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A randomized phase III prospective trial of bethanechol to prevent mucositis, candidiasis, and taste loss in patients with head and neck cancer undergoing radiotherapy: a secondary analysis

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Abstract: The aim of this study was to determine the impact of bethanechol administration concomitant to radiotherapy (RT) on oral mucositis, candidiasis and taste loss. We performed a secondary analysis of a previously conducted prospective randomized trial which evaluated the effect of bethanechol on salivary gland dysfunction before, during, and after RT for head and neck cancer (HNC), in comparison to artificial saliva. Mucositis, candidiasis and taste loss were analyzed in 36 patients. Mucositis was scored using the World Health Organization (WHO) method; candidiasis was diagnosed by means of clinical examination, whereas taste loss was assessed by the patients' subjective report of absence of taste. No significant differences were observed between groups in relation to frequency and severity of mucositis or frequency of candidiasis and taste loss. In conclusion, bethanechol does not appear to reduce the incidence of mucositis, candidiasis, and taste loss when administered during RT. (J Oral Sci 51, 565-572, 2009)

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Introduction

Radiotherapy (RT) plays an important role in the treatment of patients with head and neck cancer (HNC). However, it commonly produces toxic effects in the normal tissues, in the form of systemic alterations and oral lesions, including mucositis, candidiasis and taste loss (1,2).

Oral mucositis is a painful, debilitating, dose-limiting side-effect of therapeutic irradiation of the head and neck (3). Currently, there is no consensus on the most effective way to prevent or treat this distressing complication (4). Oral candidiasis is common in individuals with HNC, especially when RT is employed. Oral colonization (up to 93%) and infection (up to 30%) are frequently seen in these patients (5,6). The infection is marked by oral pain and/or burning and can lead to significant patient morbidity (7). Alteration or loss of taste sensation occurs as a result of the direct effect of radiation on the taste buds, with consequent changes in the saliva (8). In most instances, taste gradually returns to normal or near-normal levels within 1 year after RT. However, partial taste loss and subjective perception may persist 1-2 years after RT treatment (9).

Previous studies suggested that pilocarpine may prevent

the incidence and severity of chemotherapy (CT)- and RT-induced mucositis, possibly through stimulation of minor salivary glands (10). We hypothesized that bethanechol could also minimize RT-induced mucositis incidence and/or severity, since it has been shown to stimulate saliva production similar to pilocarpine (11). Thus, the aim of this study was to determine the efficacy of bethanechol concomitant to RT in the moderation of oral mucositis. In addition, we sought to verify the effect of bethanechol on RT-induced candidiasis and taste loss, since both complications are directly influenced by reduction of salivary flow (2,12).

Materials and Methods

This study is a secondary analysis of a previously published phase III randomized clinical trial designed to evaluate whether the use of bethanechol during RT for HNC prevented radiation-induced xerostomia and salivary flow reduction (11). Head and Neck surgeons and radiotherapists referred patients to the Oncology Service of the Universidade Federal de Minas Gerais (UFMG) Dental School, where they received assistance before, during, and after RT, on a weekly basis. Adult subjects with biopsy-proven malignant neoplasm of the head and neck region, who received external beam RT encompassing one or more major salivary glands for a minimum of 45 Gy, were included. Exclusion criteria comprised systemic conditions that might induce an adverse reaction with bethanechol (mechanical obstruction of the GI or GU tract or when the strength or integrity of the GI or bladder wall was in question; hyperthyroidism, peptic ulcer disease, epilepsy, obstructive pulmonary disease, bradycardia, vasomotor instability, atrioventricular conduction defects, hypotension, or parkinsonism); use of tricyclic antidepressants, antihistamines with anticholinergic effects, and beta blockers; and hypersensitivity to bethanechol. The Ethics Committee of the UFMG approved this randomized prospective clinical trial (protocol no. 421/04).

After obtaining informed consent, patients who would begin RT were randomly allocated into two groups: oral bethanechol (Liberan®) 25 mg, three times a day (6 a.m., 2 p.m., and 10 p.m.) (Group 1) and artificial saliva (OralBalance®) (Group 2). The latter served as control group, since it did not exert effects on the salivary gland (13). Due to different formulations between groups, it was not possible for the study to be double-blinded. The daily timing of bethanechol administration with respect to RT was not standardized, and compliance was measured by counting the number of pills remaining at the end of each week. Using the Epi-Info® software version 6.04b, six lists with a randomized sequence for patient allocation were generated (randomization codes with block-size of eight). Prior to allocation, the patients were stratified by RT treatment field (facial, cervical, and cervico-facial) and by age (≤65 and >65). Age stratification was used because at age 65, around 40% of the population reported xerostomia (14), which was an important factor for the primary purpose of the clinical trial.

