, College of Pharmacy; it has been applied as 10 ml each 6 hr daily starting from the first week after initiation of radiotherapy or radiochemotherapy (60-70 Gy in 30-35 fractions over 6-7 weeks with or without chemotherapy) up to 6-7 weeks (the end of the radiation therapy). The patients in group B (control) received a treatment based on the hospital-adopted protocol for management of OM that utilizes an in-house prepared formula "Magic Mouthwash". This formula contains nystatin 100 000 U (Julphar, UAE), tetracycline 0.02% (Triax Pharmaceuticals LLC, USA), lidocaine 0.5% (Pharma Chem Consultech, India), and dexamethasone 0.5% (Pfizer NV, Belgium), which was prepared by expert pharmacist according to a standardized method [18]; the formula was administered as a mouthwash in a similar amount, dosage form and duration as in group A according to the instruction of the medical oncologist.

Patient follow up and outcome measurements

Based on the adopted institutional protocol, the HNC patients of both groups were treated postoperatively with 30-33 fractions of radiation sessions (60-70 Gy) during 6-7 weeks (Electa Linac Synergy, Stockholm, Sweden); meanwhile, some of the enrolled patients received chemotherapy concomitantly with the radiation doses. On weekly bases, all participants were evaluated for the occurrence, onset, and severity of OM, appearance of adverse events like dysphagia, pain, and presence of swallowing difficulties during maintenance of nutrition [19]. Almost all the patients in both groups completed the treatment regimen without dropout from the study; however, a treatment delay occurs in patients who developed OM.

Statistical analysis

The presented data were analyzed utilizing SPSS 10.0 software. To describe the qualitative data, simple frequency and percentage were used. To analyze the nominal data, Fisher's exact test was utilized. Non-parametric statistics such as Mann Whitney test was used to analyze the ranking of data and some of the quantitative data which didn't show normal distribution clearly (lesion duration and pain severity). $P<0.05$ was considered of statistical significance.

Results

A total of 40 patients with squamous cell carcinoma of the head and neck were treated with radical radiation /chemoradiation and clinically evaluated for incidence and severity of OM. Their baseline user profile including demographic parameters and clinical-pathologic features were shown in Table 1. Age, sex, and smoking habits were similar in both groups. Diagnosis and treatment parameters including the site and stage of the tumor and the histopathology of all tumors that revealed all being squamous cell carcinoma were also comparable in both groups. The mean age of the patients was 55.53 years and the majority of patients (70%) were men. The primary locations of the tumor included larynx (47.5%), pharynx (22.5%), oral cavity (10%) and nasopharynx (10%). All of the tumors were new and the majority was categorized as Stages III or IV.

Table (1): Demographic characteristics and baseline data of the HNC patients

Variables	Control	NS Oil	Total	*P*-value
	n (%)	*n* (%)	*n* (%)	
Age (years)				
≤ 65	13(65)	16(80)	29(72.5)	
> 65	7(35)	4(20)	11(27.5)	0.288
Gender				
Female	5(25)	7(35)	12(30)	
Male	15(75)	13(65)	28(70)	0.490
Dental status				
Good	3(15)	0(0)	3(7.5)	
Fair	2(10)	9(45)	11(27.5)	
Bad	10(50)	6(30)	16(40)	
Edentulous	5(25)	5(25)	10(25)	0.035
Previous Medical History				
None	5(25)	10(50)	15(37.5)	
Comorbidities	15(75)	10(50)	25(62.5)	0.102
Tumor Location				
Larynx	10(50)	9(45)	19(47.5)	
Nasal cavity	2(10)	2(10)	4(10)	
Oral cavity	1(5)	3(15)	4(10)	
Others	1(5)	3(15)	4(10)	
Pharynx	6(30)	3(15)	9(22.5)	0.625
Stage of Cancer				
I	1(5)	4(20)	5(12.5)	
II	3(15)	2(20)	5(12.5)	
III	8(40)	6(30)	14(35)	
IV	8(40)	8(40)	16(40)	0.598
Total Radiation dose				
7000	13(65)	9(45)	22(55)	
6600	2(10)	6(30)	8(20)	
6300	5(25)	5(25)	10(25)	0.255
Number of fractions				
≤ 30	6(30)	7(35)	13(32.5)	
33	4(20)	9(45)	13(32.5)	
35	10(50)	4(20)	14(35)	0.102
Type of chemotherapy during RT				
None	8(40)	10(50)	18(45)	
Carboplatin	2(10)	1(5)	3(7.5)	
Cisplatin	7(35)	8(40)	15(37.5)	
Cetuximab	3(15)	1(5)	4(10)	0.733
Interruption of RT				
No	15(75)	16(80)	31(77.5)	
Yes	5(25)	4(20)	9(22.5)	>0.99
Duration of RT (week)				
Six	6(30)	8(40)	14(35)	
Seven	14(70)	12(60)	26(65)	0.507

