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A Randomized, Placebo-Controlled Study to Evaluate the Effect of Bio-Enhanced Turmeric Formulation on Radiation-Induced Oral Mucositis

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Keywords
Curcumin · Radiotherapy · Cancer · Bio-enhanced turmeric · Mucositis

Abstract

Introduction: Oral mucositis is the most common toxicity of chemoradiotherapy treatment of head and neck cancers. The present study was performed to evaluate the effect of a researched turmeric formulation on oral mucositis in patients receiving chemoradiotherapy for oral cancer. ***Methods:*** This randomized double-blinded placebo-controlled trial included 60 patients with oral cancer who had undergone radical surgery. Patients were equally randomized into 3 arms. Bio-enhanced turmeric formulation (BTF) capsules (low dose [1 g/day] or high dose [1.5 g/day]) or placebo was administered daily for 6 weeks with concurrent chemoradiotherapy. Study endpoints included the impact of the treatment on chemoradiotherapy-induced oral mucositis along with dysphagia, oral pain, dermatitis, and weight loss. ***Results:*** The incidence of grade 3 toxicity of oral mucositis, oral pain, dysphagia, and dermatitis was significantly lower in patients who received BTF than placebo. Twenty-five and 20% patients in BTF 1 g/day ($p = 0.011$) and 1.5 g/day ($p = 0.004$) arms, respectively, developed grade 3 oral mucositis compared to 65% patients in the placebo arm. Thirty-five and 30% patients in BTF 1 g/day ($p = 0.027$) and 1.5 g/day ($p = 0.011$) arms, respectively, developed grade 3 oral pain compared to 70% patients in the placebo arm. Twenty-five and 20% patients in BTF 1 g/day ($p = 0.025$) and 1.5 g/day ($p = 0.010$) arms, respectively, developed grade 3 dysphagia compared to 60% patients in the placebo arm. Ten and 5% patients in BTF 1 g/day ($p = 0.114$) and 1.5 g/day ($p = 0.037$) arms. respectively, developed grade 3 dermatitis compared to 30% patients in the placebo arm. Patients under BTF supplementation experienced significantly less weight loss and greater compliance with treatment than placebo. ***Conclusion:*** BTF (BCM-95®) can significantly reduce chemoradiotherapy-induced severe oral mucositis, dysphagia, oral pain, and dermatitis in oral cancer patients. ***Trial Registration:*** Clinical Trials Registry, India (Registration No. CTRI) (CTRI/2015/12/006413 dated December 4, 2015).

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Introduction

Head and neck cancers are the second most common cancers in India, most commonly seen in male individuals and account 30% load of India's cancer burden [1, 2]. Radiation therapy, along with chemotherapy, plays a major role in the standard treatment for head and neck cancers. Oral mucositis is the most common toxicity of chemoradiotherapy treatment of head and neck cancers [3]. Mucositis is an inflammation of the oral mucosa, characterized by the presence of erythematous areas and painful ulcerative lesions [4]. Up to 66% of all patients receiving radical radiation therapy for head and neck cancers develop severe oral mucositis [5, 6].

Oral mucositis is a major dose-limiting toxicity of radiotherapy in head and neck cancer patients. It is associated with inability to swallow and severe pain in the throat. As a result, oral mucositis affects nutrition, continuity of therapy, and quality of life and contributes to local and systemic infections [5–7]. Oral mucositis also has a considerable economic impact as it increases costs related to signs and symptoms management, nutritional support, secondary infection treatment, and hospitalizations. Management of oral mucositis includes pain control, maintenance of oral hygiene, nutritional support, oral decontamination, and management of oral bleeding [5–7]. Treatment of oral mucositis can include anti-inflammatory agents, analgesics, antibacterial agents, antifungal agents, L-glutamine, local anesthetics, topical corticosteroids, chlorhexidine, povidone-iodine mouthwashes, and systemic agents such as cyclooxygenase-2 inhibitors, N-acetylcysteine, granulocyte-macrophage colony-stimulating factor, and systemic corticosteroid [5–7]. Although many therapeutic agents have been investigated, no effective prevention or treatment has been completely successful to manage oral mucositis [8].

Despite the range of potential treatments available, no single agent has been approved by the US Food and Drug Administration for the treatment of radiation-induced mucositis [7]. Despite current guidelines for management of oral mucositis, there is still a large gap in the scientific evidence regarding standard treatments. Hence, the search for alternative products continues, and natural products, such as supplements with antioxidant and anti-inflammatory properties like curcumin, have been considered as a potential source [9]. Pro-inflammatory pathways, reactive oxygen species, and metabolic bioproducts of colonizing microorganisms are believed to play a role in amplifying the tissue injury [10]. Targeting and inhibiting nuclear factor-κB (NF-κB) could be an efficient strategy to decrease the inflammatory cell responses and consequently reduce mucositis lesions [11]. Curcumin is a well-known NF-κB inhibitor with powerful anti-inflammatory properties. It strongly inhibits cytoplasmic NF-κB activation and subsequent synthesis of cytokines such as tumor necrosis factor, interleukin (IL)-6 and IL-8, and vascular endothelial growth factor [12].

