Original Article

JOMP
Journal of Oral Medicine and Pain

pISSN 2288-9272 eISSN 2383-8493
J Oral Med Pain 2015;40(1):10-16
http://dx.doi.org/10.14476/jomp.2015.40.1.10

Comparison of the Effects of Pilocarpine Solution and Tablet on Salivary Flow Rate

Jo-Eun Park, Chan-Woo Song, Ki-Suk Kim, Mee-Eun Kim

Department of Oral Medicine, College of Dentistry, Dankook University, Cheonan, Korea

Received December 30, 2014
Revised January 13, 2015
Accepted January 20, 2015

Correspondence to:
Mee-Eun Kim
Department of Oral Medicine, College of Dentistry, Dankook University, 119, Dandae-ro, Dongnam-gu, Cheonan 330-714, Korea
Tel: +82-41-550-1913
Fax: +82-505-434-7951
E-mail: meunkim@dankook.ac.kr

Purpose: Pilocarpine has the effects on improvement of salivary flow and subjective symptoms for xerostomic patients. Because of unwanted side effects following its systemic administration, topical pilocarpine has been paid attention as an alternative. This study aimed to investigate effects of pilocarpine solution as mouthwash on salivary flow and adverse effects compared to systemic administration of 5 mg pilocarpine tablet in healthy subjects.

Methods: The study was a double blind, placebo-controlled, crossover clinical trial. Five milligrams pilocarpine tablets, 4 mL of 2% pilocarpine solution and placebo solution were given to 12 healthy volunteers (6 males and 6 females) in a predetermined order with wash-out period of at least two days and unstimulated whole saliva was collected before and after administration of each drug. Blood pressure and pulse rate was also measured and subjective effect and potential side effects were evaluated by a self-administrated questionnaire.

Results: Systemic (5 mg tablet) and topical (2% solution) use of pilocarpine significantly increased salivary flow rate in healthy subjects compared to placebo ($p<0.001$). In both the pilocarpine solution and tablet groups, salivary flow rates at 120 minutes after administration remained increased. Subjective effect on salivation was the largest in the pilocarpine tablet group, followed by the pilocarpine solution group ($p<0.05$). There was no significant difference in blood pressure and pulse rate after administration of all three drugs. Fewer side effects reported in the pilocarpine solution group than in the tablet group.

Conclusions: Two percents pilocarpine solution as mouthwash increases salivary flow rate, definitely superior to placebo solution and comparable to pilocarpine tablet, with fewer side effects in healthy subjects. It indicates a possibility of pilocarpine solution as a useful alternative of pilocarpine tablets for the xerostomic patients with systemic diseases.

Key Words: Administration, topical; Mouthwashes; Pilocarpine; Salivation

INTRODUCTION

Xerostomia is commonly due to alterations in salivary gland function either through a diminution of salivary flow or changes in the composition of saliva.[1] Long-standing xerostomia may cause a lot of complications such as dental caries, dysgeusia, burning sensation, oral mucosal soreness, difficulty in wearing dentures, periodontal disease and halitosis.[1]

As an ideal replacement to saliva does not exist yet,[2] salivary stimulants such as oral pilocarpine have mostly been used to relieve symptoms of oral dryness for patients with xerostomia. Pilocarpine is a non-specific muscarinic acetylcholine receptor agonist and primarily acts to increase salivary flow through the muscarinic 3 (M3) receptors.[3] As these are expressed on smooth muscle and glandular tissues, pilocarpine stimulates lacrimal, gastrointestinal and respiratory mucous cells.[3] For this reason, in addition to

increased salivary flow, it has a number of unwanted side effects due to its non-specific stimulation of muscarinic receptors[4] including nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, bladder tightness, frequent urination, headache, syncope, sweating, tremor, flushing, hypotension, hypertension, bradycardia and arrhythmia.[5] To minimize side effects following systemic administration of pilocarpine, topical pilocarpine may be considered as an alternative. Local administration of pilocarpine offers several benefits such as mechanical salivary stimulation, prolonged and increased topical contact, and potential decrease in systemic effects.[5-9]

A few studies have been performed on effectiveness of topical pilocarpine as mouthwash. In 1980, Mikhail[10] reported the topical use of pilocarpine for the first time and demonstrated that the 0.025%-1% pilocarpine mouthwash was effective for dry mouth relief. Kim et al.,[11] in their case study, reported improvement of subjective oral dryness with 0.02%-0.04% pilocarpine solution as mouthwash for xerostomic patients. Bernardi et al.[8] reported that mouth rinsing with 1% or 2% pilocarpine solutions for healthy subjects induced a significant objective and subjective dose-dependent increase in salivary flow and side effects did not differ between groups. To put these results together, though there are some studies indicating effects of topical applications of pilocarpine, the number of controlled study are small and objective effect has not been well established. Thus, this study aimed to investigate effects of 2% pilocarpine solution as mouthwash on salivary flow and adverse effects compared to systemic administration of 5 mg pilocarpine tablet in healthy subjects.

