

# A study on Evaluation of efficacy of bethanechol in the management of chemoradiation-induced xerostomia in oral cancer patients

M Kavitha, K Mubeen<sup>1</sup>, KR Vijayalakshmi<sup>1</sup>

Department of Oral Medicine and Radiology, Madha Dental College and Hospital, Chennai, Tamil Nadu, <sup>1</sup>Department of Oral Medicine and Radiology, Government Dental College and Research Institute, Bengaluru, Karnataka, India

## Abstract

**Objectives:** Squamous cell carcinoma is the most common oral cancer. Radiotherapy with concomitant chemotherapy is an ideal treatment modality largely used for oral cancers, which precipitates many side effects, of which the most challenging and debilitating side effect is xerostomia. This study aimed to evaluate the efficacy of bethanechol in patients with xerostomia following chemoradiation therapy for oral cancer.

**Materials and Methods:** Fifty patients with xerostomia postchemoradiation therapy, aged between 30 and 65 years, were selected based on selection criteria. Thirty patients in the study group were administered 25 mg bethanechol three times daily (TDS) and 20 patients in the control group with placebo capsules. The subjective symptoms of oral dryness were periodically evaluated at baseline, at the end of 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> weeks using a self-reported questionnaire. Salivary analysis such as whole resting saliva and whole stimulated saliva (WSS) volumes, amylase, pH and sodium potassium ratio were evaluated before and 3 weeks after bethanechol and placebo therapy.

**Results:** Twenty-four (80%) patients in bethanechol group and only 2 (10%) patients in control group showed subjective improvement in oral dryness at the end of 3<sup>rd</sup> week. A significant difference was found between two groups in whole resting and stimulated saliva volume, pH and amylase. However, there was no statistically significant difference in sodium potassium ratio with insignificant adverse effects after 3 weeks of bethanechol therapy.

**Conclusions:** 25 mg bethanechol (TDS) has shown subjective improvement in oral dryness in 24 (80%) patients with significant improvement in whole resting and WSS volumes, pH and salivary amylase with insignificant adverse effects.

**Keywords:** Bethanechol, oral cancer, radiotherapy, saliva, xerostomia

**Address for correspondence:** Dr. M Kavitha, Department of Oral Medicine and Radiology, Madha Dental College and Hospital, Kundrathur, Chennai - 600 069, Tamil Nadu, India.  
E-mail: kavitha.srnvs@gmail.com

**Received:** 17.04.2016, **Accepted:** 12.08.2017

## INTRODUCTION

Squamous cell carcinoma is the most common cancer in the oral cavity, accounting for >90% of all oral cancers.<sup>[1]</sup> It is

estimated that annually 70,000–80,000 new cases are reported in India. The high incidence of oral cancer in India is attributed to chronic use of tobacco in smoking and smokeless forms.<sup>[2]</sup>

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Kavitha M, Mubeen K, Vijayalakshmi KR. A study on Evaluation of efficacy of bethanechol in the management of chemoradiation-induced xerostomia in oral cancer patients. *J Oral Maxillofac Pathol* 2017;21:459-60.

### Access this article online

#### Quick Response Code:



#### Website:

www.jomfp.in

#### DOI:

10.4103/jomfp.JOMFP\_72\_16

The mainstay of treatment for oral cancers is surgery, radiotherapy and chemotherapy. However, radiotherapy with concomitant chemotherapy is an ideal nonsurgical treatment modality largely used for oral cancers.<sup>[3]</sup> Radiation of the head and neck precipitates many side effects such as mucositis, dysgeusia, candidiasis and radiation caries. However, the most challenging and debilitating side effect is xerostomia.<sup>[4,5]</sup>

Various treatment strategies such as topical lubricants, coating agents, salivary substitutes, or lozenges have been tried which all provide only a transient relief from xerostomia. However, the most accepted treatment is use of systemic sialogogs, which acts by the stimulation of residual functional salivary gland tissue.<sup>[4,6]</sup>

Recently, clinical trials on bethanechol, an acetylcholine analog possessing muscarinic cholinergic activity, have reported increase in whole resting and stimulated saliva with minimum side effects in xerostomia patients.<sup>[7,8]</sup> However, at present, there are no studies in India for evaluating the efficacy of bethanechol in patients with xerostomia following chemoradiation therapy. Hence, the need is felt for the study.

