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ARTICLE

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Oral administration of nanomicelle curcumin in the prevention of radiotherapy-induced mucositis in head and neck cancers

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Abstract

Oral mucositis (OM) is a complication of head and neck cancer (HNC) therapy with negative impact on the quality of life. Although definitive treatment has not yet been established, there is interest towards the use of natural compounds owing to their few side effects. Curcumin has a variety of biological and pharmacological properties including anticancer and anti-inflammatory effects.

Aim: The aim of this study is to evaluate the effect of curcumin in the form of nanomicelle on OM in HNC patients receiving radiotherapy.

Methods: In this clinical trial, 32 HNC patients were allocated to case and control groups, and respectively received nanocurcumin or placebo during radiotherapy.

Results: We found a statistically significant difference in the severity of mucositis between the 2 groups at all visits. In contrast to the control-group patients, who all developed OM in the 2nd week of radiotherapy, only 32% of the case group developed OM with no obvious oral or systemic side effects.

Conclusion: Our data show that nanomicelle curcumin is an effective agent in the prevention of OM or reducing its severity. Thus, the administration of nanocurcumin can be considered as a reasonable approach to hinder the development of OM in HNC patients requiring radiotherapy.

KEYWORDS

clinical trial, head and neck cancer, mucositis, nanomicelle curcumin, radiotherapy

1 | INTRODUCTION

Oral mucositis (OM) is defined as erythematous and ulcerative lesions of the oral mucosa. It is among the clinically important and common side effects caused by chemotherapy and radiation therapy in cancer patients.[1–3]

Mucositis lesions are often extremely painful and may lead to oral discomfort, inadequate intake of food and medications, delays in cancer treatment, longer hospitalization time and consequently more costs and higher risk of life-threatening infection.[1,4–6] These complications may limit the patient's ability to tolerate an optimal antineoplastic treatment, which

Abbreviations: HNC, head and neck cancer; NCI-CTC v.2, National Cancer Institute Common Toxicity Criteria version 2 scale; OM, oral mucositis.

can negatively impact treatment planning and prognosis.[2,6,7] It is therefore critical that mucositis can be prevented or treated to improve the overall care of patients with cancer.

In recent years, extensive research has been conducted to determine the effectiveness of a vast number of diverse interventions for the prevention or treatment of OM in cancer patients. Several agents and methods such as cryotherapy, growth factors, anti-inflammatory agents, antioxidants and low-level laser therapy (LLLT) have been tested to reduce the severity of, or prevent mucositis; however, none of them has been conclusively validated to be considered as a standard treatment.[8–12]

To date, palifermin, a keratinocyte growth factor, is the only drug for the prevention of OM that has been approved by the US Food and Drug Administration (FDA) in 2004. It was approved in the treatment of OM in patients with hematologic malignancies who receive high doses of chemotherapy and radiation therapy followed by stem cell rescue.[13] Despite being efficacious, palifermin, as a recombinant growth factor, is expensive, not simple to use, and thus unaffordable for most patients.[14–17]

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a polyphenolic compound and the major yellow pigment extracted from the rhizome of turmeric (Curcuma longa), which belongs to the ginger family, Zingeberaceae.[18] Curcumin has been shown to possesses diverse pharmacologic activities including antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic effects. All these activities appear to stem from the ability of curcumin to regulate the expression of molecules involved in the inflammatory pathway and apoptosis.[19–21] Thus, curcumin can lead to the down regulation of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1, IL-6, and IL-8, through inhibition of toll-like receptor 4 (TLR4), nuclear factor kappa B (NF-κB), and mitogen-activated protein kinase signaling pathway activations.[22–25]

The safety and tolerability of curcumin in humans, at high doses up to 12 g/day, have been well established in clinical studies. The adequate concentration of curcumin in target tissues is important for its pharmacological effects. However, under physiologic conditions, curcumin is uns‘ and exhibits limited bioavailability owing to its hydrophobicity and poor absorption, high rate of metabolism, and rapid systemic clearance.[25–28] As a result, extremely low serum and tissue levels of curcumin are observed after oral administration. In addition, the tissue distribution and the uptake of curcumin by different tissues is another determinant of its bioavailability.