Notes: Values are simple frequency and percentage.

Table 2 showed that the appearance of OM was detected at the first week of RT in around 30% and 40% of the patients in arm A and B, respectively; this value increased to around 85% and 65% in the second week of treatment. In the first 3 weeks of treatment, there were no significant differences between the 2 groups regarding the grade of OM according to the RTOG score. However, throughout week 4 to week 6, still, there were around 30% of the patients who did not show signs of OM in the NS oil-treated group vs 5% in the control group. In the last two weeks of treatment, approximately 40 % of the patients demonstrated either mild or no OM in the NS oil-treated group vs 0% in the other group as demonstrated in Table 2. The severity of dysphagia as graded by the patients was analyzed in the present study. The data of Table 3 showed that in the NS oil-treated group most of the patients experienced either no or mild dysphagia in the early weeks of RT and the minority of them developed severe or very severe dysphagia in the last 2 weeks of RT; meanwhile, only 8.3% of the patients in the NS oil-treated group showed severe dysphagia compared to 85.7% of those in the control group (*P*=0.001). The data presented in Table 4 showed that treatment with NS oil mouthwash produced a positive impact on the ability of patients to consume normal food; this effect is more obvious in the week-7 of treatment, where 41.7% of the patients in this group consumed normal food compared with 7.1% of the patients in the control group (*P*=0.016). In Table 5, the use of NS oil mouthwash produces a significant decrease in pain severity, especially in the last week of exposure to radiotherapy. During the last week of RT, the incidence of very severe and severe pain was reported in only 8.3% of patients in the NS oil-treated group compared with 85.7% of those in the control group (*P*=0.001).

Table (2): Effects of NS oil mouthwash on the onset and RTOG grade of mucositis during chemoradiation of NHC patients

RTOG Score	Control	NS Oil	Total	*P*-value
	n (%)	*n* (%)	*n* (%)	
RTOG-week 1				
Zero	12(60)	14(70)	26(65)	
One	8(40)	3(15)	11(27.5)	
Two	0(0)	3(15)	3(7.5)	0.062
RTOG-week 2				
Zero	3(15)	7(35)	10(25)	
One	6(30)	8(40)	14(35)	
Two	8(40)	4(20)	12(30)	
Three	3(15)	1(5)	4(10)	0.294
RTOG-week 3				
Zero	2(10)	4(20)	6(15)	
One	3(15)	3(15)	6(15)	
Two	5(25)	10(50)	15(37.5)	
Three	9(45)	3(15)	12(30)	
Four	1(5)	0(0)	1(2.5)	0.136
RTOG-week 4				
Zero	1(5)	6(30)	7(17.5)	
One	1(5)	2(10)	3(7.5)	
Two	2(10)	7(35)	9(22.5)	
Three	12(60)	4(20)	16(40)	

Four	4(20)	1(5)	5(12.5)	0.010
RTOG-week 5				
Zero	1(5)	6(30)	7(17.5)	
One	1(5)	2(10)	3(7.5)	
Two	1(5)	7(35)	8(20)	
Three	10(50)	4(20)	14(35)	
Four	7(35)	1(5)	8(20)	0.002
RTOG-week 6				
Zero	1(5)	6(30)	7(17.5)	
One	1(5)	2(10)	3(7.5)	
Two	0(0)	9(45)	9(22.5)	
Three	10(50)	2(10)	12(30)	
Four	8(40)	1(5)	9(22.5)	< 0.001
RTOG-week 7				
Zero	0(0)	1(8.3)	1(3.8)	
One	0(0)	4(33.3)	4(15.4)	
Two	0(0)	5(41.7)	5(19.2)	
Three	7(50)	2(16.7)	9(34.6)	
Four	7(50)	0(0)	7(27)	< 0.001

Notes: Values are simple frequency and percentage.

