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Review Article

Efficacy of Cevimeline in the treatment of Xerostomia: A systematic review

[1]Srivarshaa S N, [2]Bharathwaj V V, [3]Dinesh Dhamodhar, [4]Sathiyapriya S, [5]Prabu D, [6]Rajmohan M, [7]Sindhu R

[1]IVth year (Bachelor of Dental Surgery), [2,4,7]Senior Lecturer, [3,6]Reader, [5]Professor and Head of Department, SRM Dental College, Ramapuram, Chennai, Tamil Nadu, India

ABSTRACT:

Background: To assess the efficacy of cevimeline in the treatment of xerostomia. **Methodology:** A literature review was performed using PubMed, Wiley online library, Cochrane, and science direct using MeSH term "xerostomia and cevimeline". According to the Prisma Guidelines, the MeSH terms were altered in each search engine. **Result:** 4 out of 5 articles showed positive effects of cevimeline in the treatment of xerostomia. **Conclusion:** In the available literature, the use of cevimeline in the treatment of xerostomia is effective.

Keywords: cevimeline, xerostomia

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Corresponding author: Prabu D, Professor and Head of Department, SRM Dental College, Ramapuram, Tamil Nadu, India

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INTRODUCTION

Xerostomia is a condition in which a patient's mouth is unusually dry due to the salivary gland, which can't produce enough saliva to keep the mouth wet. This may be caused as a side effect of certain medications, ageing issues, due to radiation therapy for cancer, or due to autoimmune diseases. This condition is also known as"Dry mouth". Post-radiation xerostomia is severe and is generally irreversible; it occurs rapidly and progresses fast also. (1) It is the commonest complaint from patients undergoing radiotherapy for the oral cavity and neck region. The hallmark of radiation-induced damage is chronic inflammation and acinar atrophy of the salivary gland. (2)

Sjogren's syndrome is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands leading to dysfunction, causing diminished activity of salivary glands causing xerostomia. (3)

The pathogenesis of Sjogren's syndrome involves systemic B cells hyperactivity and T-cell lymphocytes targeting glandular epithelial cells. (4)

This may lead to difficulty in eating, swallowing, oral discomfort, tooth decay, and frequent oral infections, thereby debilitating the patient's quality of life. (5)

Along with this fatigue, parotid swelling and extra glandular manifestation are also seen. (6)

In healthy people, salivary secretions are thin and with a neutral pH. However, when affected by the radiation, it becomes more viscous with increased acidity (7), which causes the adverse effects mentioned above.

In patients with no residual salivary function moistening agents and salivary substitutes are given. In patients with residual salivary function, medications are given to increase the salivary level and improve the symptoms of xerostomia. (2)

The cholinergic drug acts upon the neurotransmitter acetylcholine, the primary neurotransmitter in the parasympathetic nervous system. These are broadly classified into two, namely: direct-acting and indirect-acting.

Direct acting directly binds and activates the muscarinic receptor. The direct acting is classified again into choline esters – e.g., acetylcholine, methacholine, carbachol, bethanechol and alkaloids – e.g., muscarine, pilocarpine, cevimeline(8)

Cevimeline is a direct-acting alkaloid type of cholinergic drug.

Cevimeline is a quinuclidine derivative of acetylcholine that binds to muscarinic acetylcholine receptors (9) with a preference for activation of the M3 receptor, which is primarily responsible for fluid

flow from the salivary gland. (5) cevimeline increases the flow rate of saliva as well as the rate at which some digestive and/or infection-fighting defence components are secreted. (10)

OBJECTIVE

To assess the effectiveness of cevimeline in the treatment of xerostomia.

MATERIALS AND METHODS

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

a) Original text
b) Full-text articles
c) Studies with randomized control trials

EXCLUSION CRITERIA

a) Articles without full text
b) Animal studies
c) Studies without cevimeline-based measures for facilitating the treatment of xerostomia were excluded.