The therapeutic properties of turmeric (*Curcuma longa*), a rhizomatous herb often used as food spice and traditionally applied as treatment for several illnesses, have been extensively studied in recent years. In animal model studies and human clinical trials, curcumin has shown beneficial effects to prevent chemotherapy- and radiotherapy-induced oral mucositis [13, 14]. Curcumin has encouraging and positive results when used for tooth pain, subgingival irrigator, cavity sealant, and also as treatment for aphthous and potentially malignant lesions [9, 15]. Curcumin also inhibits tumor growth and induced cell cycle arrest with apoptosis in various in vitro and in vivo head and neck carcinoma models [16]. Curcumin is also effective in reducing the severity of radiation-induced dermatitis and moist desquamation in cancer patients [17–19]. Despite the positive effects, a major limitation of curcumin is its poor oral bioavailability, which is due to its chemical instability, poor absorption, rapid metabolism, and systemic elimination [20]. Studies done on animals reported that the majority of curcumin taken orally is excreted in feces (≤90%) [21]. Curcumin, after limited absorption, reaches systemic circulation and undergoes metabolism in the liver to inactive metabolites, mainly curcumin glucuronide and curcumin sulfate. Rapid metabolism drastically reduces the level of free curcumin in the body, thereby leading to suboptimal levels for therapeutic benefits [22].

Numerous attempts have been made to improve oral bioavailability using adjuvants or by developing novel drug delivery systems. One of the most successful strategies to improve bioavailability of curcumin is combining curcuminoids with essential oil of turmeric. The poor absorption of curcumin is mainly due to efflux through the p-glycoprotein pathway in the intestinal epithelial cells. Turmerones in the essential oil of turmeric are specific inhibitors of p-glycoprotein and thereby increase the systemic absorption and bioavailability of free curcumin [23]. In a pilot crossover investigation in humans, the relative bioavailability of curcuminoid and essential oil complex was about 7-fold higher than normal curcumin and about 6.3-fold higher than curcumin-lecithin-piperine formula [24]. Essential oil of turmeric is also an active ingredient of the turmeric root, with potent biological activity [25]. The combination of curcumin with turmerones

(essential oil components of turmeric) has been reported to prevent inflammation and related symptoms [26]. Synergistic effects of curcuminoids with sesquiterpenoids (mainly Ar-turmerone) have also been studied by Nishiyama and coworkers for hypoglycemic effects [27].

Bio-enhanced turmeric formulation (BTF) used in this study is a combination of curcuminoids, predominantly curcumin, with the essential oil of turmeric. BTF has been shown to be clinically effective in various inflammatory conditions. The present study was performed to evaluate the efficacy of BTF in reducing the severity of oral mucositis in patients receiving adjuvant concurrent chemoradiotherapy for oral cavity cancer.

Materials and Methods

Study Design

The study was a randomized, double-blinded, three-arm trial comparing the effects of BTF at 1 g per day (arm A) versus BTF 1.5 g per day (arm B) or placebo (arm C) in oral cancer patients receiving adjuvant concurrent chemoradiotherapy. The trial was conducted at the Bhagwan Mahaveer Cancer Hospital and Research Centre in Jaipur, India, in accordance with the Helsinki Declaration. The primary objective of this study was to compare the incidence and severity of chemoradiotherapy-induced oral mucositis among the 3 arms of the study. Secondary objectives were to compare the incidence and severity of dysphagia, oral pain, dermatitis, significant weight loss (more than 3 kg from the baseline), and compliance to radiotherapy treatment (more than 3 consecutive radiation treatments missed) between the 3 arms of the study. The protocol and informed consent form were reviewed and approved by the Institutional Review Board of the Bhagwan Mahaveer Cancer Hospital and Research Centre (reference BMH/7916). The present study was also registered with the Clinical Trials Registry, India (CTRI) (CTRI/2015/12/006413).

Study Population and Inclusion/Exclusion Criteria

Patients were briefed about the study parameters, and all patients provided written informed consent before undergoing any study-related procedures. Patients who had undergone radical surgery (wide excision with modified neck dissection) for oral cavity cancer were enrolled in this study. Inclusion criteria were post-radical surgery cases of oral carcinoma with any of primary site such as buccal mucosa, alveolus, retromandibular trigone, oral tongue, lips, floor of the mouth, and hard palate. Subjects were 18–70 years old, rated with World Health Organization (WHO) performance status 0–1 with no prior history of radiotherapy to the head-neck region. Exclusion criteria were histology other than squamous cell carcinoma, recurrent cancer, abnormal renal or liver function, prothrombin time, or international normalized ratio values.