Table (3) Effects of NS oil mouthwash on patients reported severity of dysphagia during chemoradiation of HNC patients

Dysphagia Score	Control	NS Oil	Total	*P*-value
	n (%)	*n* (%)	*n* (%)	
Swallowing-week 1				
Normal	17(85)	18(90)	35(87)	
Mild	1(5)	0(0)	1(2.5)	
Moderate	2(10)	2(10)	4(10)	> 0.999
Swallowing-week 2				
Normal	9(45)	13(65)	22(55)	
Mild	1(5)	7(35)	8(20)	
Moderate	8(40)	0(0)	8(20)	
Severe	2(10)	0(0)	2(5)	< 0.001
Swallowing-week 3				
Normal	3(15)	2(10)	5(12.5)	
Mild	1(5)	9(45)	10(25)	
Moderate	10(50)	7(35)	17(42.5)	
Severe	6(30)	2(10)	8(20)	0.024
Swallowing-week 4				
Normal	1(5)	2(10)	3(7.5)	
Mild	1(5)	5(5)	6(15)	
Moderate	5(25)	11(55)	16(40)	
Severe	13(65)	2(10)	15(7.5)	0.001
Swallowing-week 5				
Normal	1(5)	2(10)	3(7.5)	
Mild	(0)	5(25)	5(12.5)	

Moderate	2(10)	10(50)	12(30)	
Severe	16(80)	3(15)	19(47.5)	
Very severe	1(5)	0(0)	1(2.5)	< 0.001
Swallowing-week 6				
Normal	1(5)	3(15)	4(10)	
Mild	0(0)	4(20)	4(10)	
Moderate	4(20)	10(50)	14(35)	
Severe	12(60)	3(15)	15(37.5)	
Very severe	3(15)	0(0)	3(7.5)	0.001
Swallowing-week 7				
Normal	0(0)	4(33.3)	4(15.4)	
Mild	1(7.1)	3(25)	4(15.4)	
Moderate	1(7.1)	4(33.3)	5(19.2	
Severe	8(57.2)	1(8.3)	9(34.6)	
Very severe	4(28.6)	0(0)	4(15.4)	0.001

Notes: Values are simple frequency and percentage.

Table (4): Effects of NS oil mouthwash on swallowing function (the diet type) consumed by HNC patients during chemoradiation

Diet type	Control	NS Oil	Total	*P*-value
	n (%)	*n* (%)	*n* (%)	
Function – week 1				
Normal	19(95)	19(95)	38(95)	
Soft	1(5)	1(5)	2(5)	>0.999
Function – week 2				
Normal	10(50)	17(85)	27(67.5)	
Soft	8(40)	2(10)	10(25)	
Liquid	2(10)	1(5)	3(7.5)	0.054
Function – week 3				
Normal	3(15)	10(50)	13(32)	
Soft	9(45)	5(25)	14(35)	
Liquid	8(40)	5(25)	13(32.5)	0.061
Function – week 4				
Normal	1(5)	8(40)	9(22.5)	
Soft	4(20)	5(25)	9(22.5)	
Liquid	15(75)	7(35)	22(55)	0.012
Function – week 5				
Normal	1(5)	4(20)	5(12.5)	
Soft	4(20)	8(8)	12(30)	
Liquid	15(75)	8(8)	23(23)	0.097
Function – week 6				
Normal	2(10)	7(35)	9(22.5)	
Soft	3(15)	8(40)	11(27.5)	
Liquid	13(65)	5(25)	18(45.5)	
Nothing	2(10)	0(0)	2(5)	0.012
Function – week 7				
Normal	1(7.1)	5(41.7)	6(23.1)	
Soft	2(14.3)	5(41.7)	7(26.9)	

Liquid	7(50)	2(16.7)	9(34.6)	
Nothing	4(28.6)	0(0)	4(15.4)	0.016

Notes: Values are simple frequency and percentage.