Bethanechol and artificial saliva were administered with irradiation and used until the end of RT. Also, topical sucralfate was administered to all patients in both groups, four times a day, concomitant to RT, as a part of our clinical protocol. Patients who eventually developed severe mucositis (i.e., multiple and very painful lesions) were subjected to daily laser applications until remission of the lesions.

Patient characteristics investigated included age, gender, race, tumor histology, tumor stage, tumor treatment modality, RT equipment, RT field, RT primary dose, chemotherapy, the number of RT sessions completed, and chemotherapy regimen.

Mucositis was weekly scored using the World Health Organization (WHO) method as follows: grade 1, soreness and erythema; grade 2, erythema or ulcers but can eat solid foods; grade 3: ulcers, requires liquid only; and grade 4: no possible feeding (15). From the scores, four time-to-event outcome variables were derived as: 1) mucositis 1 = (yes/no mucositis, number of weeks when developed a mucositis score 1 or higher); 2) mucositis 2 = (mucositis score 2 or higher/lower, number of weeks when developed a mucositis score of 2 or higher); 3) mucositis 3 = (mucositis score 3 or higher/lower, number of weeks when developed a mucositis score of 3 or higher); 4) mucositis 4 = (mucositis score 4/lower, number of weeks when developed a mucositis score of 4 or higher). If a patient's mucositis score was greater than 3, laser therapy referral was needed. Thus, the fifth variable for mucositis was laser referral = (laser therapy referred yes/no, number of sessions finished when referred to laser therapy). At the end of RT, the greatest mucositis score the patient had developed was registered, as well as a session of RT in which the patient was referred to laser therapy.

Patients were weekly examined to verify *Candida* infection, which was defined as the clinical presence of removable white intra-oral plaques or white lesions associated with erythematous lesions. Presence or absence of infection throughout the RT course and session of RT corresponding to the initial development of candidiasis were registered.

Taste loss was defined as the patient's subjective report of absence of taste. The session of RT corresponding to the development of complete taste loss was registered.

Table 1 Demographic, clinical and RT characteristics of the study group

Characteristic	Bethanechol (n = 16)	Artificial saliva (n = 20)	P[1]
Mean age (years) (SD)	59 (14)	55 (13)	0.42
Gender (%)			
Female	25.0	25.0	1.00
Male	75.0	75.0	
Staging (UICC) (%)			
Stage I / II	25.0	25.0	1.00
Stage III / IV	75.0	75.0	
Treatment plan (%)			
RT	18.8	0.0	
RT and chemotherapy	18.8	50.0	0.03
Surgery and RT	62.5	50.0	
RT equipment (%)			
Cobalt	62.5	50.0	0.52
Linear accelerator	37.5	50.0	
RT field (volume)			
Facial	6.7	10.0	
Cervical	20.0	0	0.17
Cervico-facial	73.4	90.0	
Mean RT tumor dose (Gy) (SD)	63.00 (6.03)	65.00 (7.32)	0.47

[1]*P*-values of continuous characteristics such as age, years, and RT tumor dose were derived from *t*-tests, while *P*-values for the rest categorical characteristics were from Fisher exact tests.

For statistical analysis, age, the number of RT sessions completed, and RT primary dose were treated as continuous variables. Gender, race, tumor histology, tumor stage, tumor treatment modality, RT equipment, and RT area were analyzed as categorical variables. Descriptive statistics were provided for patient characteristics by independent variables and significance was tested by Fisher exact test for categorical variables, and by *t*-test for continuous variables. Both cross-sectional analysis and survival analysis were performed on outcome measures. Frequencies and Fisher exact tests were used to analyze contingency tables of outcomes by independent variable and by patient characteristics. Survival means of outcomes by independent variables and by patient characteristics were analyzed using the Kaplan-Meier method and the log-rank tests. In addition, the association between taste loss and study group was analyzed stratified by tumor therapy modality. A two-sided P-value < 0.05 was considered statistically significant in all tests.