MATERIALS AND METHODS

This study was approved by the institutional review board at Dankook University Dental Hospital (IRB No. H-1207-007/002), Cheonan, Korea and all participants provided written informed consent before enrollment. The experiment was performed at the Department of Oral Medicine, Dankook University Dental Hospital in 2012.

1. Subjects

Twelve healthy volunteers (6 males and 6 females) were enrolled in this study. Their mean age was 24.5 years (range, 23 to 26 years) and mean body weight was 61.8 kg (range, 48 to 78 kg). Exclusion criteria were those with a history of allergy to pilocarpine; in pregnancy or breast-feeding; with cardiovascular disease (uncontrolled hypertension, arrhythmia); with renal diseases; with acute iritis or narrow-angle (angle closure) glaucoma; with pulmonary diseases including asthma and chronic obstructive pulmonary disease.

2. Study Medication

Pilocarpine tablets (Salagen Tab.; Hyundai Pharm., Seoul, Korea) containing 5 mg pilocarpine hydrochloride were used for systemic administration. Four milliliters of 2% pilocarpine solution was prepared by adding 2 mL of 4% pilocarpine ophthalmic solution (Ocucarpine Eye Drops; Samil Pharm., Seoul, Korea) to 2 mL of mouthwash commercially available (Caregargle Solution; Hanmi Pharm., Seoul, Korea) as carrier to make pilocarpine solution to mask the bitter taste of pilocarpine. The mouthwash was also used for placebo solutions. Pilocarpine solution and placebo was prepared and dispensed by 4 mL on the previous day before administration.

3. Study Design

The study was designed to compare the effects of pilocarpine solution to pilocarpine tablets and placebo solution. Comparison between pilocarpine and placebo solution was double-blinded. Fig. 1 represents our experiment flow. The whole experiment consisted of three experimental sessions; i.e., each subject was administered pilocarpine tablet, pilocarpine solution and placebo solution in the predetermined order with wash-out period of at least two days between the sessions. The volunteers were randomly allocated to 6 sex-matched groups, each consisting of 2 individuals. Prior to experiments, all subjects underwent baseline medical history taking and physical examination.

All experimental sessions were conducted between 9:00 to 12:00 in the morning to minimize the effects of diurnal variation. The subjects were instructed not to eat, drink, smoke, or perform oral hygiene, which cause the chemical or mechanical salivary stimulation, for at least 1 hour before a saliva collection. For systemic administration of pilocarpine, the subjects were asked to take the tablet with a

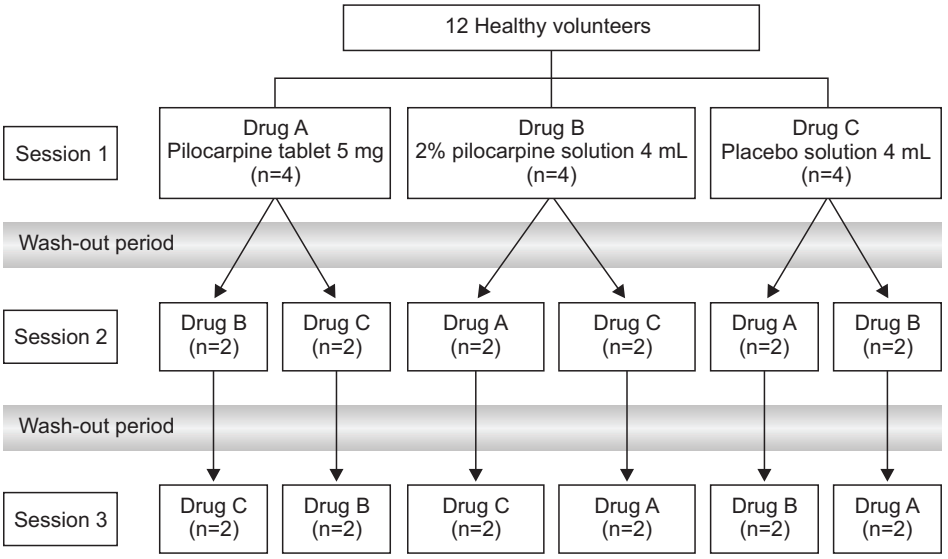

Fig. 1. The study flow chart.