SEARCH STRATEGY

Published results on the efficacy of cevimeline in the treatment of xerostomia which includes original articles and research papers in databases such as PubMed, Science Direct, Wiley Online Library, and Cochrane were taken into the study for review. MeSH phrases were used in a literature search to gather pertinent data. cevimeline and xerostomia". When the number of results became too high or too low, each search engine's MeSH words were changed in accordance with the Prisma standards.

RESULTS

The search yielded 203 articles and five eligible articles were evaluated independently.

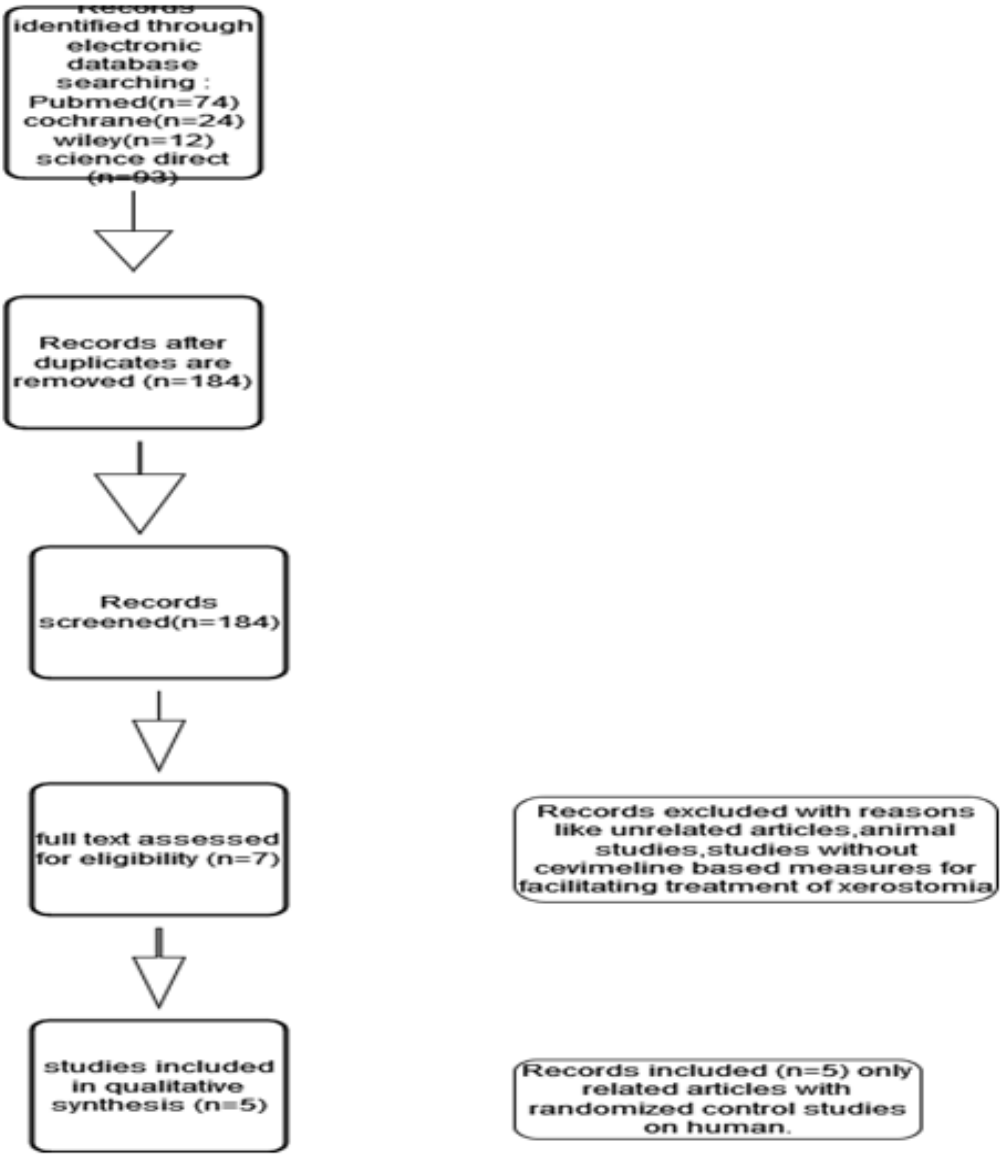

Figure 1 shows the flow chart of the reports identified, screened, evaluated for eligibility, excluded, and included in the study. Three tables were included.