Results

Study group

Fifty-five patients were considered for enrollment. Of these, 12 were not eligible to take bethanechol due to systemic conditions. All the 43 remaining patients agreed to participate and were randomized into the primary clinical trial. For the secondary analysis, however, seven could not be evaluated due to insufficient data and were excluded. The remaining 36 patients were divided as follows: 16 patients in group 1, and 20 patients in group 2. Age, gender, tumor site, tumor stage, RT equipment and RT field were similarly distributed among groups. Chemotherapy was administered concurrent with RT and consisted of 3-4 cycles of cisplatin (100 mg/m^2), each lasting 3 weeks. There was an imbalance between groups, with a significant higher frequency of patients in group 2 being submitted to combined RT and CT (P = 0.03) (Table 1). Analyses of association between each outcome variable and treatment modality were conducted to explore the potential confounding effect (Table 2). The association between taste loss and study group stratified by tumor therapy modality was analyzed to measure the bethanechol effect on taste loss after controlling for treatment modality (Table 3).

Mucositis

No significant differences were observed between groups 1 and 2 in relation to frequency and severity of mucositis. Among the five measures of mucositis, group 1 had longer average survival times in mucositis 2 (4.1 vs. 4.0 weeks), mucositis 4 (6.0 vs. 5.3 weeks), and laser referral (27.0 vs. 20.9 sessions). Shorter average survival times in

Table 2 Frequency and mean survival time of mucositis, patients referred to laser therapy, candidiasis and taste loss between study groups, stratified by treatment modality

Outcome	*n* (%)			Mean Survival time (SE)[1]			P^2	P^3
	RT *n* = 3	RT + CT *n* = 13	S + RT *n* = 20	RT *n* = 3	RT + CT *n* = 13	S + RT *n* = 20		
Mucositis 1	2 (67)	12 (92)	16 (80)	2.7 (0.4)	3.5 (0.4)	2.6 (0.2)	0.40	0.90
Mucositis 2	1 (33)	9 (69)	12 (60)	4.0 (--)	4.2 (0.3)	3.4 (0.1)	0.59	0.61
Mucositis 3	1 (33)	8 (62)	10 (50)	5.0 (--)	5.5 (0.2)	4.5 (0.2)	0.69	0.75
Mucositis 4	1 (33)	8 (62)	10 (50)	5.0 (--)	6.0 (0.3)	4.6 (0.1)	0.69	0.77
Laser	1 (33)	8 (62)	10 (50)	18.0 (--)	26.6 (1.9)	19.7 (1.1)	0. 69	0.79
Candidiasis	1 (33)	9 (69)	12 (60)	22.0 (--)	20.5 (1.7)	15.7 (0.7)	0.59	0.58
Taste loss[4]	0 (0)	13 (100)	17 (85)	-- (--)	19.4 (2.6)	19.8 (2.0)	0.001/ 0.26	0.02/ 0.64

S = surgery, RT = radiotherapy, CT = chemotherapy
[1]The mean survival times and their standard errors were underestimated because the largest observations were censored and the estimations were restricted to the largest event time. Unit of the mean survival times for mucositis 1 through 4 is week while for the other three measures is number of sessions that received radiotherapies.
[2]*P*-values Fisher Exact tests
[3]*P*-values of Log-rank tests
[4]In taste loss row, the first *P*-values from tests include RT only group while the second *P*-values are from tests excluding RT only group

Table 3 Taste loss by independent variable and tumor treatment survival analysis vs. cross-sectional analysis

Strata	Group (n)	Taste loss		P^1	P^2
		n (%)	Mean survival time (SE)		
RT only	Bethanechol (3)	0 (0)	-- (--)	--	--
(*n* = 3)	Control (0)	0 (0)	-- (--)		
RT+CT	Bethanechol (3)	3 (100)	24.7 (4.3)	--	0.25
(*n* = 13)	Control (10)	10 (100)	17.8 (3.0)		
RT + S	Bethanechol (10)	8 (80)	18.2 (2.7)	1.00	0.75
(*n* = 20)	Control (10)	9 (90)	20.8 (2.8)		

S = surgery, RT = radiotherapy, CT = chemotherapy
[1] *P*-values of Fisher exact tests
[2] *P*-values of Log-rank tests

mucositis 1 (2.9 vs. 3.4 weeks) and mucositis 3 (4.7 vs. 5.2 weeks) were found in group 1 compared to group 2. However, none of the differences were statistically significant (*P*-values of log-rank tests ranged from 0.34 to 0.58) (Table 4).