sip of water. For topical use, the subjects were instructed to maintain the solution in the mouth for 5 minutes, without swallowing and being very careful to spit the entire volume of the solution. During each session, unstimulated whole saliva was collected 6 times including before treatment (baseline data) and at 20, 40, 60, 90, 120 minutes after administration of drugs. Whole saliva was collected by having the subjects swallow to empty the mouth of saliva, then refraining from swallowing for 1 minute and expectorating into a tube. The collection volumes were determined gravimetrically: The saliva-filled tube was weighed and the weight of the tube subtracted.

After finishing a session of 120 minutes, the subjects were asked to complete a self-administrated questionnaire about subjective effectiveness on salivation and side effects experienced such as facial flushing, sweating, palpitation, nausea, dizziness, headache, increased urination and gastrointestinal irritation. Subjective effectiveness of medication tested on salivation was assessed using 10-cm visual analogue scales (VAS) (0-10): 0, no effect on salivation; 10, extreme effect on salivation. The pulse rate and blood pressure were measured and recorded before and after each session.

4. Statistical Analysis

Statistical analysis was performed using PASW Statistics version 18.0 (IBM Co., Armonk, NY, USA). Repeated measures two-way ANOVA was used to compare of the salivary flow rate, blood pressure and pulse rate among the three groups with time. The mean VAS scores among the groups were compared by one-way ANOVA. Multiple comparison test using Fisher's least significant difference test was used to determine if a difference existed among the three groups. Statistical significance was defined as $p<0.05$.

RESULTS

All of 12 subjects completed the whole experimental sessions with no drop-out. Mean wash-out periods between sessions was 4.21 days (range, 2 to 15 days).

1. Salivary Flow Rate

Table 1 and Fig. 2 represent change of salivary flow rate before and after administration of the study medication including pilocarpine solution and tablets and placebo solution. Salivary flow rate showed significant difference among time and medication groups ($p<0.001$) and there was positive interaction between time and groups ($p=0.005$). While the three medication groups did not show significant difference of salivary flow rate at baseline level, pilocarpine solution and tablet increased significantly salivary flow rate compared with placebo solution ($p<0.001$). Maximal salivary flow rate was found between 40 and 60 minutes for pilocarpine tablet group and between 60 and 90 minutes for pilocarpine solution group, and then decreased with time. However, their salivary flow rates at 120 minutes after

Table 1. Salivary flow rate following medication

Time (min)	Mean salivary flow rate			p-value
	2% pilocarpine solution	5 mg pilocarpine tablet	Placebo solution	
Baseline	0.74±0.49	0.80±0.59	0.70±0.45	
20	1.18±0.56	1.69±1.04	0.76±0.43	
40	1.38±0.52	2.56±0.84	0.80±0.50	<0.001[a]
60	1.96±0.97	2.33±0.58	0.91±0.54	
90	1.77±0.70	2.13±0.85	0.75±0.46	
120	1.45±0.61	1.55±0.89	0.71±0.37	
p-value		<0.001[b]		0.005[c]

Values are presented as mean±standard deviation.
Repeated measures two-way ANOVA was performed.
Significant difference was found among time ([a]) and medication groups ([b]) and there were interaction between time and group ([c]).

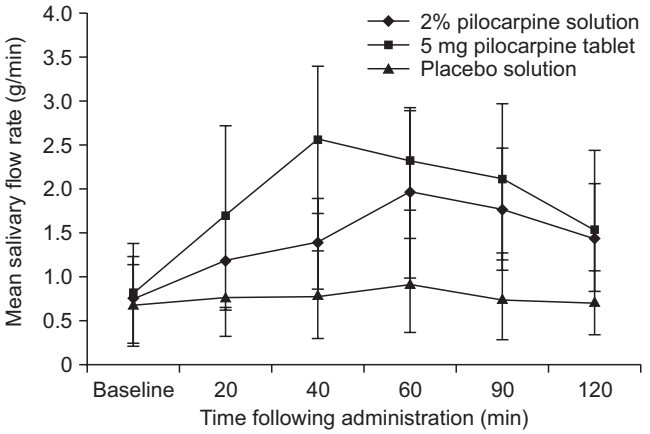

Fig. 2. A graph showing changes of salivary flow rate before and after medication.