Randomization and Intervention

A total of 60 patients were randomized equally into 3 arms (arm A, arm B, and arm C) using the computer-generated random number method. Patients in arm A received 500 mg of BTF capsules (BCM-95®; Arjuna Natural Pvt. Ltd., India) per oral 2 times a day (total dose of 1 g/day) daily, patients in arm B received 500 mg of BTF capsules 3 times a day (total dose of 1.5 g/day) daily, and patients in arm C received placebo capsules 3 times a day daily for 6 weeks of radiotherapy treatment.

The BTF consisted of turmeric extract containing 95% curcuminoids and essential oil. Turmeric extract was made by extraction of dried turmeric (*C. longa*) rhizomes with ethyl acetate. Essential oil with turmerones was made by steam distillation of turmeric rhizomes. BTF capsules were standardized to contain not less than 86% curcuminoids, with the essential oil of turmeric containing at least 45% ar-turmerones. All patients started on the study treatment on the first day of radiation, continuing until the last day of completion of radiotherapy. Radiotherapy was initiated within 4–6 weeks after radical surgery for all patients.

Efficacy Assessment and Blinding

At the start of the study, all participants were observed by a qualified dentist or dental surgeon for dental prophylaxis and verified to have no infected or loose teeth. All patients were given dietary counseling before starting radiotherapy. After thermoplastic immobilization mask preparation in a supine position, contrast enhanced CT scans with 3–5 mm slice thickness were done for radiotherapy simulation. Radiotherapy treatment planning was done on an Eclipse Treatment Planning System (Varian Medical systems). Radiotherapy was planned by using 6 MV photons with a linear accelerator (Clinac iX; Varian Medical systems) with an intensity-modulated radiotherapy technique to a total dose of 60 Gy in 30 fractions, with 2 Gy per fraction daily and 5 fractions per week for total 6 weeks. Concurrent weekly cisplatin chemotherapy to dose of 40 mg/m^2 was administered to all patients during radiotherapy. The complete blood count, renal function test, liver function test, prothrombin time, and international normalized ratio test were performed for all patients before randomization and then weekly during chemoradiotherapy treatment. Standard oral, medical, and supportive treatments were provided to all patients of all groups. All patients were recommended to consume protein-enriched powders to meet the basic nutritional requirements of the body during the treatment. All patients were evaluated and reviewed weekly during the course of chemoradiotherapy. Every week, all patients were assessed for oral mucositis, dysphagia, odynophagia, weight loss (significant if >3 kg weight loss from baseline), and compliance to radiotherapy treatment (>3 consecutive radiation fraction missed) until the completion of chemoradiotherapy. Grading of oral mucositis, dysphagia, and oral pain was performed based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. A radiation oncologist as an observer, unaware of the allocated group of the subjects, graded the mucositis at upper and lower lips, right and left buccal mucosa, right and left ventral and lateral tongue, floor of the mouth, oropharynx, soft palate/fauces, and hard palate. As only one blinded observer evaluated all the patients, calibration of assessors was not required.

Statistical Analysis

The sample size was calculated at 80% statistical power at 95% level of significance. Continuous variables were summarized as mean ± standard deviation, while nominal/categorical variables were summarized as proportion (%). Pearson's χ^2 test with cross-tabulation was used for categorical variables. One-way ANOVA was used for the analysis of variables between means of continuous observations. All statistical analyses were performed using IBM SPSS statistics version 21.

