Original article

# EFFECT OF CEVIMELINE AND PILOCARPINE ON PRODUCTION OF SALIVA: A CROSSOVER STUDY

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**Abstract**

**Objective:**

To compare the safety and efficacy of pilocarpine and cevimeline in the secretion of saliva in patients with dry mouth.

Methods: This is a randomized, crossover, double-blind trial. Half patients were administered pilocarpine 30mg, and the other half were administered cevimeline 5mg, three times a day in both cases, for a period of four weeks. After four weeks, one week washout period was provided, and then treatment was reversed in two groups for another four weeks. Patients were reevaluated at 4 and 9 weeks respectively.

**Results:**

22 patients were divided into two groups of 11 patients each, and administered the medication. Although both medications proved to increase salivary secretion, there was no statistically significant difference observed between pilocarpine and cevimeline regarding their efficacy as well as side effects.

**Conclusion:**

No significant difference was observed between pilocarpine and cevimeline in salivary production or side effects. However, further studies with sufficient sample size are recommended to find out more effective and safe drug in xerostomia patients.

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## Introduction

Saliva is essential for many reasons. It mixes with food to make it palatable and easily digestible. It contains enzyme salivary amylase. It maintains healthy oral cavity. Decrease production of saliva (hyposalivation) is associated with oral discomfort; difficulties in mastication, swallowing, tasting and speaking; and an increased risk of oral candidiasis and dental caries[1]. Lack of saliva is associated with number of oral conditions which include gingivitis, severe dental caries, etc. [2]

Xerostomia is a subjective feeling of dry mouth. It is an unpleasant symptom and affects many people. This symptom is commonly found in elderly population, mostly due to side effects of commonly prescribed drugs in this age group[2,3]. Moreover, xerostomia is also common symptom in number of medical conditions, like Sjogren's syndrome or following therapeutic radiations given for head and neck cancers[4]. Therapeutic approaches in relieving this unpleasant symptom include topical sialagogues like artificial saliva, gums, topical moisturizers; and pharmacotherapy.

Pilocarpine and cevimelin are commonly prescribed medication in xerostomia. They both increase the salivary secretion. Safety and efficacy of pilocarpine have been proved by clinical studies[5]. However, limited number of clinical studies are available to support efficacy and side effect profile of cevimeline, that too with no conclusive results[1,6,7].

Pilocarpine is a cholinergic alkaloid obtained from the leaflets of South American shrubs of genus Pilocarpus. It has dominant muscarinic action (M1 and M3 receptors) and almost no nicotinic action. It causes

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Pilocarpine; Cevimeline; Xerostomia; Saliva

anomalous cardiovascular responses, and the sweat glands are particularly sensitive to the drug[8]. Cevimeline is a quinuclidine analogue of acetylcholine with a high affinity for M3 muscarinic receptors of both lacrimal and salivary glands[6].

The aim of our study was to see the efficacy of cevimeline and pilocarpine in stimulating the salivary flow in patients with xerostomia, and to compare the side effects between two drug treatments.

**Methods**

This double blind crossover randomized trial. Patients with moderate to severe xerostomia, with no clinical evidence of oral lesions, subjective perception of dry mouth, and a non-stimulated flow of less than 2ml of saliva in 5 minutes were identified and included in the study. Exclusion criteria include patients with non-controlled chronic obstructive pulmonary disease, depression, asthma, cardiac arrhythmias, glaucoma, neurological, gastrointestinal, hematological diseases and recent use of any medication which can have interactions with cevimeline and pilocarpine. Also patients were excluded if they were possibly sensitive to the medication of study or had used alcohol or cigarettes for a long period of time. Patients were instructed to report any adverse events due to medication during the study period.

Patient fulfilling the inclusion criteria were randomly assigned to a specific treatment protocol, after obtaining a proper informed written consent from each patient. Treatment pockets were provided through a pharmacist, independent of study investigators. After proper randomization, half of the patients (Group I) were administered capsule cevimeline 30mg three times a day for four weeks. After one weak washout period, these patients then received pilocarpine 5mg capsule, three times a day for another four weeks. Other half of the subjects (Group II) received pilocarpine first followed by cevimeline in similar way, followed by washout period of one weak and subsequent reversal of treatment. Neither the patient nor the investigator knew the identity of pills, because both were of same size and color.