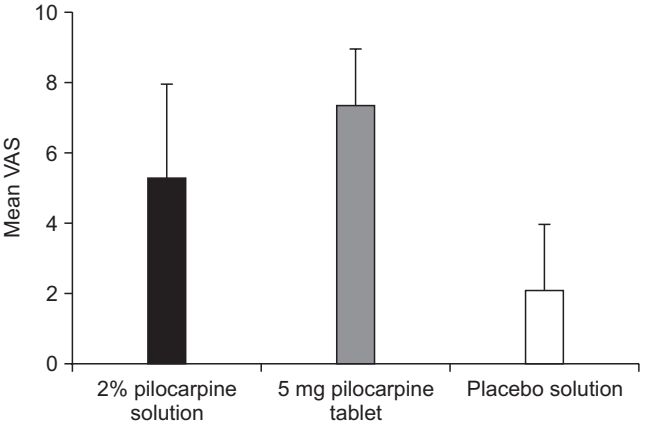

Fig. 3. Mean visual analog scales (VAS) for subjective effectiveness on salivation (0, no effect on salivation; 10, extreme effect on salivation). There were significant differences among medication groups (one-way ANOVA, p<0.05).

administration of pilocarpine remained still higher level than those before medication. Salivary flow rate in the pilocaprine tablet group changed more rapidly compared to pilocarpine solution. Placebo solution did not show any significant change in salivary flow rate throughout the whole session.

Mean VAS scores for subjective assessment was shown in Fig. 3. Pilocarpine tablet group represents significantly higher score (7.4) compared to the pilocarpine solution (5.3) (p=0.019) and placebo solution group (2.1) (p<0.001). Mean VAS of pilocarpine solution group was also significantly higher than that of placebo solution group (p=0.001).

2. Blood Pressure and Pulse Rate

Table 2 shows mean blood pressure and pulse rate before and after administration of drugs. After administration of the three drugs, increment or decrement of blood pressure and pulse rate was observed but the changes were negligible. There was no significant difference in blood pressure and pulse rate before and after administration of all three drugs.

3. Side Effect of Medication

Side effect after medication was assessed through the self-administered questionnaires. Pilocarpine tablet group reported side effect the most frequently (Table 3). Nine subjects (75%) of pilocarpine tablet group complained of one and more side effects and the most common side effects reported was sweating (33.3%, n=4) followed by palpitation (25%, n=3). Two subjects of pilocarpine solution group complained sweating (n=1) and palpitation (n=1). Chill was reported for only one subject of placebo group.

Table 2. Blood pressure and pulse rate before and after medication

Parameter	Medication	Baseline	120-min after medication	p-value
Systolic blood pressure (mmHg)	2% pilocarpine solution	116.6±7.5	112.7±9.1	
	5 mg pilocarpine tablet	113.8±10.0	115.8±10.0	0.569[a]
	Placebo solution	116.7±10.0	114.5±12.5	
	p-value	0.942[b]		0.583[c]
Diastolic blood pressure (mmHg)	2% pilocarpine solution	72.8±10.0	70.2±6.6	
	5 mg pilocarpine tablet	71.3±5.0	68.6±7.8	0.172[a]
	Placebo solution	71.4±6.7	69.2±9.3	
	p-value	0.762[b]		0.994[c]
Pulse rate (beats/min)	2% pilocarpine solution	78.3±11.3	74.7±10.0	
	5 mg pilocarpine tablet	74.0±11.2	75.0±11.7	0.465[a]
	Placebo solution	75.1±8.5	72.0±12.3	
	p-value	0.642[b]		0.728[c]

Values are presented as mean±standard deviation.
Repeated measures two-way ANOVA
There were no significant differences among time ([a]) and medication groups ([b]) and no interaction between time and medication ([c]).