### Aims and objectives

1. Quantification of whole resting saliva (WRS) and whole stimulated saliva (WSS) volumes and to assess the levels of salivary alpha amylase, sodium potassium ratio and pH in patients with chemoradiation-induced xerostomia in oral cancer before and after bethanechol therapy
2. To assess the role of bethanechol in the management of xerostomia postchemoradiation therapy in oral cancer patients.

### MATERIALS AND METHODS

The study was conducted in the Department of Oral Medicine and Radiology and consists of fifty xerostomia patients, who underwent chemoradiation therapy for oral cancer. The study was conducted in full accordance with ethical principles and was approved by an institutional ethical board.

### Method of collection of data

Fifty patients with xerostomia, aged between 30 and 65 years, were selected for the study based on set inclusion and exclusion criteria.

### Inclusion criteria

1. Patients with histopathologically diagnosed as carcinoma of buccal mucosa, gingivo-buccal sulcus,

anterior 2/3<sup>rd</sup> of the tongue, floor of the mouth, gingiva and hard palate [Figure 1]

2. Patients who received external beam radiation therapy with Tele-Cobalt 60 to a mean dose of 60–70 Gy, over 30–35 fractions, 2 Gy/day, 5 fractions a week for 6–7 weeks with concurrent chemotherapy, a single agent cisplatin, 40 mg/m<sup>2</sup> intravenous at weekly intervals
3. Patients with major salivary glands within the radiation portals
4. Patients with xerostomia immediately following chemoradiation therapy (i.e., WRS <0.1–0.2 ml/min and WSS <0.5–0.7 ml/min) based on set criteria by Epstein *et al.*<sup>[7]</sup>
5. Patients with normal liver and renal function.

### Exclusion criteria

1. Patients with carcinomas other than oral cavity
2. Patients with known allergy to many drugs
3. Patients with systemic diseases influencing salivary gland and its secretions such as diabetes and renal disease
4. Patients taking medications such as tri-cyclic anti-depressants, anti-anxiety drugs, anti hypertensives, antihistamines with anti-cholinergic effects
5. Patients suffering from salivary gland diseases
6. Patients aged over 65 years.

The details of the study were explained to the patients and written informed consents were obtained. A detailed case history was collected and thorough clinical examination was carried out and recorded in specially prepared case history pro forma.

Patients with xerostomia were divided into two groups:

1. Study group: Thirty patients with xerostomia were subjected to liver and renal function test. Patients with



**Figure 1:** Carcinoma involving anterior alveolus extending into floor of the mouth (ulcero-proliferative type)

normal liver and renal function were prescribed with bethanechol tablets 25 mg (available with a trade name of URIVOID), orally 3 times daily on empty stomach, 1 h before or 2 h after food to prevent nausea and vomiting for 3 weeks

- Control group: Twenty patients with xerostomia were prescribed with placebo capsules containing wheat flour, orally three times daily 1 h before or 2 h after food for 3 weeks.

### Method of collection of salivary sample

- Patients were called in the morning session between 9 a. m and 11.00 a. m and were made to sit in a comfortable position
- Patients were instructed not to drink (except water) or eat 1 h before saliva collection
- WRS was collected for 5 min by expectoration into sterile graduated container every 1 min and saliva volumes collected were expressed as ml/min. Patients were instructed not to swallow any saliva during the 5 min collection periods
- Stimulated whole saliva was collected after the patient chewed on a standard piece of preweighed paraffin wax (1 g). Collection of saliva was started 1 min after chewing. Patients were asked to spit into a sterile graduated container, once per minute for 5 min and the saliva volumes collected were expressed as ml/min.<sup>[7,9]</sup>

The patients in the study were followed up for 3 weeks, and subjective symptoms of oral dryness were periodically evaluated at baseline, at the end of 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> weeks using a self-reported questionnaire designed by Eisbruch *et al.* and Meirovitz *et al.*<sup>[10,11]</sup> Salivary analysis such as whole resting and stimulated saliva volumes, salivary amylase, sodium potassium ratio and pH were evaluated before and 3 weeks after bethanechol and placebo therapy using standard kit and procedure. Any adverse effects during the treatment period were recorded.