Several different means, such as the use of adjuvant like piperine, nanoparticles, liposomes, micelles, and phospholipid complexes can be taken into consideration to overcome the bioavailability challenges. In addition, the use of structural analogues of curcumin has been found with enhanced biological activity.[25–27]

To date, no clinical trial on the effect of oral curcumin on radiation-induced OM has been reported in the literature. Thus, the aim of the current study was to investigate the effect of oral curcumin on radiation-induced OM in patients with head and neck cancer (HNC). Furthermore, to improve the solubility of curcumin in aqueous solutions, its absorption and bioavailability, we have used formulated curcumin nanomicelles and tested the efficiency of these nanoparticles in treating OM clinically.

2 | MATERIAL AND METHODS

The double-blind randomized clinical trial was conducted at Imam Reza Oncology Center and Omid Hospital in Mashhad, Iran. The study protocol was approved by the institutional local ethical committee at Mashhad University of Medical Sciences (registration number: IR.mums.sd.REC.1394.14). Thirty-two patients with HNC undergoing radiotherapy who fulfilled our inclusion criteria were selected for the study. Inclusion criteria were as follows: the minimum age of 18 years; the presence of HNC; radiation therapy of 50 Gy or greater; at least 50% of patient's oral cavity was included in the field of radiation; and willingness to participate in the study and to sign the informed consent form. Exclusion criteria were as follows: a history of previous radiation therapy or chemotherapy; those undergoing a chemotherapy protocol in addition to radiotherapy; any allergy to turmeric; those who had a pre-existing oral disease such as an active oral infection or an oral ulceration.

Patients were briefed about the study and the signed informed consent form was obtained. All patients were instructed for oral hygiene care, avoiding alcohol, spicy and acidic foods, and smoking during the course of radiotherapy. Patients were randomly divided into 2 groups, namely the study and control groups, each consisting of 16 patients. Randomization was performed using a computer-generated random number table.

Patients in the study group received 80 mg/day oral nanocurcumin (1 capsule of SinaCurcumin® 80 per day) during the radiotherapy. Each soft gel of SinaCurcumin® contains 80 mg of curcumin-loaded nanomicelles to enhance the absorption and performance of curcumin in the body. The nanomicelles are prepared from GRAS (generally recognized as safe) pharmaceutical excipients and the C3-complex form of curcumin with the size of about 10 nm. SinaCurcumin® is a registered product developed in Nanotechnology Research Center of Mashhad University of Medical Science. Patients in the control group received placebo tablets (containing lactose). Nanocurcumin and placebo tablets were packaged in identical containers. During treatment, both of practitioners

TABLE 1 NCI-CTC v.2 grading scale for radiation-related mucositis. Adapted from http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf

	Grade				
	0	1	2	3	4
NCI-CTC v.2 (for radiation-related mucositis)	No changes	Erythema	Patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and non-contiguous)	Confluent pseudomembranous reaction (contiguous patches generally >1.5 cm in diameter)	Necrosis or deep ulceration