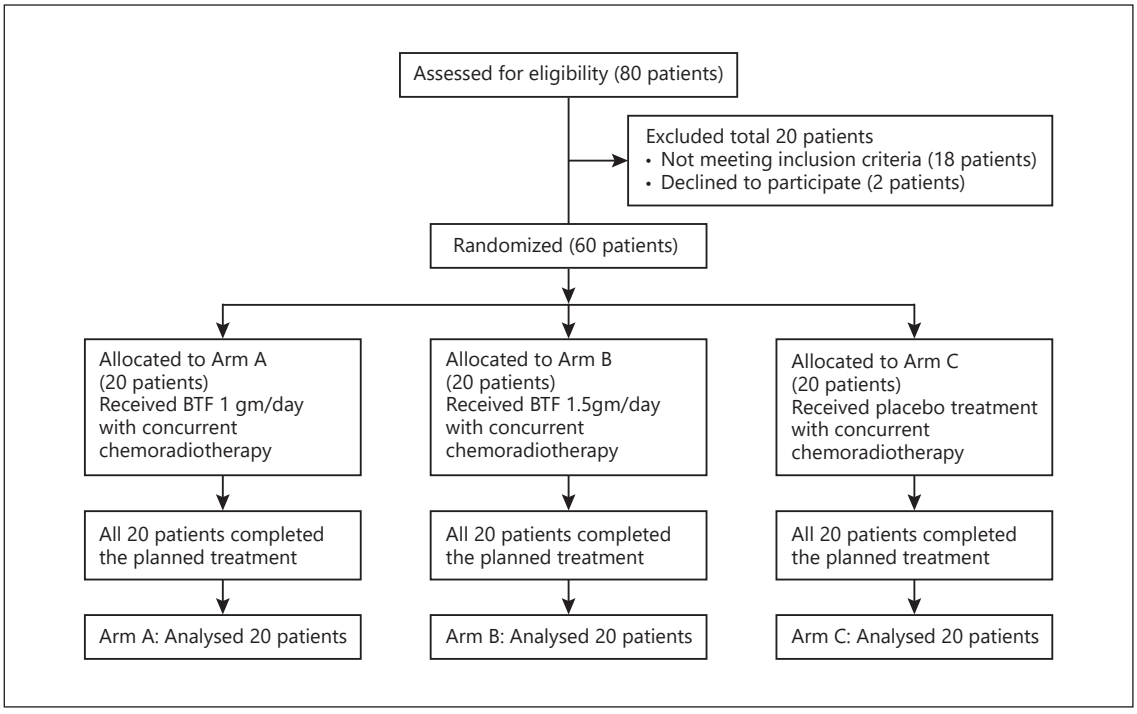

Fig. 1. Participants flow diagram.

Table 1. Baseline characteristics between the study groups

Characteristic	Arm A *N* = 20	Arm B *N* = 20	Arm C *N* = 20
Intervention	BTF 1 g/day	BTF 1.5 g/day	Placebo
Mean age, years	40	46	45
WHO performance status, *n* (%)			
Score 0	17 (85)	18 (90)	17 (85)
Score 1	3 (15)	2 (10)	3 (15)
Tobacco user, *n* (%)	17 (85)	16 (80)	18 (90)
Gender, *n* (%)			
Male	19 (95)	18 (90)	18 (90)
Female	1 (5)	2 (10)	2 (10)
Primary site, *n* (%)			
Oral tongue	14 (70)	10 (50)	15 (75)
Buccal mucosa	5 (25)	8 (40)	5 (25)
Hard palate	1 (5)	1 (5)	0
Floor of mouth	0	1 (5)	0
Stage grouping, *n* (%)			
Stage III	4 (20)	3 (15)	4 (20)
Stage IV	16 (80)	17 (85)	16 (80)
Mean number of chemotherapy cycles	5	5	5

BTF, bio-enhanced turmeric formulation; WHO, World Health Organization.

Results

Sixty patients with oral cancer who had previously undergone radical surgery were randomized equally into the 3 arms of the trial (Fig. 1). Baseline patient characteristics (sex, age, performance status, and primary tumor site) were similar between 3 arms of the study and represented in Table 1. Eight patients (13%) had a history of neoadjuvant chemotherapy before surgery. The mean age of the patients was 44 (range: 24–63) years. Fifty-five patients (92%) were male, and 5 patients were female (8%). Thirty-nine patients (65%) had carcinoma of the tongue, 18 patients (30%) had carcinoma of the buccal mucosa, 2 patients (3.3%) had carcinoma of the hard palate, and 1 patient (1.7%) had carcinoma of the floor of the mouth as primary lesion. Histopathology analysis showed a mean primary tumor size of 2.5 cm, a mean tumor depth of infiltration 11 mm, perineural invasion present in 19 patients (31.6% cases), lymphovascular invasion present in 18 patients (30%), and cut margins positive in 1 patient. Pathological nodal metastasis was observed in 23 patients (38.3%). The mean number of pathologic nodes with metastasis was 2, the mean number of nodes dissected was 26, the mean maximum size of positive nodes was 1.5 cm, and extracapsular extension was present in 6 patients (10%). All patients completed the full course of chemoradiotherapy treatment.