### Self-reported questionnaire for evaluation of xerostomia (from baseline to 3 weeks after bethanechol and placebo therapy)

- Rate your difficulty in chewing due to dryness
- Rate your difficulty in swallowing solid foods due to dryness
- Rate your mouth or throat dryness while not eating
- Rate your difficulty in talking due to dryness
- Rate the frequency of your sleeping problems due to dryness
- Rate the frequency of sipping liquids to aid swallowing food and for oral comfort.<sup>[10,11]</sup>

### Method of estimation of salivary amylase

#### Enzymatic colorimetric assay

#### Procedure

The samples and the reagent were brought to room temperature prior to use. 1 in 10 diluted saliva sample (450 µl of distilled water and 50 µl of WRS sample) was added to CoBAS cup. Reagent cassette and CoBAS cup containing saliva sample were inserted in the respective racks in fully automated analyzer (CoBAS Integra 400). The values displayed on monitor were recorded.<sup>[12,13]</sup>

### Estimation of salivary sodium

#### Method (colorimetric method): Sodium estimation comprising two steps

#### Step 1: Precipitation of sodium

- Clean dry test tubes were labeled as standard (S) and test (T)
- 1 ml of precipitating reagent and 0.02 ml of standard were added to test tube (S)
- 1 ml of precipitating reagent and 0.02 ml of WRS sample were added to test tube (T)
- Tubes were mixed well and incubated at room temperature for 5 min and then centrifuged at 2000–3000 rpm for 2 min to obtain a clear supernatant.<sup>[14,15]</sup>

#### Step 2: Color development

- Clean dry test tubes were labeled as blank (B), standard (S) and test (T)
- 1 ml of acid reagent, 0.02 ml of precipitating reagent and 0.1 ml of color reagent were added into the blank tube
- 1 ml of acid reagent, 0.02 ml of supernatant from step 1 (standard reagent) and 0.1 ml of color reagent were added into the standard tube
- 1 ml of acid reagent, 0.02 ml of supernatant from step 1 (saliva sample) and 0.1 ml of color reagent were added into the test tube
- Test tubes were mixed well and incubated at room temperature for 5 min. Measurement of the absorbance of the blank (Abs. B), standard (Abs. S) and test sample (Abs. T) against distilled water was done within 15 min at 530 nm using colorimeter.<sup>[14,15]</sup>

#### Calculations

$$\text{Sodium in mmol / l} = \frac{\text{Abs. B} - \text{Abs. T} \times 150}{\text{Abs. B} - \text{Abs. S}}$$

### Estimation of salivary potassium

Procedure: Clean dry test tubes were labeled as blank (B), standard (S) and test (T).

- 1 ml of potassium reagent and 0.02 ml of deionized water were added in the blank tube
- 1 ml of potassium reagent and 0.02 ml of standard

reagent were added in the standard tube

- 1 ml of potassium reagent and 0.02 ml of WRS sample were added in the test tube
- Test tubes were mixed well and incubated at room temperature for 5 min. Measurement of the absorbance of the standard (Abs. S) and test sample (Abs. T) against blank was done within 15 min at 630 nm using colorimeter.<sup>[14,15]</sup>

**Calculations**

$$\text{Potassium in mmol / l} = \frac{\text{Abs. T} \times 5}{\text{Abs. S}}$$

**Estimation of salivary pH**

The saliva pH was measured using pH indicator strips with a range of 3.5–6.0 and 6.5–9.0 against the standards assigned by the manufacturer before and 3 weeks after administration of bethanechol and placebo capsules.<sup>[16]</sup>

The results of the study were statistically analyzed.

**RESULTS**

**Age distribution**

The overall mean age in the study sample was found to be 47.74 years.

**Gender distribution**

In the study group, 63% of patients were males and 37% of patients were females, whereas in the control group, 60% of patients were males and 40% of were females.

The subjective symptoms due to oral dryness were evaluated with planned questionnaire designed by Eisbruch *et al.* and Meirovitz *et al.* [Tables 1 and 2].