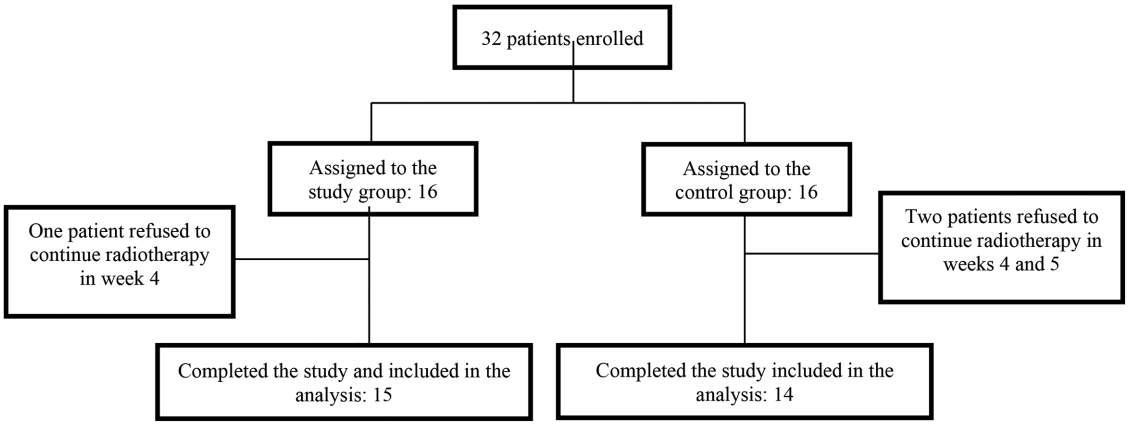

FIGURE 1 Flow of patients in the clinical trial

and patients were unaware of medications they were using. The participants were asked to record any side effects associated with the drug, such as vomiting, nausea, or rash.

In an oral examination, participants were evaluated for OM before the initiation of radiotherapy (day 0) and subsequently on days 7, 14, 21, 28, 35, and 42 of the radiotherapy course. A deviation of ±1 day for the oral evaluation was permitted.

The research team scored the grade of OM based on the National Cancer Institute Common Toxicity Criteria version 2 scale (NCI-CTC v.2). According to NCI-CTC v. 2, the occurrence and severity of OM is graded using an ordinal score ranging between 0 (none) and 4 (the highest) as observed at any site within the oral cavity (see Table 1). The weights of all patients were measured before and after the radiotherapy courses to assess the nutritional condition.

3 | STATISTICAL ANALYSIS

Data were analyzed by independent sample *t*-test and Mann-Whitney and Friedman tests using SPSS software version 16. *P* value <0.05 was considered statistically significant.

4 | RESULTS

Thirty-two patients with HNC undergoing radiotherapy consented to participate in this study. One patient in the study group and 2 patients in the control group refused to continue their radiotherapy treatment in weeks 4 and 5. Thus, 29 patients were available for the analysis (Figure 1).

No significant difference was observed for age, gender, radiation dose, artificial teeth, body weight, smoking habit, type, and location of the primary tumors among the subjects of the 2 groups (Table 2). Tumors of the buccal mucosa and the tongue were most commonly found among the study and control group patients. The oral cavity of all patients in both groups was examined weekly up to week 6, and the grading of OM was assessed by National Cancer Institute Common Toxicity Criteria version 2 scale (NCI CTC v.2).

Strikingly, we observed a delay in the onset of OM (grade 1) for the study group as compared to the control group ($P = 0.002$; Table 3). Thus, within the control group, 37.5% of the cases (6/16) exhibited mucositis grade 1 after 1 week, which increased to 50% (8/16) after 2 weeks. In contrast, in the study group, none showed that of grade 1 after 1 week, and only 25% (4/16) developed grade 1 in week 2.

The severity of mucositis increased gradually in all patients and was the greatest after 6 weeks. Notably, during this period, the grade of mucositis was lower in the study group than in the control group, which showed statistically significant differences ($P < 0.05$; Table 3). For example, mucositis grade 3 was observed after 3 weeks in the control group (in 50% of the cases) whereas the study group reached this grade after 4 weeks (33.3% of the cases).

Strikingly, at the end of radiation therapy course, NCI-CTC v.2 score of the study group subjects ranged from 1 to

TABLE 2 Patient characteristics

Parameter	Study group	Control group	*P* value
Mean age (years)	62.18 ± 15.07	55.87 ± 15.33	0.25
Gender distribution			
Males	9	10	0.719
Females	7	6	
Tumor location			0.854
Buccal mucosa	6 (37.5%)	8 (50%)	
Tongue	3 (18.8%)	4 (25%)	
Palate	3 (18.8%)	3 (18.75%)	
Floor of the mouth	4 (24.9%)	1 (6.25%)	
Type of tumor			
squamous cell carcinoma	12 (75%)	14 (87.5%)	0.365
Adenoid cystic carcinoma	3 (18.75%)	2 (12.5%)	
Mucoepidermoid carcinoma	1 (6.25%)		
Smoking habit	5 (31.3%)	7 (43.8%)	0.465
Body weight (kg)	67.18 ± 8.35	68.37 ± 7.12	0.433
Artificial teeth	7 (43.7%)	5 (31.2%)	0.465
Average radiation dose (cGy)	6090 ± 555.69	6212.5 ± 604.29	0.364