Effect on Oral Mucositis

All the patients in all 3 arms experienced grade 0 mucositis at week 1 and progressed to grade 1 after 2 weeks of chemoradiotherapy treatment. However, from fourth week onward, patients in arms A and B showed a decrease in the incidence and severity of mucositis compared to arm C. Arm B had significant improvement compared to arm C at week 4 ($p = 0.017$). After 5 weeks of treatment, 35% of the patients in arm C progressed to grade 3, whereas only 20 and 15% in arms A and B, respectively, progressed to grade 3 mucositis. At the end of 6 weeks of treatment, 75 and 80% of arms A and B, respectively, had grade 2 mucositis, whereas 65% of the patients in arm C were progressed to grade 3 oral mucositis. The difference in mucositis severity between arms A and C ($p = 0.011$) as well as arms B and C ($p = 0.004$) was found to be statistically significant. Weekly assessments of oral mucositis of arms A, B, and C are represented in Figure 2.

Effect on Oral Pain

All the patients in 3 arms had grade 0 oral pain at week 1 and progressed to grade 1 after 2 weeks of treatment. However, from third week onward, patients in arms A and B showed a decrease in the incidence and severity of oral pain compared to arm C. After 4 weeks of treatment, 5 and 15% of the patients in arms A and C, respectively, progressed to grade 3 oral pain, whereas none of them progressed from grade 2 oral pain to grade 3 in arm B. After 5 weeks of treatment, only 5% of patients had grade 3 oral pain, which was significantly different from 35% of patients in arm C. After 6 weeks of treatment, the majority (70%) of the patients in arm C progressed to grade 3, whereas only 35 and 30% in arms A and B progressed to grade 3 mucositis. The treatment difference between arms A and C ($p = 0.027$) as well as arms B and C ($p = 0.011$) was found to be statistically significant. Week-wise assessment of oral pain, dysphagia, and dermatitis of arms A, B, and C is represented in Figure 2.

Effect on Dysphagia

All the patients in 3 arms had grade 0 dysphagia at week 1. In arms A and B, only 30 and 25% of patients had grade 1 mucositis; however, the majority of patients in arm C (55%) had grade 1 mucositis. All the patients with grade 0 progressed to grade 1 or 2 by the third week, and all the patients with grade 1 progressed to grade 2 or 3 by the end of the fourth week. However, patients in arms A and B showed a decrease in the incidence and severity of dysphagia compared to arm C. At the end of 6 weeks of treatment, 25 and 20% had grade 2 in arms A and B, respectively, whereas 60% of the patients in arm C were having grade 3 dysphagia. The difference between the arms A and C ($p = 0.025$) as well as B and C ($p = 0.010$) was statistically significant. Week-wise assessment of dysphagia of arms A, B, and C is represented in Figure 2.

Effect on Dermatitis

All the patients in 3 arms had grade 1 dermatitis till the third week of treatment. After 4 weeks of treatment, 10 and 15% of the patients in arms A and C, respectively, progressed to grade 2 dermatitis, whereas none of them progressed from grade 1 in arm B. After 5 weeks of treatment, all of the patients in arm C progressed to grade 2, whereas only 80% in arm A ($p = 0.035$) and 75% in arm B ($p = 0.017$) progressed to grade 2 dermatitis, which were statistically significant. At the end of 6 weeks of treatment, 20 and 5%, respectively, had grade 3 dermatitis in groups A and B, whereas 30% had grade 3 dermatitis in arm C. The difference between arms B and C was found to be statistically significant ($p = 0.037$). Table 2 presents the data at the end of chemoradiotherapy treatment. Week-wise assessment of dermatitis of arms A, B, and C is represented in Figure 2.