**Whole resting and whole stimulated saliva volume in the study and control groups**

The difference in mean whole resting and WSS volume between the two groups was found to be statistically significant at 3 weeks ( $P < 0.001$ ) [Table 3 and Graphs 1 and 2].

**Salivary amylase level in the study and control groups**

The difference in mean salivary amylase level between the two groups was found to be statistically significant at 3 weeks ( $P < 0.001$ )<sup>[9]</sup> [Table 3].

**Sodium and potassium concentration in the study and control groups**

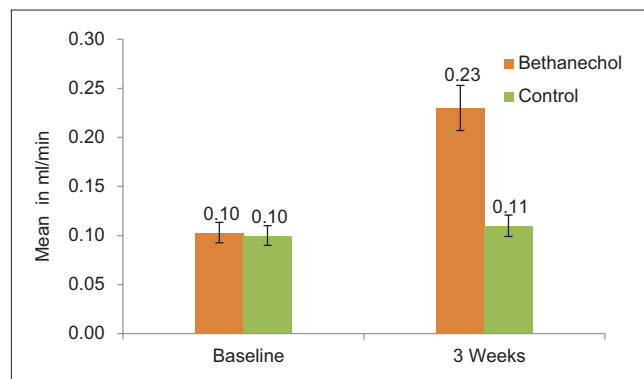
The difference in mean salivary sodium potassium ratio between the two groups was not found to be statistically significant at 3 weeks ( $P > 0.05$ ) [Table 3].

**Salivary pH in study and control groups**

The difference in mean salivary pH between the two groups was found to be statistically significant at 3 weeks ( $P < 0.001$ ) [Table 3].

**Side effects of bethanechol**

In the study group, three patients reported frequent urination as adverse effect (10%) and only one patient had



**Graph 1:** Mean whole resting saliva at baseline and after 3 weeks in bethanechol and control groups

**Table 1: Evaluation of symptoms of oral dryness in bethanechol group from baseline to 3 weeks assessed using self-reported questionnaire**

| Self-reported questionnaire | Time interval        | Difficulty in chewing (%) | Difficulty in swallowing solid foods (%) | Mouth or throat dryness while not eating (%) | Difficulty in talking (%) | Frequency of sleeping problems (%) | Frequency of sipping liquids for oral comfort and to aid swallowing (%) |
|-----------------------------|----------------------|---------------------------|--|--|---------------------------|------------------------------------|---|
| Number of patients          | 30                   | 30                        | 30                                       | 30   | 30                        | 30                                 | 30  |
| Status worsened             | Baseline             | -                         | -  | -  | -                         | -                                  | -   |
|                             | 1 <sup>st</sup> week | -                         | -  | -  | -                         | -                                  | -   |
|                             | 2 <sup>nd</sup> week | -                         | -  | -  | -                         | -                                  | -   |
|                             | 3 <sup>rd</sup> week | -                         | -  | -  | -                         | 1 (3.3)                            | -   |
| Status remained the same    | Baseline             | 30 (100)                  | 30 (100)                                 | 30 (100)                                     | 30 (100)                  | 30 (100)                           | 30 (100)  |
|                             | 1 <sup>st</sup> week | 11 (36.66)                | 11 (36.66)                               | 9 (30)                                       | 10 (33.33)                | 12 (40)                            | 10 (33.33)  |
|                             | 2 <sup>nd</sup> week | 9 (30)                    | 10 (33.33)                               | 8 (26.66)                                    | 8 (26.66)                 | 10 (33.3)                          | 9 (30)  |
|                             | 3 <sup>rd</sup> week | 8 (26.66)                 | 9 (30)                                   | 6 (20)                                       | 7 (23.33)                 | 8 (26.66)                          | 7 (23.33)   |
| Status improved             | Baseline             | -                         | -  | -  | -                         | -                                  | -   |
|                             | 1 <sup>st</sup> week | 19 (63.33)                | 19 (63.33)                               | 21 (70)                                      | 20 (66.66)                | 18 (60)                            | 20 (66.66)  |
|                             | 2 <sup>nd</sup> week | 21 (70)                   | 20 (66.66)                               | 22 (73.33)                                   | 22 (73.33)                | 20 (66.66)                         | 21 (70)   |
|                             | 3 <sup>rd</sup> week | 22 (73.33)                | 21 (70)                                  | 24 (80)                                      | 23 (76.66)                | 21 (70)                            | 23 (76.66)  |

