

Oral Manifestations of Patients Taking Anti-Hypertensive Medications

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Abstract

Background and Aim: High blood pressure is a common cardiovascular disease. Most cardiovascular medications have adverse oral side effects. This study aimed to determine the prevalence of oral manifestations associated with the intake of anti-hypertensive medications.

Materials and Methods: This cross-sectional analytical study examined 142 patients with a history of hypertension referred to Dr. Heshmat Hospital in Rasht who were taking one of the four drug categories of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers. The patients' demographic information, medications, and oral symptoms such as mucosal burning, xerostomia, angioedema, and lichenoid reactions were recorded. The data were analyzed by SPSS version 24 using Fisher's exact test and Chi-square test ($P < 0.05$).

Results: From 142 participants, 103 were males and 39 were females; 58.4% of the participants were 61 years or older. Concomitant use of beta-blockers and angiotensin receptor blockers (especially metoprolol and losartan) had the highest frequency among patients. Xerostomia was the most common side effect; angioedema was not reported in any patient. The prevalence of xerostomia increased with age ($P = 0.044$) but it was not correlated with gender ($P = 0.119$). Lichenoid reactions and burning mouth were neither age-related nor gender-related ($P > 0.05$ for all).

Conclusion: Oral complications are inevitable in patients taking anti-hypertensive medications, and in most cases it is not possible to change or decrease the dosage of medications. Therefore, regular dental examinations and palliative treatment can play a role in improving the patients' quality of life.

Key Words: Antihypertensive Agents, Mouth, Adverse Effects

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Introduction

Hypertension is among the most common cardiovascular diseases, and its prevalence in adults in developed countries is about 20% to 30%, [1] while it is 2-5% in children and

adolescents. [2-4] Anti-hypertensive drugs are an effective treatment choice for half of hypertensive patients. [5-7] These medications can cause oral side effects within a few weeks of starting the drug intake. [8-11] The oral

mucosal lesions are usually detectable by taking a history and clinical examination. However, due to the clinical similarity of the lesions, they may be missed in some cases. [6]

The severity of complications is associated with some patient- and medication-related factors. Patient-related factors include gender, age, underlying diseases, and genetics. The drug-related factors include the method of drug administration, duration, dosage, and the drug metabolism. [12]

The side effects of anti-hypertensive drugs include xerostomia, lichenoid reactions, mucosal burning, dysgeusia, gingival hypertrophy, angioedema, and bleeding. Drug-induced xerostomia is a side effect of more than 500 types of drugs [13-15] which can be found in 80% to 100% of the cases in the United States according to a systematic review. [10,16] Many systemic drugs and metal restorations can cause oral lichenoid reactions, although their pathogenesis is still unknown. They are clinically and histologically similar to lichen planus lesions, but they are unilateral and have a traumatic pattern. [14,17] Angioedema is a common clinical manifestation that occurs as a rapid but painless swelling of the lips, tongue, and areas around the eyes, and is caused by contact with a particular allergen or medication in susceptible patients. Angioedema involving the oropharynx can be life-threatening, [12,14,18] which is induced by angiotensin-converting enzyme inhibitors. [10,11]

Oral mucosal burning occurs in the absence of any evidence of oral mucosal pathology with a burning or itching sensation on the tip and sides of the tongue, lips, and frontal palate [10,11] Almost 33% of oral mucosal burning cases due to drug intake are dose-dependent. [10] This study was designed to evaluate the prevalence of side effects of four anti-hypertensive medications.

Materials and Methods

This cross-sectional analytical study evaluated 142 patients referred to an affiliated hospital after obtaining ethical approval

(GUMS.97.1756) from the ethics committee. The inclusion criteria were:

1. Pharmacotherapy to control blood pressure
2. Not having symptoms of cardiac ischemia or myocardial infarction such as chest pain or ECG changes, severe heart failure, pulmonary edema, impaired consciousness, brain symptoms (possibility of hypertensive encephalopathy or stroke), ocular disorders, history of allergy to captopril, and pregnancy.

Patients with uncontrolled hypertension treated with intravenous nitrate were not selected. Also, patients taking medications to control other systemic diseases that can cause oral symptoms and side effects similar to antihypertensive drugs such as diabetics, and those with hypothyroidism and hyperthyroidism were excluded from the study. After obtaining written informed consent from the patients, the patients' medical records, as well as age, gender, oral symptoms, blood pressure level, and history of similar lesions were assessed. The Fox [19] questionnaire was first used to evaluate the patients' xerostomia and for subjective evaluation with dichotomous yes/no answers. A "yes" answer to at least three questions indicated decreased saliva [20]:

1. Do you feel that your mouth is dry when eating?
2. Do you have difficulty swallowing different foods?
3. Do you need to drink water to swallow dry food?
4. Do you feel that the amount of saliva in your mouth has decreased?
5. Do you feel xerostomia at night or when you wake up?
6. Do you have dry mouth during a trip?
7. Do you use chewing gum or chocolate to improve mouth dryness?
8. Do you wake up at night thirsty?
9. Do you have trouble feeling the taste of food?
10. Do you suffer from oral mucosal burning?