Table 1: Characteristics of interventions in the study

Author Name	Year	Sample Size	Duration	Intervention
MARK S. CHAMBERS et al.[1]	2007	255	52 weeks	Test group: cevimeline Control group: placebo
Rose S. Fife et al. [3]	2002	75	6 weeks	Test group: cevimeline Control group: placebo
K. C. M. Leung et al. [5]	2007	50	24 weeks	Test group: cevimeline Control group: placebo
David L. Witsellet al. [7]	2011	54	6 weeks	Test group: cevimeline Control group: placebo
Dianne Petroneet al. [9]	2002	197	12 weeks	Test group: cevimeline Control group: placebo

The features of the studies that are picked for the systematic review are displayed in Table 1. The following traits were investigated: The author's name, the year the study was conducted, the sample size and demographic data like gender and study interventions were all provided. The papers that were included were all exclusively oral cavity-based randomised controlled trials. Cevimeline has been used as the test group for assessing the treatment of xerostomia compared with others (control group – placebo.)

Table 2: Characteristics of outcome and effect measures

Author Name	Year	Effect Measures	Results
MARK S. CHAMBERS et al. [1]	2007	A global evaluation questionnaire, a xerosis questionnaire using a 100mm visual analogue scale, and measurement of unstimulated and stimulated salivary flow.	Both trials found no significant changes in stimulated salivary flow, while cevimeline treated participants saw a considerably higher increase in the objective measure of unstimulated flow than placebo recipients.
Rose S. Fife et al. [3]	2002	A global evaluation questionnaire (better, no change, worse), visual analogue scale (feeling of mouth, dryness of mouth, dryness of tongue, ability to speak without drinking liquids and ability to chew and swallow food.), salivary flow.	Treatment with cevimeline, 30 mg three times a the day seems to be well tolerated and to provide substantive relief of xerostomia symptoms.
K. C. M. Leung et al. [5]	2007	Xerostomia Inventory (XI), the General Oral Health Assessment Index (GOHAI), the Ocular Surface Disease Index (OSDI) and the Medical Outcomes Short Form (SF-36) questionnaire, sialometry, examination of the oral cavity for the degree of xerostomia.	After taking cevimeline, the XI and GOHAI score significantly improved, as did the objective grading of the oral cavity's xerostomia symptoms.
David L. Witsellet al. [7]	2011	OHIP-49 AND UW-QOL	During the six weeks of the study, the severity of xerostomia decreased from baseline.
Dianne Petrone et al. [9]	2002	Self-evaluation test, visual analogue scale, Schirmer's test.	Patients taking 30 mg of cevimeline three times daily had statistically significant improvements in their subjective global assessment of dry eyes (P 0.0453), dry mouth (P 0.0004), and increased salivary flow (P 0.007). Patients receiving the 30mg dosage also showed greater objective improvement (increased salivary and lacrimal flow rates, as measured by Schirmer's test) than did patients receiving placebo.

Table 2 shows the effect measures, I.e., the tests taken to analyze the efficacy of cevimeline in the treatment of xerostomia and its effect on the mouth.

Table 3: Characteristics of bias in different studies taken for review

Author Name	Random sequence	Allocation Concealment	Blinding Of Outcome	Incomplete Outcome	Selective Bias
MARK S. CHAMBERS et al.[1]	+	+	+	+	+
Rose S. Fife et al.[3]	+	+	+	+	+
K. C. M. Leung et al.[5]	+	+	+	+	?
David L. Witsell et al. [7]	?	+	+	+	+
Dianne Petrone et al. [9]	+	-	+	+	+

+: low risk of Bias;-: High risk of Bias;?: unclear risk of Bias

Table 3 shows the bias analysis of the included studies, categorised as high risk, low risk and unclear risk of Bias.