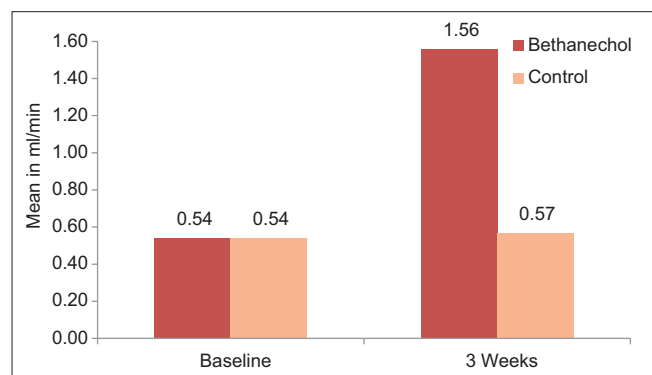
**Table 2: Evaluation of symptoms of oral dryness in control group from baseline to 3 weeks assessed using self-reported questionnaire**

| Self-reported questionnaire | Time interval        | Difficulty in chewing (%) | Difficulty in swallowing solid foods (%) | Mouth or throat dryness while not eating (%) | Difficulty in talking (%) | Frequency of sleeping problems (%) | Frequency of sipping liquids to aid swallowing and for oral comfort (%) |
|-----------------------------|----------------------|---------------------------|--|--|---------------------------|------------------------------------|---|
| Number of patients          | 20                   | 20                        | 20                                       | 20   | 20                        | 20                                 | 20  |
| Status worsened             | Baseline             | -                         | -  | -  | -                         | -                                  | -   |
|                             | 1 <sup>st</sup> week | -                         | -  | -  | -                         | -                                  | -   |
|                             | 2 <sup>nd</sup> week | -                         | -  | -  | -                         | -                                  | -   |
|                             | 3 <sup>rd</sup> week | -                         | -  | -  | -                         | -                                  | -   |
| Status remained the same    | Baseline             | 20 (100)                  | 20 (100)                                 | 20 (100)                                     | 20 (100)                  | 20 (100)                           | 20 (100)  |
|                             | 1 <sup>st</sup> week | 20 (100)                  | 20 (100)                                 | 20 (100)                                     | 20 (100)                  | 20 (100)                           | 20 (100)  |
|                             | 2 <sup>nd</sup> week | 20 (100)                  | 20 (100)                                 | 19 (95.0)                                    | 20 (100)                  | 20 (100)                           | 19 (95)   |
|                             | 3 <sup>rd</sup> week | 20 (100)                  | 20 (100)                                 | 18 (90)                                      | 20 (100)                  | 20 (100)                           | 19 (95.0)   |
| Status improved             | Baseline             | -                         | -  | -  | -                         | -                                  | -   |
|                             | 1 <sup>st</sup> week | -                         | -  | -  | -                         | -                                  | -   |
|                             | 2 <sup>nd</sup> week | -                         | -  | 1 (5)  | -                         | -                                  | 1 (5)   |
|                             | 3 <sup>rd</sup> week | -                         | -  | 2 (10)                                       | -                         | -                                  | 1 (5)   |