Patients were evaluated three times during the study period, i.e. at the beginning (baseline), after four weeks (end of first medication session) and after another five weeks (end of the second medication session after one week washout period. Patients were instructed, not to eat or drink 60 minutes prior to saliva collection.

Two saliva samples were taken at each visit. The first saliva sample was obtained by asking the patient to spit as much as he or she could into a Dixie cup for five minutes. After five minutes, the cup was collected and saliva measured using a 1ml pipette. This provided an unstimulated flow rate. Second sample was taken after having the patient chew a block (1cm x 1cm) of unflavored wax, and saliva taken and measured in similar fashion as previous one. This provided stimulated flow rate.

Simultaneously, at each follow up, side effects due to medications were assessed through weekly questionnaire which patient had to complete and bring along at each visit. This was to determine whether there were any marked differences in experienced side effects between two medications. Statistical-analysis of the primary end points was carried out with ANOVA, and post hoc t-test. Side effects were compared using weekly questionnaire, and responses were 0-5 Likert scale.

**Results**

31 patients were screened, out of which, 22patients fulfilled the inclusion criteria and were included in the study. After properly evaluating the patients and taking their baseline investigations, and after collecting their baseline stimulated and unstimulated salivary flow, patients were randomized to treatment. Out of 22 patients, 11 were randomized into pilocarpine-cevimeline (pc) sequence, and another 11 were administered after proper randomization into cevimeline-pilocarpine (cp) sequence. Patients of both sequence groups were well matched by age, sex, race at baseline. All patients completed the study and none left in between.

Most of the cases of dry mouth were due to medication (15/22; 68%). Others were due to Sjogren's syndrome (2/22; 9.09%), radiation therapy (3/22; 13.63%), and unknown etiology (2/22; 9.09%). No significant difference was observed in baseline characteristics between two groups. Each group was given a washout period of one week to make it sure that there is no carryover effect of the drug in either group.

**Unstimulated salivary flow rate:**

There was an increased production of saliva per five minutes for both pilocarpine-cevimeline (3.84ml/5mts.) as well as cevimeline-pilocarpine (1.9ml/5min.) sequence groups at the end of 4 weeks. Difference between the two groups was not statistically significant (p=0.162) Table 1. Almost similar increased production of saliva was observed at the end of 9 weeks (3.96ml/5min). In pilocarpine-cevimeline sequence group, and, 1.52 ml/5 min. In cevimeline-pilocarpine sequence group). Again difference between two groups was not statistically

significant (p=0.113) Table 1.

**Table 1. Unstimulated salivary flow rate (ml/5min.)**

| | Pilocarpine-cevimeline (pc) | Cevimeline-pilocarpine (cp) | P-value |
|---|---|---|---|
| **Baseline** | 1.81 | 0.92 | |
| **4 week** | 3.84 | 1.95 | 0.162 |
| **9 weeks** | 3.96 | 1.52 | 0.113 |

**Stimulated salivary flow rate:**

Again there was an increased production of saliva per five minutes in pilocarpine-cevimeline sequence (9.02ml/5min) and cevimeline-pilocarpine sequence (7.2ml/5min) groups at the end of 4 weeks, and the difference between the two groups was again not statistically significant (p=0.306) Table 2. At the end of 9 weeks, production of stimulated saliva increased to 10.4ml/5min (pilocarpine-cevimeline sequence group) and 5.46ml/5min (cevimeline-pilocarpine sequence group) from baseline. Difference between two sequence groups was again not statistically significant (p=0.122) Table 2.

**Table 2. stimulated salivary flow rate:**

| | Pilocarpine-cevimelin (pc) sequence | Cevimeline-pilocarpine (cp) sequence | P-value |
|---|---|---|---|
| **Baseline** | 1.81 | 0.92 | |
| **4 weeks** | 9.02 | 7.2 | 0.306 |
| **9 weeks** | 10.4 | 5.46 | 0.122 |

**Side effects:**

Side effects were observed by both the groups. These were headache, nausea, gastric upset, diarrhea, pain around eyes and sweating. Comparing the two groups, no statistically significant difference in scoring of Likert scale on questions framed regarding side effects, was observed between two groups Table 3.