Table (5): Effects of NS oil mouthwash on the pain score of NHC patients during chemoradiation

Pain Score	Control	NS Oil	Total	*P*-value
	n (%)	*n* (%)	*n* (%)	
Pain-week 1				
No pain	16(80)	18(90)	34(85)	
Mild	2(10)	0(0)	2(5)	
Moderate	2(10)	2(10)	4(10)	0.541
Pain-week 2				
No pain	8(40)	11(55)	19(47.5)	
Mild	2(10)	6(30)	8(20)	
Moderate	8(40)	3(15)	11(27.5)	
Severe	2(10)	0(0)	2(5)	0.077
Pain-week 3				
No pain	4(20)	4(20)	8(20)	
Mild	0(0)	6(30)	6(15)	
Moderate	10(50)	5(25)	15(37.5)	
Severe	6(30)	5(25)	11(27.5)	0.044
Pain-week 4				
No pain	2(10)	3(15)	5(12.5)	
Mild	1(5)	2(10)	3(7.5)	
Moderate	4(20)	10(50)	14(35)	
Severe	12(60)	5(25)	17(42.5)	
Very severe	1(5)	0(0)	1(2.5)	0.106
Pain-week 5				
No pain	2(10)	2(10)	4(10)	
Mild	1(5)	4(20)	5(12.5)	
Moderate	1(5)	9(45)	10(25)	
Severe	13(65)	5(25)	18(45)	
Very severe	3(15)	0(0)	3(7.5)	0.002
Pain-week 6				
No pain	2(10)	3(15)	5(12.5)	
Mild	1(5)	5(25)	6(15)	
Moderate	2(10)	7(35)	9(22.5)	
Severe	12(60)	5(25)	17(42.5)	
Very severe	3(15)	0(0)	3(7.5)	0.018
Pain-week7				
No pain	0(0)	3(25)	3(11.5)	
Mild	1(7.1)	4(33.3)	5(19.2)	
Moderate	1(7.1)	4(33.3)	5(19.2)	
Severe	7(50)	1(8.3)	8(30.8)	
Very severe	5(35.7)	0(0)	5(19.2)	0.001

Notes: Values are simple frequency and percentage.

Discussion

Based on previous data regarding the use of topical oral solution to manage OM, there is no standard formula for magic mouthwash. Accordingly, each healthcare facility recommends an in-house formula of a topical solution and labels it as the magic mouthwash. The variation of these formulas does not limit the selection of the constituents, combinations or doses used in these mixtures. However, the technical difficulties and high cost are the major problems, among others, associated with this approach. For the first time, we conducted a pilot open-label randomized study to evaluate the efficacy of NS oil mouthwash in chemoradiation-induced OM in HNC patients undergoing radiotherapy or chemoradiation. The results clearly demonstrated the benefits of NS oil in decreasing the severity and duration of OM; in addition to the improvement of other associated toxicities such as dysphagia and pain, compared with the standard care followed in our institution. In this study, the standard care protocol used in the control group demonstrated a significant effect on the treatment-induced OM; however, the severity of OM was significantly higher in this group during the study compared with the NS oil-treated group. The severity of OM varies greatly ranging from mild redness to large painful ulcerative areas that need high doses of narcotic analgesics for effective management. The presence of ulcers provides an important site of entry for many infectious organisms within the mucosal lining, especially in neutropenic cancer patients. Moreover, the importance of OM as a risk factor for sepsis was also well recognized. These factors predispose to suspending the radio-chemotherapy and abort the treatment with consequent suboptimal cancer therapy [20]. Typically, radiotherapy-induced OM starts within the first week of exposure to radiation and peaks progressively during the course of treatment [21]. In the current study, OM was usually reported in the first week of RT and the severity increased with the increase in the number of cycles. However, this change was reported more in the control group than in the NS oil-treated group. The multifactorial bases of OM pathophysiology include tissue damage, inflammation, and microbial growth that contribute to the secondary infection of the ulcerated areas; this will definitely need multi-targeted therapy that includes analgesic, anti-inflammatory, and antimicrobial agents. Although many agents have been evaluated over the past four decades to prevent and/or treat OM induced by cytotoxic treatment (radiotherapy, chemotherapy or both), only a few of them were proved to be effective [22-24]. Only two compounds, benzydamine hydrochloride that acts as a mucosal coating agent [25] and palifermin, the recombinant human keratinocyte growth factor [26,27], were found to be more effective than a placebo in the management of neck and head radiotherapy-induced OM. The present pilot study specifically evaluated the efficacy of a natural product mouthwash in controlling established OM pain with positive results. Many other studies utilized other rinse agents, including “magic mouthwash” and chlorhexidine [28], phenytoin [29], sucralfate [30] and diclofenac [22] did not demonstrate well-recognized benefits in reducing OM-associated pain when compared with a placebo. Moreover, because of the adverse effects arising from the use of synthetic drugs, increasing attention has been focused on the use of natural products. Many data evaluating the use of various natural products for the management of chemotherapy- and radiotherapy-induced OM revealed promising results in this regard [31]. In the present study, the NS oil mouthwash significantly reduces the severity of RT-induced OM and the associated complications compared with the “magic mouthwash” formula (control group). This result was in tune with the finding of Lotfy and Zayed that