**Table 3: Salivary analysis at baseline and after 3 weeks in bethanechol and control groups**

| Salivary analysis                       | Mean±SD                    |                                   |                        |                               | P       |
|---|----------------------------|-----------------------------------|------------------------|-------------------------------|---------|
|   | Study group                |                                   | Control group          |                               |         |
|   | Before bethanechol therapy | 3 weeks after bethanechol therapy | Before placebo therapy | 3 weeks after placebo therapy |         |
| Whole resting saliva volume (ml/min)    | 0.10±0.01                  | 0.23±0.03                         | 0.10±0.02              | 0.11±0.02                     | <0.001* |
| Whole stimulated saliva volume (ml/min) | 0.54±0.06                  | 1.56±0.25                         | 0.54±0.05              | 0.54±0.05                     | <0.001* |
| Salivary amylase (U/ml)                 | 24.13±0.56                 | 24.77±0.39                        | 23.87±0.42             | 23.88±0.42                    | <0.001* |
| Salivary sodium (mEq/l)                 | 22.51±0.87                 | 22.24±0.86                        | 22.47±0.81             | 22.44±0.82                    | 0.408   |
| Salivary potassium (mEq/l)              | 28.75±0.77                 | 28.76±0.772                       | 28.45±0.66             | 28.43±0.726                   | 0.136   |
| Sodium potassium ratio                  | 0.78±0.03                  | 0.77±0.03                         | 0.79±0.03              | 0.79±0.03                     | 0.267   |
| Salivary pH                             | 5.5±0.16                   | 5.7±0.19                          | 5.5±0.19               | 5.5±0.21                      | <0.001* |

\*Statistically significant. SD: Standard deviation

**Graph 2: Mean whole stimulated saliva at baseline and after 3 weeks in bethanechol and control groups**

sweating (3.3%), with overall percentage of adverse reactions of about 13.3% in patients treated with bethanechol.

## DISCUSSION

Bethanechol, a centrally acting parasympathomimetic drug, is currently indicated for the treatment of postoperative and postpartum nonobstructive urinary retention and neurogenic atony of the urinary bladder with retention, which brings about wonderful results with less adverse reactions.<sup>[7,17]</sup>

Xerostomia associated with radiotherapy for head and neck cancer has its onset during the first 2 weeks, progresses and reaches maximum at the end of 6 weeks.<sup>[18,19]</sup> The salivary quantity drops from the usual normal values of WRS volume of 0.3–0.4 ml/min and WSS volume of 1–3 ml/min.<sup>[20]</sup> The composition of saliva also shows alterations such as decreased alpha amylase,<sup>[21,22]</sup> increased sodium potassium ratio,<sup>[23]</sup> and decreased salivary pH,<sup>[21,22]</sup> against normal values (normal levels of salivary amylase =  $27 \pm 3.8$ – $1440 \pm 160$  U/ml,<sup>[12]</sup> sodium potassium ratio = 0.5,<sup>[24]</sup> and pH = 6–7).<sup>[24]</sup> There are several ways to clinically assess the signs and symptoms of xerostomia, but the most accepted is self-reported questionnaire designed by Eisbruch *et al.* and Meirovitz *et al.*<sup>[10,11]</sup> Hence, we have used the same in our study.

The statistically significant increase in WRS and WSS volume in the study group could be explained based on the fact that, after oral administration of bethanechol, it is rapidly absorbed from gastrointestinal tract and pharmacologic effects appear in 30 min, reaching maximum effectiveness in 60–90 min and it stimulates functional residual salivary tissues outside the radiation field, chiefly minor glands rather than those glands that were included in the radiation portals, with a duration of action of 6–8 h.<sup>[8]</sup>

The results of our study are similar to results of studies by Epstein *et al.*,<sup>[7]</sup> Gorsky *et al.*,<sup>[8]</sup> Jham *et al.*<sup>[17]</sup> and Chainani-Wu *et al.*<sup>[25]</sup> who also reported significant increases in whole resting and WSS volumes.

The time taken for acinar regeneration after radiotherapy of oral cancer is found to be 6–12 months and hence there was no significant improvement in WRS and WSS after 3 weeks in the control group.<sup>[18]</sup>

Salivary amylase is an enzyme synthesized primarily in the acinar cells and less consistently in the proximal cells of the intercalated ducts and is a good indicator of the function of salivary glands.<sup>[26]</sup>

The significant increase in the level of amylase is reported and substantiated by Turner and Sugiyama<sup>[27]</sup> by the fact that bethanechol acts on residual acinar cells, causing stimulation of muscarinic receptors, which activates phosphatidylinositide metabolism and induces an increase in intracellular Ca<sup>2+</sup> concentration resulting in Ca<sup>2+</sup>-dependent amylase secretion.