3 with a mean score of 1 ± 0.84, whereas that of the control group ranged from 2 to 4 with a mean score of 1.78 ± 0.42. ($P = 0.005$; Table 3). Furthermore, within the study group, no patient developed grade 4 mucositis, while in the control group 50% of patients (7/14) developed grade 4 mucositis. A comparison of the mean Severity of OM between the study and control groups in all visits is shown in Figure 2.

Interestingly, when body weights of patients were examined before and after the radiotherapy courses, the study group showed an average loss of 0.43 ± 0.81 kg whereas that of the control group was 1.32 ± 0.87. This difference in body weight change between the 2 groups was statistically different ($P = 0.003$). It is noted that administration of nanocurcumin did not cause detectable side effects or discomfort.

5 | DISCUSSION

OM is known as a common complication of cancer therapy. OM lesions can be extremely irritating, which severely affect the patients' quality of life by causing swallowing difficulty and pain, leading to nutrient deficiency and dehydration. These lesions can also increase the risk of local or systemic infection during periods of profound immunosuppression. Therefore, the control of OM is important and indispensable for prognosis and improving the quality of life. A wide variety of agents have been tested to prevent or treat OM,

TABLE 3 Severity of oral mucositis in the control and study groups during the course of radiation therapy

	Study group						Control group						Significance
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	mean± SD	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	mean± SD	
Week 1	16(100%)	0(0)%	0(0)%	0(0)%	0(0)%	0	10(62.5%)	6(37.5%)	0(0)%	0(0)%	0(0)%	0.37 ± 0.50	0.007
Week 2	9(56.3%)	4(25%)	3(18.8%)	0(0)%	0(0)%	0.62 ± 0.80	0(0)%	8(50%)	8(50%)	0(0)%	0(0)%	1.5 ± 0.51	0.002
Week 3	0(0)%	11(68.8%)	5(31.3%)	0(0)%	0(0)%	1.31 ± 0.47	0(0)%	2(12.5%)	6(37.5%)	8(50%)	0(0)%	2.37 ± 0.71	<0.001
Week 4	0(0)%	5(33.3%)	5(33.3%)	5(33.3%)	0(0)%	2.00 ± 0.84	0(0)%	1(6.7%)	4(26.7%)	10(66.7%)	0(0)%	2.60 ± 0.63	0.011
Week 5	0(0)%	4(26.7%)	3(20%)	8(53.3%)	0(0)%	2.26 ± 0.88	0(0)%	0(0)%	2(14.3%)	7(50%)	5(35.7%)	3.21 ± 0.69	0.006
Week 6	0(0)%	4(26.7%)	1(6.7%)	10(66.7%)	0(0)%	2.40 ± 0.91	0(0)%	0(0)%	2(14.3%)	5(35.7%)	7(50%)	3.35 ± 0.74	0.005

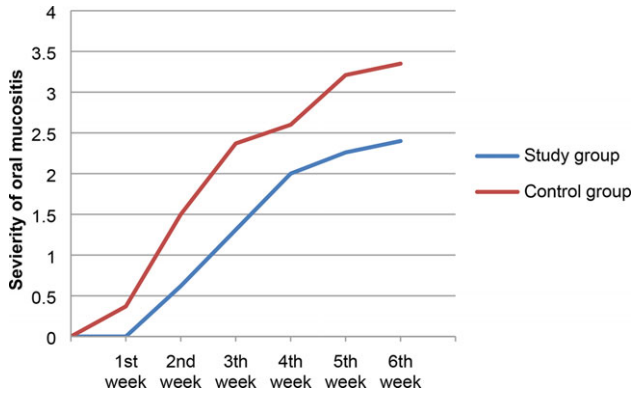

FIGURE 2 Comparison of the mean Severity of OM between the study and control groups in all visits

among which the use of natural-based compounds has been of increasing interest in recent years, owing to lower undesirable side effects compared with chemical drugs.