demonstrate effective attenuation of tissue damage by the use of NS oil in 5-fluorouracil-induced OM in rats [32]. Moreover, Canakci et al reported that topical application of NS oil effectively prevents the superficial erosion of the RT-induced nasal mucositis in rats [33]. Radiation-induced OM is one of the most reported complications of RT that impairs the patient's quality of life with consequent attempts to reduce the dose of radiation and treatment termination [34,35]. Oral mucositis is characterized by the initiation of inflammatory changes with the direct or indirect effect of radiation and can be associated with mucosal ulceration. The reported cytoprotective effects of NS oil in the current study can be attributed to the well-recognized pleiotropic activity of its constituents that include anti-oxidant, cytoprotective, anti-inflammatory and analgesic activities [36-38]. The present study also showed that majority of patients during the period of treatment in the NS oil arm consumed either normal or soft food; while most of them in the control group consumed liquid food and an appreciable number of them took nothing by mouth especially towards the end of RT. The reported differences in the consumption of solid and semi-solid diet between the NS oil treated group and the control group could be probably attributed to the less severity and early reversal of OM noted in the study group. Thus it can be concluded that NS oil mouthwash helped the patients in the study group to maintain a better food intake during the RT period. The presented data indicated that NS oil mouthwash was effective and better when compared to the magic mouthwash formula in the management of RT-induced OM with regard to its severity and duration. However, considering the limitation of small sample size the data by itself can only partially prove the efficacy of NS oil in radiotherapy-induced mucositis. However, further studies are necessary to conclusively prove the clinical significance of NS oil mouthwash in RT-induced oral mucositis. According to our knowledge, this pilot study is a first trial that reveals the clinical benefits of a natural product like NS oil in the management of radiation- or chemoradiation-induced oral mucositis in HNC patients. Although the targeted small sample size might be satisfactory as a first attempt, the initiation of larger sample trials bare highly suggested to confirm or not the present data. Moreover, the limited patient sample did not represent the only study limitation, the lack of extended follow-up evaluation and/or utilizing surrogate markers may also affect the quality data. However, the strength of this pilot study is the uniformity of the baseline patient's characteristics and their full compliance during the study.

Conclusion

The results of this pilot study demonstrate that using *Nigella sativa* oil as a mouthwash is significantly superior to the "magic mouthwash" in the management of oral mucositis and associated pain and dysphagia induced by a head and neck radiotherapy with or without chemotherapy. However, further investigations are recommended to fully elucidate the use of NS oil mouthwash in larger sample randomized trials.

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Availability of data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

References

1- Chiappelli F. The molecular immunology of mucositis: implications for evidence-based research in alternative and complementary palliative treatments. Evidence Based Complementary and Alternative Medicine. 2005; 2:489-494. doi: 10.1093/ecam/neh129

2- Raber-Durlacher JE, Elad S, Barasch A. Oral mucositis. Oral Oncology. 2010; 46:452-456. doi: 10.1016/j.oraloncology.2010.03.012.

3- Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). International Journal of Radiation Oncology, Biology, Physics. 1995; 31:1341-1346. 31:1341-1346. doi: 10.1016/0360-3016(95)00060-C

4- Russo G, Haddad R, Posner M, Machtay M. Radiation treatment breaks and ulcerative mucositis in head and neck cancer. Oncologist. 2008; 13:886-898. doi: 10.1634/theoncologist.2008-0024

5- Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiotherapy Oncology. 2003; 66:253-262. doi: 10.1016/S0167-8140(02)00404-8

6- Bensadoun RJ, Magne N, Marcy PY, Demard F. Chemotherapy- and radiotherapy-induced mucositis in head and neck cancer patients: new trends in pathophysiology, prevention, and treatment. European Archive of Otorhinolaryngology. 2001; 258:481-487. PMID: 11769997

7- Chan A, Ignoffo RJ. Survey of topical oral solutions for the treatment of chemo-induced oral mucositis. Journal of Oncology Pharmacy Practice. 2005; 11:139-143. doi: 10.1191/1078155205jp166oa

8- Ahmad I, Tripathi J, Sharma M, Karchlli MS, Umer L. *Nigella sativa*–a medicinal herb with immense therapeutic potential (a systematic review). International Journal of Biological and Pharmaceutical Research. 2014; 5:755-762.

9- Toma CC, Simu GM, Hanganu D, Olah N, Georgiana Vata FM, Hammami C, Hammami M. Chemical composition of the Tunisian *Nigella sativa*. Note I. Profile on the essential oil. Farmacia. 2010; 58:458-464.

10- Gharby S, Harhar H, Guillaume D, Roudani A, Boulbaroud S, Ibrahimi M, et al. Chemical investigation of *Nigella sativa* L. seed oil produced in Morocco. Journal of Saudi Society of Agricultural Sciences. 2015; 14:172-177. doi: 10.1016/j.jssas.2013.12.001

11- Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, et al. A review on therapeutic potential of *Nigella sativa*: a miracle herb. Asian Pacific Journal of Tropical Biomedicine. 2013; 3:337-52. doi: 10.1016/S2221-1691(13)60075-1

12- Perveen T, Haider S, Zuberi NA, Saleem S, Sadaf S, Batool Z. Elevated 5-HT levels following repeated administration of *Nigella sativa* L. (black seed) oil create antidepressant effects in rats. Scientia Pharmaceutica. 2014; 82:161-170. doi: 10.3797/scipharm.1304-19

13- Bakathir HA, Abbas NA. Detection of the antibacterial effect of *Nigella sativa* ground seeds with water. African Journal of Traditional and Complementary Alternative Medicine 2011; 8:159-164. doi: 10.4314/ajtcam.v8i2.63203

14- Ghonime M, Eldomany R, Abdelaziz A, Soliman H. Evaluation of immunomodulatory effect of three herbal plants growing in Egypt. Immunopharmacology and Immunotoxicology. 2011; 33:141-145. doi: 10.3109/08923973.2010.487490

15- Abu-Zinadah OA. Using *Nigella sativa* oil to treat and heal chemical induced wound of rabbit skin. Journal of King Abdulaziz University Science. 2009; 21:335-346.

16- Mostafa M, Alaaeldin E, Aly UF, Sarhan HA. Optimization and characterization of thymoquinone-loaded liposomes with enhanced topical anti-inflammatory activity. AAPS PharmSciTech. 2018; 19:3490-500. doi: 10.1208/s12249-018-1166-1

17- Mouwakeh A, Telbisz Á, Spengler G, Mohácsi-Farkas C, Kiskó G. Antibacterial and resistance modifying activities of *Nigella sativa* essential oil and its active compounds against Listeria monocytogenes. In Vivo. 2018; 32:737-743. doi: 10.21873/ invivo.11302

18- Anonymous. Magic mouthwash. Pharmacist's Letter. 2007; 23:230703.

19- Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004; 100:1995-2025. doi: 10.1002/cncr.20162

20- Sonis ST. Pathobiology of oral mucositis: novel insights and opportunities. Journal of Supportive Oncology. 2007; 5:3-11.