DISCUSSION

In this systematic review, five studies have been considered to assess cevimeline's efficacy in the treatment of xerostomia. Global evaluation questionnaire, visual analogue scale, XI, GOHAI, OSDI, SF-36, OHIP-49, UW-QOL, and Schirmer's test were used in various studies for assessing the effectiveness of cevimeline in the treatment of dry mouth.

Mark S. Chamber et al. (2007) conducted a randomised controlled trial with 255 subjects with xerostomia secondary to radiation. The subjects who received more than 40Gy of external beam radiotherapy as a treatment for at least four months before the study were included. The subjects received cevimeline at a dosage of 45mg t.i.d for 52 weeks. Test grp and control grp. Using a global evaluation questionnaire, xerosis questionnaire using a visual analogue scale and measurement of stimulated and unstimulated salivary flow, the mean change from baseline of the numeric global evaluation score significantly improved at each study visit. (1)

Rose S.Fife et al (2002) conducted a randomised controlled trial with 75 subjects who had xerostomia in patients with Sjogren's syndrome who received 30mg of cevimeline three times daily, 60mg of cevimeline three times daily or placebo for six weeks. 23,25,27 patients were randomised to receive placebo; cevimeline hydrochloride-30mg tid and 60mg tid, respectively. Sixty-one patients completed the study. Fourteen patients withdrew from the study because of adverse events, the most frequent being nausea. Subjective responses were determined using global patient evaluation and visual analogue scales. The salivary flow was measured objectively. Therapy with cevimeline, 30mg 3 times daily, seems well tolerated and provides substantive relief of xerostomia symptoms. 60 mg three times daily was associated with an increased intestinal tract disorder. (3)

KCM Leung et al. (2007) conducted a randomised, double-blind, placebo-controlled crossover. Fifty subjects (southern Chinese patients with Sjogren's syndrome (primary or secondary) who were split into two groups, each twenty-five received Cevimeline hydrochloride, 30 mg and placebo capsules three times per day over ten weeks, respectively. A washout period of 4 weeks duration was used to avoid potential carryover effects from the previous treatment. The total course of the study was 24 weeks. Six [two from the control group: placebo and four from the test group: cevimeline) withdrew from the study during the trial due to time constraints and side effects like dizziness, palpitation and lack of perceived response. The effect measures: XI, GOHAI, and Objective measures showed significant improvement in the treatment of xerostomia, but in patients with lower SF-36 value, the usage of cevimeline did not show any improvement, use of cevimeline in the treatment of xerostomia did not increase the salivary flow. Excessive sweating, heat sensation, palpitations, and gastrointestinal disturbance were the few side effects reported by the patients. (5)

David L. Witsell et al. (2011) conducted a randomised, double-blind, placebo-controlled study. Fifty-four subjects with radiation-induced xerostomia were split into two groups, with 28 and 26 patients who received 30 mg of cevimeline TID and placebo TID, respectively, for six weeks. Out of which, 3 and 2 withdrew from each group due to adverse effects. At the end of the 6th week, 25 and 24 patients completed the trial. OHIP-49 and UW-QOL were used to assess the efficacy of cevimeline in the treatment of xerostomia. The possible related adverse effect was a headache. Few withdrew due to the recurrence of cancer also. Though the severity of xerostomia is reduced from the baseline in six weeks, it was concluded that the efficacy of cevimeline in alleviating the xerostomia symptoms and complaints remains unclear. (7)