**Table 3. Comparison of side effects between pilocarpine-cevimeline sequence and cevimelin-pilocarpine sequence groups.**

| | Pilocarpine-cevimeline (pc) sequence group | Cevimeline-pilocarpine (cp) sequence group | Mean difference | P-value |
|---|---|---|---|---|
| **Did you felt improvement in dry mouth this week, and have more saliva** | 2.64 | 1.82 | 0.82 | 0.36 |
| **Did you felt worse this week** | 0.66 | 0.98 | -0.32 | 0.10 |
| **Did you noticed increase in sweating this week** | 1.53 | 1.02 | 0.51 | 0.25 |
| **Did you felt more tear in eyes this week** | 0.18 | 0.67 | -0.49 | 0.35 |
| **Did you had more frequent and severe headache this week** | 0.8 | 0.5 | 0.3 | 0.18 |
| **More nausea this week** | 1.15 | 0.68 | 0.47 | 0.32 |
| **Any pain felt around eyes this week** | 0.39 | 0.68 | -0.29 | 1.12 |
| **Unusual GIT upset this week** | 0.71 | 1.20 | -0.49 | 0.2 |
| **Diarrhea this week** | 0.36 | 0.63 | -0.27 | 0.11 |

**Discussion**

Pilocarpine and cevimeline are two US-FDA approved medications for xerostomia due to any cause[6]. Both drugs increase the salivary secretion, thus improving the symptoms in patients of dry mouth[1,6,9]. In the present study, both pilocarpine as well as cevimeline significantly increase the salivary flow rate, both unstimulated and stimulated compared to baseline, at 4 weeks. ($p< 0.034$—unstimulated pilocarpine-cevimeline sequence; $p< 0.023$—unstimulated cevimeline-pilocarpine sequence; $p< 0.04$—stimulated pilocarpine-cevimeline sequence; and $p<0.052$—stimulated cevimeline-pilocarpine sequence groups). Comparing the two sequence groups, there was no statistically significant difference in salivary flow rate (both unstimulated as well as stimulated) at 4 weeks.

After a one week washout period, and reversing the treatment sequences, there was again a significant increase in both stimulated as well as unstimulated salivary flow rates in both groups compared to baseline, but no statistically significant difference was observed between two sequence groups. Results were similar to the a study[9], in which 12 patients were administered two medications in similar design which we followed in our study, and which also showed increase salivary flow rate and decrease in symptoms associated with xerostomia, and no statistically significant differences were found between two sequence arms.

Chainani-Wu et.al. 2006[1] in an open label crossover study on 20 patients of dry mouth compared three medications, pilocarpine, cevimeline and bethanechol. This study showed a significantly increased salivary flow rates with bethanechol compared to pilocarpine. There were many dropouts in their study, and out of 20 patients, only six took cevimeline and pilocarpine[9]. This may be the reason of more effectiveness of bethanechol. In our study, all the patients' completed the study, took the medication and there was no statistically significant difference in rate of salivary flow in both medication groups.

Another study[6] compared the efficacy of pilocarpine and cevimeline on large size sample (40 male volunteers). This study concluded cemiveline to be more effective than pilocarpine. This may be because only immediate response to **drugs were included here, because the study des**ign was different i.e. patients salivary flow rate was measured at 20,40, 60, 80,140 and 200 minutes after drug administration which were compared with the baseline. No long term effects of drugs were observed in this study.

Comparing the side effects, Chainani-Wu et.al. 2006[1] found that most common side effects like sweating were experienced more with pilocarpine. A double-blind, randomized trial[10] while evaluating the safety and efficacy of two dosages of cevimeline for treatment of xerostomia in Sjogren's syndrome concluded that 30mg of cevimeline three time a day resulted in substantial improvement in increasing salivary flow rate and most common side effects were sweating, abdominal pain and nausea. In the present study, cevimeline (30mg three times a day) was compared with pilocarpine (5mg three times a day) for salivary production as well as side effects. No difference was observed between two drugs as for as frequency and severity of side effects are concerned.

Among the limitations to present study was small sample size. Further studies, with large sample size, and placebo controlled are recommended to know real status of drug efficacy and safety in xerostomia patients.

**Conclusion**

Cevimeline and pilocarpine were compared for their safety and efficacy in xerostomia patients. No statistically significant difference was observed in rate of saliva production or side effects observed. However, further studies with sufficient sample size are recommended in future to evaluate the best and safe drug in patients with dry mouth.

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