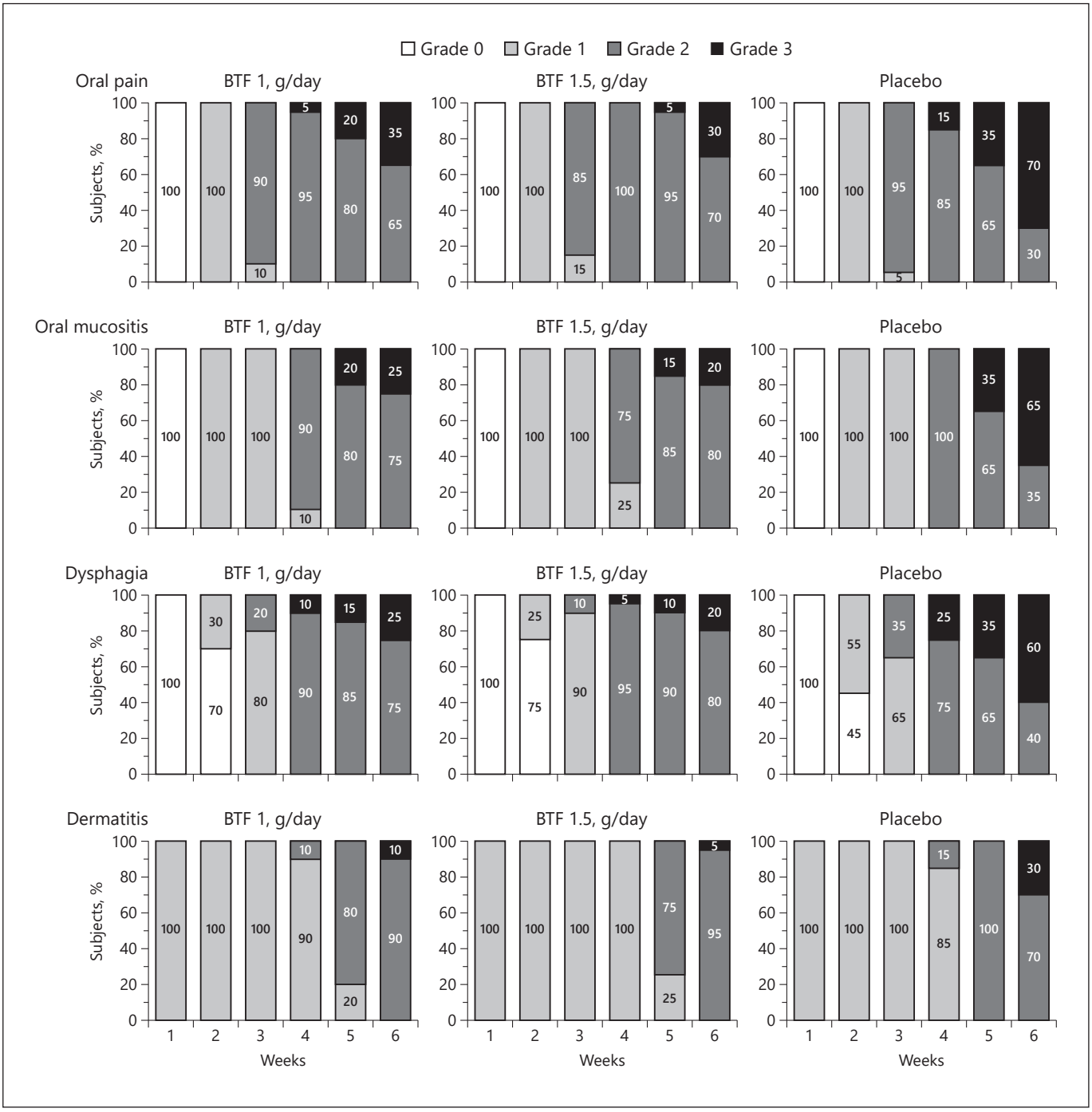

Fig. 2. Weekly assessment of oral pain, oral mucositis, dysphagia, and dermatitis in arm A (BTF 1 g/day), arm B (BTF 1.5 g/day), and arm C (placebo). BTF, bio-enhanced turmeric formulation.

Requirement of tube feeding was decreased in arms A and B compared to arm C (placebo) (Table 3). Twenty-five % of the patients in arm A ($p = 0.025$) and 20% of the patients in arm B ($p = 0.010$) required tube feeding, compared to 60% of patients in arm C (Table 3). More patients (55% patients) from the arm C group (placebo) required admission to the hospital for treatment compared to arms A (20% patients) ($p = 0.022$) and B (15% patients) ($p =$

Table 2. Dysphagia, oral pain, and oral mucositis after 6 weeks

Parameters	Arm A ($N = 20$) n (%)	Arm B ($N = 20$) n (%)	Arm C ($N = 20$) n (%)	p value*		
				arms A and B	arms A and C	arms B and C
Oral mucositis grade 2	15 (75)	16 (80)	7 (35)	0.705	0.011	0.004
Oral mucositis grade 3	5 (25)	4 (20)	13 (65)			
Oral pain grade 2	13 (65)	14 (70)	6 (30)	0.736	0.027	0.011
Oral pain grade 3	7 (35)	6 (30)	14 (70)			
Dysphagia grade 2	15 (75)	16 (80)	8 (40)	0.705	0.025	0.010
Dysphagia grade 3	5 (25)	4 (20)	12 (60)			
Dermatitis grade 2	18 (90)	19 (95)	14 (70)	0.548	0.114	0.037
Dermatitis grade 3	2 (10)	1 (5)	6 (30)			

*Pearson χ^2 test.

Table 3. Treatment completion and Ryles tube insertion details

Parameter	Arm A ($N = 20$) n (%)	Arm B ($N = 20$) n (%)	Arm C ($N = 20$) n (%)	p value*		
				arms A and B	arms A and C	arms B and C
Treatment completed	16 (80)	17 (85)	9 (45)	0.677	0.022	0.008
Treatment interrupted	4 (20)	3 (15)	11 (55)			
Ryles tube inserted	5 (25)	4 (20)	12 (60)	0.705	0.025	0.010
Ryles tube insertion – not required	15 (75)	16 (80)	8 (40)			
Admission during RT	4 (20)	3 (15)	11 (55)	0.677	0.022	0.008
Admission not required during RT	16 (80)	17 (85)	9 (45)			

*Pearson χ^2 test.