In group 1, 19% of the patients did not develop mucositis, 25% developed greatest mucositis grade 1, and 56% had greatest grades 2 or 3. In group 2, 15% of the patients did not develop mucositis, 25% developed greatest mucositis grade 1, and 60% showed greatest grades 2 or 3. In both groups, no patient developed grade 4 (Table 5). The percentage of patients who required laser therapy for mucositis was smaller in group 1 (44%) than that in group 2 (60.0%) (Table 4). However, none of the differences were statistically significant (*P*-values of Fisher exact and Log-rank tests were 0.50 and 0.34, respectively).

No significant differences were observed among the three tumor treatment modalities in relation to frequency and severity of mucositis (Table 2).

Table 4 Frequency and mean survival time of mucositis, patients referred to laser therapy, candidiasis and taste loss between study groups

Outcome	Positive *n* (%)		Mean survival time (SE)[1]		P^2	P^3
	Group 1	Group 2	Group 1	Group 2		
Mucositis 1	13 (81)	17 (85)	2.9 (0.3)	3.4 (0.3)	1.00	0.51
Mucositis 2	9 (56)	13 (65)	4.1 (0.3)	4.0 (0.2)	0.73	0.58
Mucositis 3	7 (44)	12 (60)	4.7 (0.1)	5.2 (0.2)	0.50	0.42
Mucositis 4	7 (44)	12 (60)	6.0 (0.4)	5.3 (0.2)	0.50	0.39
Laser	7 (44)	12 (60)	27.0 (2.2)	20.9 (1.1)	0.50	0.34
Candidiasis	8 (50)	14 (70)	18.1 (1.4)	19.8 (1.2)	0.31	0.42
Taste loss	11 (69)	19 (95)	22.6 (2.4)	19.3 (2.0)	0.07	0.13

[1]The mean survival times and their standard errors were underestimated because the largest observations were censored and the estimations were restricted to the largest event time. Unit of the mean survival times for mucositis 1 through 4 is week while for the other three measures is number of sessions that received radiotherapies.
[2]*P*-values of Fisher Exact tests
[3]*P*-values of Log-rank tests

Table 5 Frequency and greatest severity of mucositis in study groups throughout treatment course

Study group	Mucositis grading		
	Grade 0	Grade 1	Grades 2-3
	%	%	%
Group 1	18.8	25.0	56.3
Group 2	15.0	25.0	60.0

Candida infection

Candida infection was not identified in any patient before RT. The frequency of candidiasis during RT was smaller in group 1 (50%) than in group 2 (70%) and the mean session of development of candidiasis in group 1 was shorter than that in group 2 (18th and 20th session, respectively). However, neither of these differences was statistically significant (*P*-value of 0.31 from Fisher exact test for frequency comparison and *P*-value of 0.42 from log-rank test for mean survival time comparison) (Table 2).

No significant differences were observed among the three tumor treatment modalities in relation to frequency and severity of candidiasis (Table 4).

Taste loss

No patient complained of taste loss before RT. The frequency of taste loss was at the edge of significantly smaller in group 1 (69%) during RT, in comparison to group 2 (95%) ($P = 0.07$ from Fisher exact test). Similarly, the mean session of development of taste loss in group 1 was not significantly longer than in group 2 (23rd and 19th session, respectively) ($P = 0.13$ from log-rank test) (Table 2).

The frequency of taste loss was 0% in the RT only group, 100% in the RT+CT group, and 85% in the RT+surgery group ($P = 0.001$ from Fisher exact test). However, when comparing the frequencies of taste loss between RT+CT group and RT+surgery group, the significance disappeared ($P = 0.26$ from Fisher exact test). The mean survival time was not estimated because all three cases in the RT only group were censored. Therefore, the overall significance of log-rank test with *P*-value = 0.02 was not valid. The RT+CT group had essential identical mean survival time as the RT+surgery group (19.4 vs. 19.8 sessions) (*P*-value of log-rank test = 0.64) (Table 4).

Stratification analysis by tumor therapy modality further confirmed that there were no significant differences in frequency and severity of taste loss in the study groups (Table 3). In the RT only stratum, all three cases were in group 1 and did not develop taste loss at the end of the study. Therefore, the frequencies of taste loss in the two groups were 0% and no valid mean survival time was estimated. In the RT+CT stratum, all three cases in group 1 and all 10 cases in group 2 developed taste loss at the end of the study. Therefore, the frequencies of taste loss

in the two groups were 100%. Mean survival time in group 1 was longer than in group 2 (24.7 vs. 17.8 sessions). However, the difference was not statistically significant (*P*-value of log-rank test = 0.25). In RT+surgery stratum, eight (80%) out of 10 cases in group 1 and nine (90%) out of 10 cases in group 2 developed taste loss at the end of the study, showing no significant difference (*P*-value of Fisher exact test = 1.00). Mean survival time was 18.2 sessions in group 1 and 20.8 sessions in group 2 with *P*-value of log-rank test = 0.75.