Table 3. Side effects reported after medication (n=12)

Side effect	Subject		
	2% pilocarpine solution	5 mg pilocarpine tablet	Placebo solution
Sweating	1 (8.3)	4 (33.3)	-
Palpitation	1 (8.3)	3 (25.0)	-
Nausea	-	1 (8.3)	-
Dizziness	-	1 (8.3)	-
Warmth	-	1 (8.3)	-
Gastrointestinal irritation	-	1 (8.3)	-
Frequent urination	-	1 (8.3)	-
Chill	-	-	1 (8.3)

Values are presented as number (%).

DISCUSSION

This study demonstrated that 2% pilocarpine solution as mouthwash increased salivary flow rate in healthy subjects compared to placebo, whose effect was comparable to oral administration of 5 mg pilocarpine tablet.

Various concentration of pilocarpine solution ranging from 0.02% to 2% was tried in previous studies. Bernardi et al.[8] reported that 2% pilocarpine solution induced a significant elevation in salivary flow in healthy subjects subjectively and objectively. We also investigate effects of 2% solution on salivation to compare with that by 5 mg pilocarpine tablet. Five milligrams pilocarpine tablet in current study produced increased salivary flow rate of 1.76 g/min, similar to the results by previous studies[12-16] and by 2% solution of Bernardi et al.'s study.[8] However, salivary flow rate of 1.22 g/min induced by 2% pilocarpine solution in this study was significantly lower than that by pilocarpine tablet ($p<0.001$; Table 1). The discrepancy between the study of Bernardi et al.[8] and ours can be, in part, due to methodological difference. We instructed the subjects to hold 4 mL 2% solution containing 80 mg of pilocarpine for 5 minutes in the mouth while they used 10 mL 2% solution containing 200 mg of pilocarpine for 1 minute. Peters et al.[15] indicated a positive correlation between plasma pilocarpine levels and whole saliva output and close similarity between the mean blood plasma pilocarpine curves and the mean parotid and whole saliva volume curves. Aromdee et al.[16] also reported that there was linear correlation between saliva flow and plasma concentration of pilocarpine. According to these findings, it is assumed that plasma concentration of our solution was lower than that of 2% pilocarpine solution used in the study of Bernardi et al.,[8] which suggests that amount of pilocarpine applied at a time may affect absorption through the oral mucosa more strongly than its application time. However, the other factors including contact area of the oral mucosa should also be considered.

The oral mucosa's accessibility, excellent blood supply, by-pass of hepatic first-pass metabolism and permeability profile make it an attractive site for local and systemic drug delivery.[17] In addition, topical pilocarpine solution has some benefits including prolonged contact to acting site and mechanical stimulation. Previous studies showed that <1% pilocarpine solution did not increase the salivary flow

rate significantly but improved subjective symptoms of xerostomia.[10,11] Topical pilocarpine stimulates minor salivary gland directly and mucin production occurs. Mucin has an important role in relieving xerostomic symptoms.[18]

Another advantage of solution is that various concentrations are available according to the severity of symptoms. In this study, mean increased salivary flow rate of 1.22 g/min with 2% pilocarpine solution was 70% level of that by pilocarpine tablet (1.76 g/min). Lower concentration of pilocarpine solution may be effectively used for xerostomic patients without significant decrease of salivary flow rate.

Previous studies indicated that salivary flow rate reached the maximum between 30 and 60 minutes after systemic administration of pilocarpine,[9,12,19] which agreed with our study. However, 2% pilocarpine solution in this study had the peak between 60 and 90 minutes after administration. This result may mean that absorption through the oral mucosa is slower compared to that by systemic administration. During the whole experimental session of 120 minutes, salivary flow rate remained elevated above baseline in both pilocarpine solution and tablet groups. It is well known that pilocarpine tablet increase salivary secretion with a duration of 3 to 5 hours.[20] However, as no such data on pilocaropine solution was available, its effect on duration needs to be investigated after 120 minutes. As there were a few studies about salivary flow induction by oral permucosal pilocarpine in human, sbsorption, distribution and excretion of pilocarpine following topical application to the oral mucosa in human are needed to be studied.

In this study, pilocarpine solution and tablet had no significant effects on blood pressure and pulse rate, supported by previous studies.[8,9,21] In this study, adverse effects were more frequently reported in the pilocarpine tablet group than the 2% solution group. Adverse effects tend to decrease over time and might be diminished by starting with a low dose.[22,23] Thus, it is thought that slower absorption of topical solution might be related to its less adverse effects.