21- Sonis ST. The pathobiology of mucositis. National Review of Cancer. 2004; 4:277-284. doi: 10.1038/nrc1318

22- Clarkson JE, Worthington HV, Furness S, McCabe M, Khalid T, Meyer S. Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Systematic Review. 2010;8:CD001973. doi: 10.1002/14651858.CD001973.pub4

23- Rodríguez-Caballero A, Torres-Lagares D, Robles-García M, Pachón-Ibáñez J, González-Padilla D, Gutiérrez-Pérez JL. Cancer treatment-induced oral mucositis: A critical review. International Journal of Oral and Maxillofacial Surgery. 2012; 41:225-238. doi: 10.1016/j.ijom.2011.10.011

24- Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Systematic Review. 2011;4:CD000978. doi: 10.1002/14651858.CD000978.pub5

25- Epstein JB, Silverman S, Paggiarino DA, Crockett S, Schubert MM, N.N. Senzer NN, et al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: Results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer. 2001; 92:875-885. doi: 10.1002/1097-0142(20010815)92:4<875: aid-cncr1396>3.0.co;2-1

26- Le QT, Kim HE, Schneider CJ, Muraközy G, Skladowski K, Reinisch S, et al. Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: A randomized, placebo-controlled study. Journal of Clinical Oncology. 2011; 29:2808-2814. doi: 10.1200/JCO.2010.32.4095

27- Henke M, Alfonsi M, Foa P, Giralt J, Bardet E, Cerezo L, et al. Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: A randomized, placebo-controlled trial. Journal of Clinical Oncology. 2011; 29:2815-2820. doi: 10.1200/JCO.2010.32.4103

28- Dodd MJ, Dibble SL, Miaskowski C, MacPhail L, Greenspan D, Paul SM, et al. Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics. 2000; 90:39-47. doi: 10.1067/moe.2000.105713

29- Baharvand M, Sarrafi M, Alavi K, Jalali Moghaddam E. Efficacy of topical phenytoin on chemotherapy-induced oral mucositis: A pilot study. Daru Journal of Pharmaceutical Sciences. 2010; 18:46-50. PMID: 22615593

30- Dodd MJ, Miaskowski C, Greenspan D, MacPhail L, Shih AS, Shiba G, et al. Radiation-induced mucositis: A randomized clinical trial of micronized sucralfate versus salt and soda mouthwashes. Cancer Investigation. 2003; 21:21-33. PMID: 12643006

31- Panahi Y, Saadat A, Shadboorestan A, Ahmadi A. An updated review of natural products intended to prevent or treat oral mucositis in patients undergoing radio-chemotherapy. Current Trends in Pharmacy and Biotechnology. 2016; 17:949-61. doi: 10.2174/1389201017666160808094008

32- Lotfy AM, Zayed M. Immunohistochemical study of the effect of *Nigella sativa* extract on chemotherapy-induced oral mucositis in albino rats. Cairo Dental Journal. 2009; 25:159-166.

33- Canakci H, Asli A, Yilmaz S, Şeneldir H, Kir G, Eriş AH, et al. Evaluation of the effect of topical application of *Nigella sativa* on acute radiation-induced nasal mucositis. Journal of Craniofacial Surgery. 2018;29: e279-e282. doi: 10.1097/SCS.0000000000004314

34- Praetorius NP, Mandal TK. Alternate delivery route for amifostine as a radio-/chemo-protecting agent. Journal of Pharmacy and Pharmacology. 2008; 60:809-8015. doi: 10.1211/jpp.60.7.0001

35- Al-Ansari S, Zecha JA, Barasch A, de Lange J, Rozema FR, Raber-Durlacher JE. Oral mucositis induced by anticancer therapies. Current Oral Health Reports. 2015; 2:202-211. doi: 10.1007/s40496-015-0069-4

36- Ustun K, Taysi S, Sezer U, Demir E, Baysal E, Demir T, et al. Radio-protective effects of *Nigella sativa* oil on oxidative stress in tongue tissue of rats. Oral Diseases. 2014; 20:109-113. doi: 10.1111/odi.12082

37- Kanter M, Coskun O, Uysal H. The anti-oxidative and antihistaminic effect of *Nigella sativa* and its major constituent, thymoquinone on ethanol-induced gastric mucosal damage. Archive of Toxicology. 2006; 80:217-224. doi: 10.1007/s00204-005-0037-1

38- Cingi C, Eskiizmir G, Burukoglu D, Erdoğmuş N, Ural A, Ünlü H. The histopathological effect of thymoquinone on experimentally induced rhinosinusitis in rats. American Journal of Rhinology and Allergy. 2011;25: e268-e272. doi: 10.2500/ajra.2011.25.3703