Discussion

This was the first study evaluating the effect of bethanechol administration concomitant to RT on mucositis, candidiasis, and taste loss. In the literature, the prevalence of taste loss shortly after RT ranges from 53-88%, with a relative taste loss developing in over 90% of the patients when a dose of 60 Gy is used (16). In our study, taste loss was reported by 68.8% of the patients who used bethanechol and by 95% of those who used artificial saliva. This value was at the edge of significantly smaller ($P = 0.07$) and it is possible bethanechol could have been statistically beneficial if the study sample was larger. On the other hand, considering the frequency of taste loss was 0% in the RT only group, 100% in the RT+CT group, and 85% in the RT+surgery group, perhaps taste loss was influenced mainly by the cancer treatment plan. Currently, the efficacy of sialogogues used concomitant to RT to prevent xerostomia is still debatable (17,18). Determining whether these drugs can prevent taste loss would represent an additional benefit of using them during RT, since taste loss can affect the quality of life and lead to weight loss (2,19). Regarding the mean session of development of taste loss, no differences were observed between groups 1 and 2 (23rd and 19th session). This is in agreement with the literature, according to which the greatest degree of taste compromise is reached during the third and fourth weeks of treatment (16). Other methods of prevention of taste loss are direct shielding of healthy tissues or placement of these tissues outside the radiation field by means of shielding or repositioning prostheses (2). Cytoprotection by the administration of amifostine during RT has also been recently reported (20), whereas zinc supplements may be useful in increasing taste acuity in patients with residual hypogeusia following RT (21).

Mucositis frequency and severity did not differ between groups. Still, the frequency and severity rates observed in groups 1 and 2 (56.3% and 60% of the patients developed mucositis grades 2-3, respectively) can be considered as fairly good results, considering that up to 80% of the irradiated patients may develop mucositis. Moreover, although 20-30% of the patients who develop mucositis will require artificial feeding (22), this was not observed in our study. However, it can not be determined based on our data whether artificial feeding would eventually be needed, since some patients were subjected to laser therapy. Another important factor was that patients in both groups of our study were prescribed sucralfate during RT. Although this was not the ideal setting, sucralfate was administered following our clinical protocol for mucositis prophylaxis, and because it would not alter the primary purpose of the clinical trial. Since no differences on mucositis grading were observed between groups 1 and 2, the obtained results are most likely attributable to sucralfate, an agent that may prevent mucositis (23). Thus, based on our findings, bethanechol has no benefit on the moderation of frequency and severity of mucositis.

We also investigated the occurrence of *Candida* infection in our study group. Although without statistical significance ($P = 0.22$), the frequency of candidiasis was smaller in patients using bethanechol (50%), in comparison to those who used artificial saliva (70%). Previous authors have reported infection rates ranging from 17-29% (15,17). Data from one of our previous studies with a sample very similar to the present one showed *Candida* infection rates of 52% (24). Thus, the obtained results are discouraging, since infection rates in both groups were very high. When candidiasis did occur, no differences regarding session of initial development were seen between groups 1 and 2 (15th and 16th session, respectively). Our study did not show any advantages for the group using bethanechol in terms of frequency and session of development of candidiasis.

One drawback of this study was the small sample size. This resulted in low test power to detect small differences between groups. Another issue was the difference in the anti-cancer treatment regimen observed between groups. Such a difference was not observed in the primary clinical trial; however, the exclusion of seven patients led to a higher percentage of patients in group 2 being submitted to RT+CT. This was overcome using additional statistical studies (survival analysis). Also, specifically in relation to the mucositis evaluation, the wide variety of treatment protocols used (bethanechol, sucralfate, and in some cases, laser therapy) complicated data interpretation.

In conclusion, our results showed bethanechol was not capable of preventing radiation-induced mucositis, candidiasis, or taste loss when administered during RT. Further studies with larger samples are warranted to determine the usefulness of sialogogues in preventing these significant side effects of HNC treatment.

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