A visual analog scale (VAS) was then used to assess the severity of xerostomia. The patients were asked to mark on a 10-cm chart on paper

that was calibrated from 0 to 10 based on the amount of dryness they felt in their mouth: zero indicated no xerostomia while number 10 indicated maximum rate of xerostomia [21]. Oral mucosal burning was asked subjectively. Complete external and internal examination was performed to assess angioedema and the patients were asked about the history of rapid and painless swelling in their head and face. Presence of oral lichenoid reactions was assessed by oral examination using disposable gloves, dental mirror, and sterile gauze under appropriate lighting, and the data were recorded in patient records.

The data were analyzed by SPSS 24 (SPSS Inc., IL, USA). Since the data had normal distribution according to the Kolmogorov-Smirnov test, the Fisher's exact test was used to analyze lichenoid reactions and oral mucosal burning, and the Chi-square test was used to analyze xerostomia. A significance level of $P < 0.05$ was considered.

Results

Analysis of the available data showed that out of 142 participants, 103 were males and 39 were females; 58.4% of the participants were 61 years or older. Duration of drug use was divided into 4 periods of less than 1 year, between 1 to 5 years, between 5 to 10 years, and more than 10 years with a frequency distribution of 13.4%, 54.9%, 21.1%, and 10.6%, respectively. The most commonly used antihypertensive drugs by the participants were beta-blockers, and angiotensin receptor blockers with a frequency of 64.1% (Table 1). A combination of metoprolol and losartan was more commonly prescribed.

The incidence of lichenoid reactions, oral mucosal burning, angioedema, and xerostomia was 0.7%, 4.2%, 0%, and 40.8%, respectively (Chi-square test, $P < 0.001$), and xerostomia was the most commonly recorded complication.

By evaluating the correlation of age and oral complications, it was found that angioedema was not seen in any patient. The prevalence of xerostomia was significantly different between different age groups ($P = 0.044$), and its prevalence increased with age. The P-values for lichenoid reactions and oral mucosal burning

were 0.999 and 0.593, respectively, indicating no significant difference.

There was no significant difference between males and females in the frequency of oral complications ($P = 0.266$, $P = 0.346$, and $P = 0.119$ for lichenoid reactions, oral mucosal burning, and xerostomia, respectively).

Also, the frequency of lichenoid reactions, oral mucosal burning, and xerostomia was not significantly different in different age groups based on duration of drug administration ($P = 0.460$, $P = 0.921$, and $P = 0.119$, respectively).

Regarding the number of medications taken, among those who took a combination of drugs, only one of them who took beta-blockers and angiotensin receptor blockers was suffering from lichenoid reactions. Also, 11 patients who took beta-blockers and angiotensin-converting enzyme inhibitors, 4 patients who took beta-blockers and angiotensin receptor blockers, and 1 patient who took beta-blockers, diuretics, and angiotensin receptor blockers showed signs of oral mucosal burning. None of those who used a combination of drugs had angioedema. Finally, according to the data in Table 1, the most common antihypertensive drug that caused intraoral complications was beta-blockers.

The VAS score for xerostomia had no correlation with the type of medication taken ($P = 0.504$), but the highest mean score belonged to Metoral and losartan.

Discussion

Of 142 participants who took part in this study, 103 were males and 39 were females. In a study conducted by Habbab et al, the number of males taking medication was higher than females; however, the side effects did not differ significantly between males and females, similar to our results. [19] Also, the highest age group participating in the present study was over 60 years of age, which was 58.4% of the total sample, while in the study by Kumar et al, the highest number of patients belonged to the age group of 41-50 years. [20] This is due to a higher number of medications taken by the elderly compared with younger individuals. [21] The results of the present study showed that

Table 1: Frequency distribution of using anti-hypertensive drugs and their oral complications (based on using one or more groups)