Table 4. Weight loss after 6 weeks of chemoradiotherapy

Parameter	Arm A ($N = 20$)	Arm B ($N = 20$)	Arm C ($N = 20$)	p value		
				arms A and B	arms A and C	arms B and C
Weight loss (mean ± SD)*	3.18±1.30	3.03±1.35	4.55±1.78	0.946	0.014	0.006
Weight loss (>3 kg from baseline) (n, %)**	12 (60)	5 (25)	15 (75)	0.311	0.025	0.002
Weight loss (≤3 kg from baseline) (n, %)**	8 (40)	15 (75)	5 (25)			

*One-way ANOVA. **Pearson χ^2 test.

0.008). Forty-two of 60 patients completed the treatment without any significant interruption in radiotherapy treatment. Eighteen of 60 patients (30%) had significant treatment interruption/gap (>3 consecutive radiation fraction missed). Patients in arm B (BTF 1.5g/day) had better treatment compliance and fewer treatment interruptions during chemoradiotherapy treatment than other arms (Table 3). Fifteen % of patients in arm B had significant treatment interruption in radiotherapy compared to 20% of patients in arm A ($p = 0.677$) and 55% of

patients in arm C ($p = 0.008$). More patients (75% patients) in arm C (placebo) developed significant weight loss (>3 kg from baseline) during the treatment than patients in arm A (60% of patients) ($p = 0.025$) and arm B (25% of patients) ($p = 0.002$) (Table 4).

Discussion

In the present study, the incidence of grade 3 oral mucositis, dysphagia, and oral pain was significantly lower in patients receiving BTF (arms A and B) than placebo (arm C). The incidence of grade 3 dermatitis was significantly lower in arm B patients who received BTF 1.5 g/day. Patients in BTF arms had better treatment compliance and fewer treatment interruptions during chemoradiotherapy treatment than placebo arm. Requirement of Ryles tube insertion, hospital admission, and weight loss during chemoradiotherapy treatment was significantly lower in BTF arms than the placebo arm. These results clearly indicate that the supplementation of BTF effectively prevented chemoradiotherapy-induced dysphagia, mucositis, oral pain, and dermatitis.

Earlier studies suggest that curcumin has anti-inflammatory properties, and by reducing the inflammation and pain, curcumin might have contributed toward lower severe mucositis, oral pain, and dysphagia [28]. Curcumin-induced anti-inflammatory effect appears to be mediated by upregulation of PPAR-γ and downregulation of NF-κB and NF-κB-regulated genes [29]. Curcumin's anti-inflammatory activities include its ability to modulate signaling molecules such as pro-inflammatory cytokines, apoptotic proteins, cyclooxygenase-2, C-reactive protein, prostaglandin E_2, adhesion molecules, tumor necrosis factor-alpha, IL-1β, IL-6, and transforming growth factor-β [28]. These molecules are critical regulators of inflammation, and the inhibition and suppression of these molecules explain the anti-inflammatory property of curcumin [30, 31]. Anti-inflammatory properties of curcumin reflect the protective action of curcumin in reducing oral mucositis, dysphagia, and oral pain in our study.

The denuded epithelium due to oral mucositis may also provide access to the oral microbial flora and promote colonization of oral bacteria, which contributes to the underlying pathogenesis and exacerbate the condition [32]. Curcumin increases re-epithelialization of the epidermis; migration of myofibroblasts, fibroblasts, and macrophages to the wound bed; promotion of neovascularization; and greater deposition of collagen; and increases levels of transforming growth factor-β1; and enhances the healing of radiation-induced skin ulcers [33, 34]. Curcumin has also been reported to have strong antibacterial effects by inhibiting bacterial growth, epithelial cell adherence, and cellular invasion in a mucositis model of epithelial cells in vitro [35]. Since breakage of the mucosal barrier allows pathogens to penetrate the mucosa and increase inflammation, the antibacterial property of curcumin might have contributed to accelerated healing of oral mucositis [36].

Multiple animal studies and human clinical trial have also shown that curcumin effectively reduces radiation-induced mucositis [13, 14, 37, 38]. A preclinical laboratory study on rats showed that topical application of curcumin effectively prevented radiation-induced oral mucositis [13]. Curcumin gargle reduces the incidence and severity of radiation-induced oral mucositis [14]. In a single-blinded, randomized trial in 80 head-neck cancer patients receiving chemoradiotherapy, curcumin gargle was compared with povidone-iodine gargle. The curcumin arm had delayed onset and less severe oral mucositis compared to the povidone-iodine gargle ($p < 0.001$). Thirty-six% patients developed high-grade mucositis in the curcumin group, versus 85% patients in the povidone-iodine group [14].