A number of recent studies have investigated the role of natural agents such as glutamine, vitamins, honey, Aloe Vera gel, and zinc for the management of OM in cancer patients. The results of these studies showed a positive effect of zinc supplements on severe OM after radiotherapy. Furthermore, a recommendation was made against the use of intravenous glutamine for the treatment of mucositis in patients receiving high doses of chemotherapy.[11,29,30] However, because of insufficient research and evidence, no guideline for the use of natural agents in the treatment of OM was possible.

Recent investigations have demonstrated the role of curcumin as an antioxidative, anti-inflammatory, anti-microbial, and anticarcinogenic agent with multifaceted therapeutic activities suggesting possible benefits for treating OM. Elad et al assessed the tolerability and efficacy of curcumin mouthwash in the management of OM in a pilot study on 7 pediatric patients receiving doxorubicin-based chemotherapy.[31] They concluded that curcumin mouthwash is safe and efficacious. Recently, Patil et al reported that mouthwash with 0.4% curcumin is safe and effective in controlling the signs and symptoms of OM in 10 cancer patients receiving radiotherapy and chemotherapy.[30] Saldanha and Almeida also showed that turmeric mouthwash was more effective than saline on mucositis.[32] Rao et al evaluated the efficacy of turmeric on radiation-induced mucositis. They concluded that Gargling together with turmeric provides significant benefit in HNC patients by delaying and reducing the severity of OM.[15] Furthermore, a nontoxic drug consisting of curcumin, alpha-tocopherol, and sunflower oil administered orally to rats has been effective in the prevention of radiation-induced ulceration of OM in these animal models.[33]

Several studies have documented the poor bioavailability of curcumin as a limiting factor for its pharmacological effects.[26,27,34,35] A previous pharmacokinetic study has demonstrated that curcumin-entrapped nanoparticles produce significantly higher oral bioavailability when compared to curcumin administered with an absorption enhancer.[36] In contrast to solvent-solubilized free curcumin, which is rapidly metabolized and excreted upon intravenous injection in rats, nanocurcumin was shown to dramatically enhance the overall curcumin systematic exposure.[37]

The goal of this study was to examine the efficacy of an oral nanocurcumin (SinaCurcumin®) on OM in a group of patients with HNC undergoing radiotherapy (Figure 1 and Table 2).

In the present study, exposure to ionizing radiation caused OM in both study and control groups. However, in patients receiving oral nanocurcumin, the onset of mucositis was delayed and the severity of mucositis was reduced as compared to the control group receiving placebo (Table 3). These data indicated that curcumin in the form of nanomicelle is effective in prevention and management of OM. Importantly, nanocurcumin was well tolerated by patients, with no evidence of toxic or side effects. Furthermore, the better food intake owing to the reduced OM can cause the lower weight loss of the participants in the study group

To the best of our knowledge, this is the first clinical report evaluating the effectiveness of nanocurcumin with enhanced bioavailability orally administered for the management of radiation-induced OM. Most of the previous studies on the anticancer function of curcumin were limited to animal models or in vitro experiments. However, several clinical studies have previously assessed the efficacy of curcumin as topical agent in the prevention and treatment of OM.

Thus, our data provides a strong evidence that nanocurcumin can be used as an effective and safe agent in the management of OM. Although curcumin nanoparticles are able to sustain the plasma level of curcumin, future research efforts should focus on targeted drug delivery systems for curcumin. Given the limited number of subjects and the effectiveness of nanocurcumin in our study, we suggest further studies with an increases number of patients to corroborate our current results. Furthermore, this study based on the NCI-CTC v2 grading system, only investigates the objective findings; for future studies, it is recommended to use the NCI-CTC v3 Scoring system, and to evaluate both objective and functional findings.

Taken together, we recommend using nanocurcumin as part of the standard supportive care for radiotherapy-induced OM in HNC patients. Moreover, these results warrant further investigations to delineate the most effective doses of nanocurcumin.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest in this study.

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