In our study, increased sodium potassium ratio was observed after radiotherapy (0.78) similar to studies by Ben-Aryeh *et al.*<sup>[28]</sup> and could be due to effect of ionizing radiation on the reabsorption ability of the tubuli. The level of sodium ions in resting saliva did not show significant alteration after bethanechol therapy. The sodium and potassium levels in the saliva depend on the reabsorption ability of the tubuli and tubular secretion, respectively,<sup>[24,29]</sup> and are proportionate to the flow rate.<sup>[29]</sup> Since bethanechol acts on muscarinic cholinergic receptors and increases salivary flow rate, there may be time lapse in reabsorption of sodium from intercalated duct as explained by Case *et al.*<sup>[29]</sup>

There is an increase in pH values after bethanechol therapy (5.5–5.7) which is statistically significant ( $P < 0.001$ ) and may be explained based on increased flow rate and bicarbonate secretion.<sup>[30]</sup> However, there is no significant change in the control group.

In our study, side effects reported in the bethanechol group were insignificant and only three patients had urinary emergency (10%) and one patient had sweating (3.3%); however, no patient discontinued the drug during 3 weeks of therapy.

## CONCLUSIONS

This is a preliminary study for evaluating the efficacy of bethanechol in the management of xerostomia in patients treated for oral cancer. The following observations were noted in the study.

1. There was a significant improvement in subjective symptoms of xerostomia in 80% of patients treated with bethanechol
2. There was a significant increase in the whole resting and stimulated saliva volumes, salivary amylase level and salivary pH in the bethanechol group compared to control group. However, there was no significant change in sodium potassium ratio in patients treated with bethanechol and control groups
3. There was an insignificant adverse effect in the bethanechol group.

Thus, 25 mg bethanechol (TDS) administration in patients undergoing chemo-radiation therapy for oral cancer has shown significant improvement in salivary secretion [Figures 2 and 3]. The results of our study encourage for further studies on large sample size with a follow-up of more than 3 weeks.