Dianne Petrone et al. (2002) conducted a randomised, double-blind, placebo-controlled study. One hundred ninety-seven patients with xerostomia due to Sjogren's syndrome were included in the trial. Seventy patients were given placebo,65 patients were given 15mg of cevimeline three times daily, and 62 patients were given 30 mg of cevimeline three times daily for 12 weeks. Three were from the placebo, 19 (9 from 15mg

and ten from 30mg) from the test group due to adverse effects. Self-evaluation test, visual analogue scale, and Schirmer test were used to assess the efficacy of cevimeline in the treatment of xerostomia. Treatment with cevimeline with a dosage of 30 mg three times daily resulted in substantive improvement by increasing the rate of saliva in patients with Sjogren's syndrome. The 15-mg dosage relieved some symptoms, and both dosages were well tolerated. (9)
Out of 197,162 patients reported adverse effects: nausea, sinusitis, increased sweating, headache, diarrhoea, and pharyngitis.
Mark.S Chamber, Rose S Fife, K.C.M. Leung, David L. Witsell, and Dianne Petronestudies showed a low risk of Bias.

CONCLUSION

All the articles taken for this systematic review proved that cevimeline, a cholinergic agent with a preference for the M3 receptor, decreases the symptoms or severity of xerostomia in patients with Sjogren's syndrome or patients having xerostomia due to radiation. It must also be noted that according to the studies mentioned above, it generally reduces the severity and does not increase the salivary flow(except in one study).

REFERENCE

1. Chambers MS, Posner M, Jones CU, Biel MA, Hodge KM, Vitti R, Armstrong I, Yen C, Weber RS. Cevimeline for the treatment of postirradiationxerostomia in patients with headandneck cancer. Int J RadiatOncolBiol Phys. 2007 Jul 15;68(4):1102-9. doi:10.1016/j.ijrobp.2007.01.019. Epub 2007 Mar 26. PMID: 17379432.
2. Guchelaar HJ, Vermes A, Meerwaldt JH. Radiation-induced xerostomia: pathophysiology, clinical course and supportive treatment. Support Care Cancer. 1997 Jul;5(4):281-8. doi:10.1007/s005200050075. PMID: 9257424.
3. Fife RS, Chase WF, Dore RK, Wiesenhutter CW, Lockhart PB, Tindall E, Suen JY. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. Arch Intern Med. 2002 Jun 10;162(11):1293-300. doi: 10.1001/archinte.162.11.1293. PMID: 12038948.
4. Venables PJ. Management of patients presenting with Sjogren's syndrome. Best Pract ResClinRheumatol. 2006 Aug;20(4):791-807. doi: 10.1016/j.berh.2006.05.003. PMID:16979538.
5. Leung KC, McMillan AS, Wong MC, Leung WK, Mok MY, Lau CS. The efficacy of cevimeline hydrochloride in the treatment of xerostomia in Sjögren's syndrome in southern Chinese patients: a randomised double-blind, placebo-controlled crossover study. Clin Rheumatol. 2008 Apr;27(4):429-36. doi: 10.1007/s10067-007-0723-x. Epub 2007 Sep 26. PMID: 17899308.
6. Delli K, Spijkervet FK, Kroese FG, Bootsma H, Vissink A. Xerostomia. Monogr Oral Sci. 2014;24:109-25. doi: 10.1159/000358792. Epub 2014 May 23. PMID: 24862599.
7. Witsell DL, Stinnett S, Chambers MS. Effectiveness of cevimeline to improve oral health in patients with postradiationxerostomia. Head Neck. 2012 Aug;34(8):1136-42. doi: 10.1002/hed.21894. Epub 2012 Jan 9. PMID: 22231734.
8. Pakala RS, Brown KN, Preuss CV. Cholinergic Medications. 2022 Feb 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 30844190.
9. Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum. 2002 Mar;46(3):748-54. doi: 10.1002/art.510. PMID: 11920411.
10. Suzuki K, Matsumoto M, Nakashima M, Takada K, Nakanishi T, Okada M, Ohsuzu F. Effect of cevimeline on salivary components in patients with Sjögren syndrome. Pharmacology. 2005 May;74(2):100-5. doi: 10.1159/000084031. Epub 2005 Feb 18. PMID: 15722648.