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Double blind randomized prospective trial of bethanechol in the prevention of radiation-induced salivary gland dysfunction in head and neck cancer patients

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ABSTRACT

This study assessed the prophylactic bethanechol use to prevent salivary gland dysfunction during radiotherapy. A total of 97 head and neck cancer patients were allocated into two groups: Bethanechol or Placebo. Bethanechol group presented significantly improve of salivary parameters. Bethanechol was effective in decreasing the salivary gland damage.

Radiation-induced hyposalivation and consequent xerostomia are the most common and disturbing side effects after radiation therapy for head and neck cancer (HNC). These complications significantly increase the risk of oral and dental diseases [1,2]. Several strategies such as amifostine [3], intensity-modulated radiotherapy – IMRT [2], surgical salivary gland transfer [4] and concomitant systemic sialogogues [5–10] have been used to combat medication-induced xerostomia. Previous studies have suggested that pilocarpine administration during radiotherapy (RT) prevent salivary gland dysfunction with significant subjective reduction in xerostomia because of its ability to promote functional stimulation of the salivary gland [5,6,9,10]. However, the prophylactic use of pilocarpine is still controversial because of its toxic side effects [10,11]. In addition, few publications have documented the evidence that bethanechol may be useful in decreasing the incidence and/or severity of xerostomia with minimal side effects [8,11,12].

Hence, this study evaluated the bethanechol effect in a prospective double blind setting in order to reduce or ameliorate xerostomia and hyposalivation. In addition, with the improvement of salivary flow, it would be expected a satisfactory condition of speaking, chewing, and swallowing, resulting in better quality of life. The objectives of this trial were (1) to evaluate the efficacy of the prophylactic use of bethanechol on reducing the xerostomia complain on head and neck irradiated patients through observer-assessed toxicity grading, (2) to verify its influence on salivary flow using sialometry, and (3) to determine its benefits on salivary gland function based on salivary gland scintigraphy. In addition, the safety of this drug was also assessed.

Methods

This was a prospective, double-blinded, randomized controlled trial which enrolled patients diagnosed with primary oral, oropharynx or nasopharynx carcinomas and were scheduled to undergo Three-dimensional radiotherapy (RTC3D) or Intensity modulated radiation therapy (IMRT). Radiation consisted of once-daily megavoltage (6 MV), given at 1.8–2.12 Gy per fraction, 5 days per week.

Both parotid and submandibular glands were contoured using anatomical atlas and corresponding dose in the irradiated volumes of 25%, 50%, 75% and 100% of each gland was acquired using a dose–volume histogram (DVH). Bethanechol and placebo were administered one tablet (25 mg tablets) taken twice a day from the beginning of RT and continued until 1 month after the end of treatment.

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Xerostomia grade was assessed weekly from baseline to 3 months after completion of treatment using observer-based grade and scored according to the subjective measures of the Eisbruch et al. [13] scale. Whole unstimulated saliva (UWS) and whole stimulated saliva (SWS) flows were collected. Following, the samples were weighed and the salivary flow rate was calculated and adjusted in ml/min [14]. All patients underwent saliva collection and also salivary gland scintigraphy in three phases: baseline, during RT (range 30–35 Gy), and 2 months after completion of treatment.

Results

A total of 105 patients were assessed for eligibility. However, 8 patients were excluded from the study due to hyperthyroidism ($n = 2$); angina ($n = 3$); use of tricyclic antidepressants ($n = 1$), or declining participation ($n = 2$). Therefore, 97 patients were randomized by sealed envelope method and allocated into two similarly distributed groups:

Bethanechol group consisted of 48 patients (37 men and 11 women), age-range from 21 years to 75 years (mean age = 55.86 ± 10.44). Considering the tumor sites, in 29 patients the neoplasm was located in the oral cavity, 15 in the oropharynx and 4 in the nasopharynx. With regard to the RT, the RTC3D was performed in 26 patients and the IMRT in 22 patients (Table 1).

Placebo group was composed of 49 patients (39 men and 10 women), age-range from 28 years to 75 years (mean age 55.84 ± 10.38). The tumor sites were the oral cavity ($n = 27$), oropharynx ($n = 11$) and nasopharynx ($n = 11$). In this group, the RTC3D was performed in 26 patients and the IMRT in 23 patients (Table 1).

Among the 97 randomized patients, 6 in the Bethanechol group were lost of follow-up because death ($n = 3$) and declined to participate during the study ($n = 3$). Regarding Placebo group, 7 patients lost of follow-up: severe oral mucositis need hospitalization ($n = 2$), declined to participate during the study ($n = 2$) and death ($n = 3$). Therefore, the results of 84 patients were analyzed: 42 from Bethanechol group and 42 from Placebo group. These patients completed the entire study period and the median follow-up time was 19 weeks.