**Figure 2:** Appearance of oral mucosa in postirradiated xerostomia patient before bethanechol therapy



**Figure 3:** Intraoral photograph showing moist mucosa after bethanechol therapy

## Acknowledgment

We would like to express our heartfelt thanks and acknowledge staffs of Department of Radiotherapy and Biochemistry, Bangalore Medical College and Research Institute, and Victoria Hospital, Bangalore, Karnataka, for extending their help during the conduction of the study.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Silverman S Jr. Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. *J Am Dent Assoc* 2001;132 Suppl:7S-11S.
- Solomon MC, Carnelio S, Gudattu V. Molecular analysis of oral squamous cell carcinoma: A tissue microarray study. *Indian J Cancer* 2010;47:166-72.
- Hancock PJ, Epstein JB, Sadler GR. Oral and dental management related to radiation therapy for head and neck cancer. *J Can Dent Assoc* 2003;69:585-90.
- Jham BC, da Silva Freire AR. Oral complications of radiotherapy in the head and neck. *Braz J Otorhinolaryngol* 2006;72:704-8.
- Hey J, Setz J, Gerlach R, Vordermark D, Gernhardt CR, Kuhnt T, *et al.* Effect of cisplatin on parotid gland function in concomitant radiochemotherapy. *Int J Radiat Oncol Biol Phys* 2009;75:1475-80.
- Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, *et al.* Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 1993;329:390-5.
- Epstein JB, Burchell JL, Emerton S, Le ND, Silverman S Jr. A clinical trial of bethanechol in patients with xerostomia after radiation therapy. A pilot study. *Oral Surg Oral Med Oral Pathol* 1994;77:610-4.
- Gorsky M, Epstein JB, Parry J, Epstein MS, Le ND, Silverman S Jr, *et al.* The efficacy of Pilocarpine and Bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;97:190-5.
- Navazesh M, Kumar SK, University of Southern California School of Dentistry. Measuring salivary flow: Challenges and opportunities. *J Am Dent Assoc* 2008;139 Suppl:35S-40S.
- Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan C, Eisbruch A. Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2006;66:445-53.
- Eisbruch A, Rhodus N, Rosenthal D, Murphy B, Rasch C, Sonis S, *et al.* How should we measure and report radiotherapy-induced xerostomia? *Semin Radiat Oncol* 2003;13:226-34.
- Ashok L, Sujatha GP, Hema G. Estimation of salivary amylase and total proteins in leukemia patients and its correlation with clinical feature and radiographic finding. *Indian J Dent Res* 2010;21:486-90.
- Kruse-Jarres JD, Kaiser C, Hafkenscheid JC, Hohenwallner W, Stein W, Bohner J, *et al.* Evaluation of a new alpha-amylase assay using 4,6-ethylidene-(G7)-1-4-nitrophenyl-(G1)-alpha-D-maltoheptaoside as substrate. *J Clin Chem Clin Biochem* 1989;27:103-13.
- Sharma A, Hirulkar NB, Ranka P. Effect of hyperglycemias on electrolytes Imbalance. *Int J Pharm Biol Arch* 2011;2:526-33.
- Gupta V, Chandrasekar T, Ramani P, Anuja. Determining toothache severity in pediatric patients: A study. *J Indian Soc Pedod Prev Dent* 2006;24:140-3.
- Kharevich O, Shipman B, Goldman BM, Nahon M. Saliva to buffer saliva in elderly patients with xerostomia: A pilot study. *J Prosthodont* 2011;20:135-8.
- Jham BC, Teixeira IV, Aboud CG, Carvalho AL, Coelho Mde M, Freire AR, *et al.* A randomized phase III prospective trial of bethanechol to prevent radiotherapy-induced salivary gland damage in patients with head and neck cancer. *Oral Oncol* 2007;43:137-42.
- White SC, Pharaoh MJ. *Oral Radiology: Principles and Interpretation*. 6<sup>th</sup> ed. New Delhi: Reed Elsevier India Private Limited; 2011. p. 18-23.
- Berk LB, Shivnani AT, Small W Jr. Pathophysiology and management of radiation-induced xerostomia. *J Support Oncol* 2005;3:191-200.
- Dawes C. Salivary flow patterns and the health of hard and soft oral tissues. *J Am Dent Assoc* 2008;139 Suppl:18S-24S.
- Dreizen S, Brown LR, Handler S, Levy BM. Radiation-induced xerostomia in cancer patients. Effect on salivary and serum electrolytes. *Cancer* 1976;38:273-8.
- de Barros Pontes C, Polizello AC, Spadaro AC. Clinical and biochemical evaluation of the saliva of patients with xerostomia induced by radiotherapy. *Braz Oral Res* 2004;18:69-74.
- Anderson MW, Izutsu KT, Rice JC. Parotid gland pathophysiology after mixed gamma and neutron irradiation of cancer patients. *Oral Surg Oral Med Oral Pathol* 1981;52:495-500.
- Guyton AC, Hall JE. *Textbook of Medical Physiology*. 11<sup>th</sup> ed. Philadelphia: Elsevier Inc; 2006. p. 793-5.
- Chainani-Wu N, Gorsky M, Mayer P, Bostrom A, Epstein JB, Silverman S Jr, *et al.* Assessment of the use of sialogogues in the clinical management of patients with xerostomia. *Spec Care Dentist* 2006;26:164-70.
- Chitra S, Shyamala Devi CS. Effects of radiation and alpha-tocopherol on saliva flow rate, amylase activity, total protein and electrolyte levels in oral cavity cancer. *Indian J Dent Res* 2008;19:213-8.
- Turner RJ, Sugiya H. Understanding salivary fluid and protein secretion. *Oral Dis* 2002;8:3-11.
- Ben-Aryeh H, Gutman D, Szargel R, Laufer D. Effects of irradiation on saliva in cancer patients. *Int J Oral Surg* 1975;4:205-10.
- Case RM, Howorth AJ, Padfield PJ. Effects of acetylcholine, isoprenaline and forskolin on electrolyte and protein composition of rabbit mandibular saliva. *J Physiol* 1988;406:411-30.
- Martin CJ, Young JA. A microperfusion investigation of the effects of a sympathomimetic and a parasympathomimetic drug on water and electrolyte fluxes in the main duct of the rat submaxillary gland. *Pflugers Arch* 1971;327:303-23.