In a comparative study between curcumin mouthwash versus chlorhexidine mouthwash, there was a statistically significant difference in the numerical rating scale ($p = 0.000$), erythema ($p = 0.050$), ulceration ($p = 0.000$), and WHO scale ($p = 0.003$) between the 2 groups [39]. In that study, curcumin was better than chlorhexidine mouthwash, leading to more rapid wound healing and better patient compliance in treatment of chemoradiotherapy-induced oral mucositis [39]. The role of a curcumin gel local application was also compared with chlorhexidine gel in 40 patients of oral cancers receiving chemoradiotherapy, where mucositis was significantly lower in patients treated with the curcumin gel [40].

A systematic review of 5 published clinical trials by Normando et al. [41] evaluated the effects of curcumin in the management of oral mucositis in cancer patients undergoing chemotherapy and/or radiotherapy. In these trials, curcumin was applied topically as a gel or as a mouthwash. Patients receiving curcumin experienced reduced grade of mucositis, pain, erythema intensity, and ulcerative area. This systematic review suggested that topical application of curcumin is effective in controlling symptoms of oral mucositis [41]. Adhyaryu et al. [42] performed an open-label controlled trial that compared 95 head and neck cancer patients receiving 2 g of curcumin/day during chemoradiotherapy. A significant de-

crease in the incidence of mucositis was observed, from 92 to 51%, and in grade 3 and 4 mucositis from 51.6 to 12.8% in the control and curcumin-treated groups, respectively. Curcumin increased patient compliance for the planned radiotherapy treatment, from 52.6 to 89.0% [42]. Curcumin oral topical applications effectively reduced the severity of oral mucositis in a clinical trial on patients diagnosed with lichen planus [43].

Despite its many benefits, the effectiveness of oral supplementation with curcumin has been limited by its poor absorption into the bloodstream through the digestive tract. Research articles have shown the poor pharmacokinetic, pharmacodynamic, and bioavailability properties of curcumin [44, 45]. BTF is a proprietary combination of curcuminoids and essential oil of turmeric with turmerones. Previously, BTF has shown the radioprotective effect in patients of carcinoma prostate by reducing the severity of radiotherapy-related urinary symptoms [46].

Arun et al. [47] in a randomized trial evaluated the role and effect of curcuminoid essential oil combination (1.5 g/day) on chemoradiotherapy-induced oral mucositis in 61 head-neck cancer patients. They found that the combination reduced the incidence and severity of oral mucositis significantly compared to the placebo arm ($p < 0.001$) [47]. In our study, patients treated with BTF had lower oral mucositis than placebo, showing its effectiveness in preventing against radiation-induced mucositis. Also, patients in the BTF (1.5 g/day) arm were able to maintain better food intake, presumably due to the lower incidence of severe mucositis, oral pain, and dysphagia. Likewise, patients in the BTF 1.5 g/day arm had lower weight loss and increased compliance of treatments than the placebo or BTF 1g/day arm.

Strength of the Study

A randomized, double-blind, placebo-controlled study design with a well-defined population of patients to minimize the biases in the results was the strength of this study. Only one blinded observer evaluated all the patients every week, so calibration of assessors was not required. All patients in the study received standard radiotherapy treatment with intensity-modulated radiotherapy technique by a modern linear accelerator along with weekly cisplatin-based concurrent chemotherapy.

Limitations of the Study

A single center-based study with a small number of patients is one of the limitations of the study. Larger, multicentric trials are recommended to confirm the findings of the study.

Conclusion

The BTF used in this study significantly reduces chemoradiotherapy-induced severe oral mucositis, dysphagia, and oral pain in the subpopulation of head and neck cancer patients studied here. This formulation can be considered as a useful dietary supplement during radiotherapy of head-neck cancer patients to effectively manage the oral mucositis or dysphagia and to improve compliance to treatment.

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Statement of Ethics

The study was conducted in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Bhagwan Mahaveer Cancer Hospital and Research Centre (Reference BMH/7916). Prior to any study-related screening procedures, written informed consent was obtained by the principal investigator from each patient before enrolling them in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Tej Prakash Soni, Anil Kumar Gupta, Lalit Mohan Sharma, Harish Singhal, Shantanu Sharma, and Ravindra Singh Gothwal provided substantial contributions to the conception and design of the work and acquisition, analysis, and interpretation of data for the work. Tej Prakash Soni provided project administration support and wrote the original draft. All authors reviewed and approved the final manuscript.

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