Table 1
Clinical characteristics of 97 head and neck cancer patients.

Variables	Category	Bethanechol ($n = 48$)	Placebo ($n = 49$)	p
Age (years)	Mean ± SD	55.86 ± 10.44	55.84 ± 10.38	0.617
	Range	21–75	28–75	
	Median	59	56	
Gender	Male	37 (77.1%)	39 (79.6%)	0.764
	Female	11 (22.9%)	10 (20.4%)	
Tumor Site	Oral cavity	29 (60.40%)	27 (55.10%)	0.139
	Orapharynx	15 (31.30%)	11 (22.40%)	
	Nasopharynx	4 (8.30%)	11 (22.40%)	
Clinical Stage	II	5 (10.40%)	8 (16.30%)	0.685
	III	15 (31.30%)	15 (30.60%)	
	IV	28 (58.30%)	26 (53.10%)	
Treatment	RT + SUR	13 (27.10%)	12 (24.50%)	0.455
	RT + CT	22 (45.80%)	25 (51.00%)	
	SUR + RT + CT	13 (27.10%)	10 (20.40%)	
	RT	0	2 (4.10%)	
Type of RT	RTC3D	26 (54.20%)	26 (53.10%)	0.913
	IMRT	22 (45.80%)	23 (46.90%)	

SD = Standard Deviation; RT = Radiotherapy; SUR = Surgery; CT = Chemotherapy; RTC3D = Three dimensional Conformal Radiotherapy; IMRT = Intensity Modulated Radiation Therapy.

Bethanechol-related toxicity

When toxicities were compared between the groups, none statistical difference was noted. No patient experienced severe (Grade 3) toxicity and no one dropped out of the study due to adverse effects.

Xerostomia complaint

After the first week of radiotherapy, not one patient in the Bethanechol group reported Grade III xerostomia. However, 2 (4.4%) patients in the Placebo group already presented severe xerostomia ($p = 0.004$). After all visits, it was seen that patients in the Bethanechol group always presented a significantly lower incidence of Grade II–III xerostomia when compared with patients in the control group. This significant difference in xerostomia severity was also observed at 3 months after the end of RT: 16 (38.0%) patients in the Bethanechol group reported Grade III xerostomia whereas 30 (71.42%) patients in the Placebo group did ($p < 0.0041$). It was also noted that after bethanechol therapy was stopped, the number of patients with Grade 3 xerostomia increased substantially from 7 out of 42 patients (1 month after RT) to 16 (3 months after RT) (Supplementary Table 2). No significant difference was noted between xerostomia complaint and radiation technique (RTC3D or IMRT).

Salivary flow

At baseline, the mean UWS and SWS were 0.65 and 1.34 ml/min for the Bethanechol group, versus 0.79 and 1.13 ml/min for the Placebo ($p = 0.546$; $p = 0.198$, respectively). During RT, the mean UWS and SWS were 0.55 and 0.71 ml/min for the Bethanechol group, versus 0.36 and 0.46 ml/min for the Placebo ($p = 0.008$; $p = 0.005$, respectively). After 2 months of the end of RT, the mean UWS and SWS were 0.29 and 0.38 ml/min for the Bethanechol group, versus 0.06 and 0.23 ml/min for the Placebo ($p = 0.008$; $p = 0.005$, respectively). A significant higher UWS and SWS volume was noted for the comparison of Bethanechol and Placebo for the IMRT group at 2 months after the end of RT (Table 2).

Scintigraphy exams

At baseline, no difference was seen in uptake or excretion rates between the groups for any of the glands. During and 2 months after RT, it was noted that patients in both the Bethanechol and Placebo groups presented a significant and progressive reduction in excretion rate for the parotid and submandibular glands. However, we observed a significant difference between the groups for both gland during RT and for submandibular gland at 2 months (Supplementary Table 3).

In addition, excretion rates were associated with radiation technique at 2 months after the end of RT. It was also observed that patients in the Bethanechol group who underwent IMRT showed a significantly better excretion rate in comparison to patients in the placebo group who underwent IMRT and to patients in the bethanechol group who underwent RTC3D (Table 2).

Discussion

Bethanechol is a cholinergic agonist formed by a carbamic ester of β-methylcholine, which stimulates gland function by acting on the muscarinic-receptor [15]. Few studies have shown its applicability to the improvement of xerostomia and hyposalivation with minimal side effects [8,11,12]. In the Epstein et al. [11] study, a significant increase in UWS ($p = 0.003$) and SWS production was demonstrated ($P = 0.001$). Later on, in the Gorsky's et al. [12] trial,

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