Anti-hypertensive drugs	Frequency of use	Xerostomia		Angioedema		Oral mucosal burning		Lichenoid reactions	
		No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)
1.Beta blockers	11(7.7%)	6(1/7)	5(8/6)	11(7/9)	0(0)	11(8/1)	0(0)	11(8)	0(0)
2.Diuretics	2(1.4%)	2(2/4)	0(0)	2(1/4)	0(0)	2(1/5)	0(0)	2(1/4)	0(0)
3.Angitensin-converting enzymes	4(2.8%)	4(4/8)	0(0)	4(2/9)	0(0)	4(2/9)	0(0)	4(2/9)	0(0)
4.Angiotensin receptor blockers	18 (12.7%)	11(13/1)	7(12/1)	18(12/9)	0(0)	18(13/2)	0(0)	17(12/3)	0(0)
1,2	2 (1.2%)	2(2/4)	0(0)	2(1/4)	0(0)	2(1/5)	0(0)	2(1/4)	0(0)
1,3	4(2.8%)	3(3/6)	1(1/7)	4(2/9)	0(0)	3(2/2)	11(16/7)	4(2/9)	0(0)
1,4	91 (64.1%)	53(63/1)	38(65/5)	91(64/08)	0(0)	87(64)	4(66/7)	91(64/5)	1(100)
2,3	1 (0.7%)	0(0)	1(1/7)	1(0/7)	0(0)	1(0/7)	0(0)	1(0/7)	0(0)
2,4	2 (1.4%)	0(0)	2(3/4)	2(1/4)	0(0)	2(1/5)	0(0)	2(1/4)	0(0)
3,4	1 (0.7%)	0(0)	1(1/7)	1(0/7)	0(0)	1(0/7)	0(0)	1(0/7)	0(0)
1,2,4	5(3.5%)	3(3/6)	2(3/4)	5(3/6)	0(0)	4(2/9)	1(16/7)	5(3/6)	0(0)
1,3,4	1(0.7%)	0(0)	1(1/7)	1(0/7)	0(0)	1(0/7)	0(0)	1(0/7)	0(0)
Total	142(100)	84(100)	58(100)	142(100)	0(0)	136(100)	6(100)	141(100)	1(100)

simultaneous use of angiotensin receptor blockers and beta-blockers (especially concomitant use of metoprolol and losartan), followed by the use of angiotensin receptor blockers had the highest frequency of use. On the other hand, beta-blockers had oral side effects more than others. These results are inconsistent with the data reported by Valizadeh et al, who reported that beta-blockers were prescribed for 48% of patients. [22] Valizadeh et al. stated that most of the medications prescribed in the first phase of hypertension were beta-blockers (atenolol) and then angiotensin converting enzyme inhibitors (captopril), but in the second phase, angiotensin converting enzyme inhibitors and diuretics had the highest rate of consumption. [22] William and Elliott also found that the most commonly

recommended regimen was beta-blockers and angiotensin converting enzyme inhibitors alone, which differed from the results of this study. [23] In a study by Arunkumar et al, beta-adrenergic blockers and calcium channel blockers were prescribed more than others; their results were also different from ours. [9] Wright in a five-year study on 37,000 patients reported that the most common drugs consumed were thiazide diuretics and beta-blockers. [24] These differences are due to the fact that in addition to medical guidelines, the pathology, and experience and personal opinion of the physicians are also effective in prescribing drugs and for the same reason, it should be noted that the generalizability of our results is low. [24] In the present study, similar to studies by Kumar

et al, [20] and Arunkumar et al, [9] xerostomia with 40.8% was the most prevalent finding. In a study conducted by Villa et al, xerostomia in adults under pharmaceutical therapy was three times more common than in those who did not take any medication. [21] This result was not unexpected as xerostomia is already a common oral adverse effect of several medications. [9]

In a study by Kumar et al, with subjective assessment of the saliva, a decrease in saliva flow was recorded in 16.99% of the patients, which was less than the rate in our study. [20] This difference can be explained by using different measures for assessment of xerostomia.

In our study, 0.7% of the patients had lichenoid reactions, compared with 4.5% in the study by Kumar et al [20]. Based on the results, only xerostomia increased with age and there was a difference between the age groups ($P=0.044$) in terms of xerostomia prevalence, in line with the study done by Shirzaei and Bagheri, which was conducted on 400 patients referred to Zahedan Dental School. [25] This result can be due to changes in salivary glands associated with aging and systematic diseases such as diabetes mellitus. [9]

In a case-control study by Villa et al, the patients received diuretics, angiotensin converting enzyme inhibitors, and beta-blockers. They showed chronic and severe periodontitis in patients in the case group. [21] They only assessed periodontal parameters whilst our study evaluated four types of drug-induced complications, including xerostomia, lichenoid reactions, oral mucosal burning, and angioedema. [19] In the current study, only 1 case of lichenoid reaction was found as the result of combined use of beta-blockers and angiotensin receptor blockers. This side effect is caused by several medications and many cases are not severe enough to force the physicians to change the medication. Besides, since the National Committee for the Prevention, Diagnosis, Evaluation, and Treatment of Patients with Hypertension (JNC-7) recommended diuretics and beta-blockers individually or in combination with other drugs as the first line of treatment, in many cases, it is

not possible to eliminate them from the treatment regimen. [22] In this study, most individuals with xerostomia used losartan and metoprolol. However, the highest VAS score (8) was related to spironolactone, metoprolol, and losartan. This VAS score can be due to difficulty in swallowing and chewing. [21]

Although xerostomia is not a side effect of angiotensin receptor blockers and beta-blockers, [26] our study, similar to some others, showed that xerostomia was caused by the synergistic effect of drugs. (10-12)

Conclusion

In the present study, the only complication was xerostomia among the four drug categories and their side effects, which increased with age. In general, oral complications in people with systemic diseases that require long-term drug treatment are unavoidable, and in most cases, it is not possible to change the medication or decrease the dosage. Therefore, in these patients, regular dental examinations and the use of empirical therapy can play a significant role in improving their quality of life.

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