This study confirmed that 2% pilocarpine solution could increase the salivary flow rate significantly with few side effects in healthy subjects. However, xerostomia is mostly occurred in elderly patients who usually have one or more systemic diseases. In addition, they are taking polypharmacy due to their systemic diseases, which may restrict systemic use of pilocarpine. Further studies are needed to find optimal concentration of pilocarpine solution in order to induce maximum effects and minimum side effects in these patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Mandel ID. Sialochemistry in diseases and clinical situations affecting salivary glands. Crit Rev Clin Lab Sci 1980;12:321-366.
2. Sreebny LM. Xerostomia: diagnosis, management, clinical complications. In: Edgar WM, O'Mullane DM, eds. Saliva and oral health. 2nd ed. London: British Dental Association; 1996. pp. 43-46.
3. Ishii M, Kurachi Y. Muscarinic acetylcholine receptors. Curr Pharm Des 2006;12:3573-3581.
4. Frydrych AM, Davies GR, Slack-Smith LM, Heywood J. An investigation into the use of pilocarpine as a sialagogue in patients with radiation induced xerostomia. Aust Dent J 2002;47:249-253.
5. Hamlar DD, Schuller DE, Gahbauer RA, et al. Determination of the efficacy of topical oral pilocarpine for postirradiation xerostomia in patients with head and neck carcinoma. Laryngoscope 1996;106:972-976.
6. Lockhart PB, Fox PC, Gentry AC, Acharya R, Norton HJ. Pilot study of controlled-release pilocarpine in normal subjects. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:517-524.
7. Berk L. Systemic pilocarpine for treatment of xerostomia. Expert Opin Drug Metab Toxicol 2008;4:1333-1340.
8. Bernardi R, Perin C, Becker FL, et al. Effect of pilocarpine mouthwash on salivary flow. Braz J Med Biol Res 2002;35:105-110.
9. Taweechaisupapong S, Pesee M, Aromdee C, Laopaiboon M, Khunkitti W. Efficacy of pilocarpine lozenge for post-radiation xerostomia in patients with head and neck cancer. Aust Dent J 2006;51:333-337.
10. Mikhail AR, inventor. Pilocarpine mouthwash for dry mouth relief. United States patent US 4,209,505. 1980 Jun 24.
11. Kim JH, Park JH, Kwon JS, Ahn HJ. Effect of pilocarpine mouthwash on xerostomia. Korean J Oral Med 2011;36:21-24.
12. Fox PC, Atkinson JC, Macynski AA, et al. Pilocarpine treatment of salivary gland hypofunction and dry mouth (xerostomia). Arch Intern Med 1991;151:1149-1152.
13. Wiseman LR, Faulds D. Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. Drugs 1995;49:143-155.
14. Ferguson MM. Pilocarpine and other cholinergic drugs in the management of salivary gland dysfunction. Oral Surg Oral Med Oral Pathol 1993;75:186-191.

15. Peters GR, Novak E, Batts DH, Bye A, Nichols DJ, Francom SF. Multiple-dose, double-blind, placebo controlled intravenous tolerance and pharmacokinetic study of trospectomycin sulfate (U-63, 366F) in healthy male volunteers. Int J Clin Pharmacol Ther Toxicol 1990;28:361-368.
16. Aromdee C, Ferguson MM, Ledger R, Wall J. A pilot study of the disposition of pilocarpine in plasma, saliva and urine after a single oral dose. Eur J Pharm Sci 1999;8:81-83.
17. Hearnden V, Sankar V, Hull K, et al. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Adv Drug Deliv Rev 2012;64:16-28.
18. Zimmerman RP, Mark RJ, Tran LM, Juillard GF. Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. Int J Radiat Oncol Biol Phys 1997;37:571-575.
19. Fox PC. Salivary enhancement therapies. Caries Res 2004;38:241-246.
20. Fox PC, van der Ven PF, Baum BJ, Mandel ID. Pilocarpine for the treatment of xerostomia associated with salivary gland dysfunction. Oral Surg Oral Med Oral Pathol 1986;61:243-248.
21. Salagen tablet. In: Physician's desk reference: PDR. 51th ed. Montvale: Medical Economics Books; 1997. pp. 1546-1547.
22. Aframian DJ, Helcer M, Livni D, Robinson SD, Markitziu A, Nadler C. Pilocarpine treatment in a mixed cohort of xerostomic patients. Oral Dis 2007;13:88-92.
23. Tsifetaki N, Kitsos G, Paschides CA, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. Ann Rheum Dis 2003;62:1204-1207.