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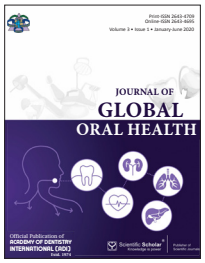

Research Article

Assessment of effects of duration and dosage of Amlodipine on gingival health - A Prospective Study

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ABSTRACT

Objectives: Calcium channel blockers are one of the most commonly used drugs for the management of cardiovascular disorders and are known for causing gingival overgrowth as an adverse effect. Disfiguring gingival overgrowth triggered by this medication is not only esthetically displeasing but also often impairs nutrition and access to oral hygiene, resulting in increased susceptibility to oral infection, caries, and periodontal diseases. The present study aimed to correlate the incidence of the extent of gingival enlargement in hypertensive patients receiving amlodipine and also a correlation of the extent of gingival enlargement with the dosage and duration of intake of Amlodipine. **Materials and Methods:** Hypertensive patients attending the outpatient of the Department of Oral Medicine and Radiology were selected for the study. A detailed history of the subjects was recorded for single or multiple drug usage, including the intake of amlodipine medications for hypertension, the dose and duration of the drug usage, following which a clinical examination was performed to evaluate the grades of gingival enlargement and local factors affecting the same. **Results:** The majority of the patients (81%) received 5 mg of amlodipine medication, and more than 40% of patients were receiving amlodipine for more than one year. More than 50% of patients had grade 2 gingival enlargement. There was a significant correlation between gingival enlargement and amlodipine dosage. Also noted was an association between gingival enlargement and duration of receiving amlodipine. **Conclusion:** Even with a minimal dose of amlodipine, significant gingival enlargement is seen; hence, regular follow-up with a suitable dental evaluation referral for examining gingival and periodontal status becomes imminent. Therefore, dental professionals need to identify and then guide the patient to seek the necessary medical intervention for the same.

Keywords: Antihypertensives, Amlodipine, Drug-induced gingival enlargement

INTRODUCTION

Non-communicable diseases (NCDs) are a group of diseases that affect individuals over an extended period, causing a socio-economic burden to the nation. Among the various NCDs, the major ones include diabetes mellitus, tobacco-induced diseases, cardiovascular diseases, and hypertension. India has had a rise in cases of NCDs, and in 2008, the number of deaths accounting for NCDs was 5.2 million.[1] Hypertension and cardiovascular diseases affect large numbers of adult populations, not only in India but also worldwide.[2] The number of hypertensive individuals is anticipated to nearly double from 118 million in 2000 to 213 million by 2025.[3] Current clinical guidelines emphasize the use of more than one agent to achieve targeted blood pressure in the majority of hypertensive patients, and Amlodipine is a widely accepted and effective component of combination antihypertensive therapy. Calcium channel blockers are one of the most commonly used drugs for the management of cardiovascular disorders and are considered in the first line of

the management of hypertension, especially in subjects above the fourth decade presenting with essential hypertension.[4]

Amlodipine, a dihydropyridine used for the treatment of hypertension and angina, was first reported for causing gingival overgrowth as a side effect by Seymour *et al.*, in 1994.[5] Can medication-induced gingival overgrowth lead to significant esthetic, functional, and speech disturbances? This is an important adverse effect noted with various drugs, including amlodipine. In this regard, the present study aimed to correlate the incidence of the extent of gingival enlargement in hypertensive patients receiving amlodipine and to correlate the extent of gingival enlargement (GE) with the dosage and duration of intake of Amlodipine.

MATERIALS AND METHODS

The present study was a cross-sectional study to evaluate hypertensive patients receiving amlodipine and complaining of gingival enlargement. The study was conducted following ethical clearance from the Institutional Ethical Committee. Ethical approval number IRB no: 2015/P/OM/32 DATED 20/01/2015.

Inclusion criteria and exclusion criteria

1. Patients with the chief complaint of gingival enlargement and receiving amlodipine for hypertension for at least one year
2. Patients with a known history of hypertension and receiving Amlodipine.
3. Patients who are receiving any other medication are known to induce gingival hyperplasia (other than Amlodipine)
4. Pregnant woman
5. Patients unwilling to participate in the study.

A total of 153 hypertensive patients attending the outpatient of the Department of Oral Medicine and Radiology of our college were selected. An informed consent from the patient is taken for participation in the study. A detailed history of the subjects was recorded for single or multiple drug usage, including the intake of amlodipine medications for hypertension, the dose (per day), and the duration of the drug usage. Following a detailed history regarding drug details, a clinical examination was performed to check for gingival enlargement as outlined by Bökenkamp *et al.*,[6] and local factors affecting the same were assessed according to guidelines by Greene and Vermillion[7], and gingival inflammation was assessed using the Gingival Index.[8]

Statistical analysis

The collected information of the data was entered into Microsoft Excel and then subjected to statistical analysis using SPSS 11 software. The data were further subjected to descriptive statistics, and chi-square was done to know the association between the variables.

RESULTS

Among 153 patients, 75 (49%) were males and 78 (51%) were females, and the ages of the subjects ranged between 30 and 80 years. The majority of the patients (81%) received 5 mg of amlodipine medication; gingival enlargement was seen with as low a dosage as 2.5 mg [Table 1]. More than 40% of patients were receiving amlodipine for more than one year [Table 2]. With regard to gingival enlargement, more than 50% of patients had grade 2 gingival enlargement [Figure 1]. There was also a significant correlation between gingival enlargement and amlodipine dosage (P = 0.016) [Table 3].

Gingival index score - 51% of patients had moderate inflammation [Table 4]. Also noted was the association between gingival enlargement and the duration of receiving amlodipine (P = 0.020) [Table 5].

DISCUSSION

Amlodipine is a second-generation calcium channel blocker (CCB) with high vascular selectivity that reduces peripheral resistance while preserving myocardial contractility. Common adverse effects reported include peripheral edema, which is a common adverse effect of amlodipine apart from dizziness, fatigue, headache, palpitations, and nausea.[4]

Drug-influenced gingival enlargement (DIGE) refers to the overgrowth of gingival tissue as a side effect associated with the use of systemic medication.[9] More than 35 prescribed medicines have been linked to cause gingival enlargement. Among these, CCBs are some of the most common etiologies of DIGE.

Typically, it is more severe in the maxillary and mandibular anterior facial and labial surfaces.[10] Calcium

Table 1: Dosage distribution of Amlodipine among subjects.

Dosage of Amlodipine	No. of patients	Percentage
2.5 mg	23	15
5 mg	124	81
10 mg	6	3.9

Table 2: Duration of intake of Amlodipine among subjects.

Duration of intake	No. of patients	Percentage
>1 month–1 year	27	17.6
1–5 years	63	41.2
5–10 years	34	22.2
10–15 years	17	11.1
>15 years	12	7.8

channel-induced gingival enlargement ensues when the periodontium becomes an inadvertent target of the drug. The mechanism of action in DIGE involves multiple factors. These drugs have an inhibitory effect on sodium and calcium cation channels, resulting in the blockage of the influx of calcium ions into fibroblasts. This, in turn, causes a decline in e-cadherin, a gene molecule crucial for epithelial cell-to-cell adhesion and for transforming growth factor (TGF)-beta 1. The interplay of growth factors TGF-beta, matrix metalloproteinases, and interleukin-6 leads to reduced collagenase activity, which results in decreased collagen breakdown and the accumulation of collagen and other extracellular matrix.[9]

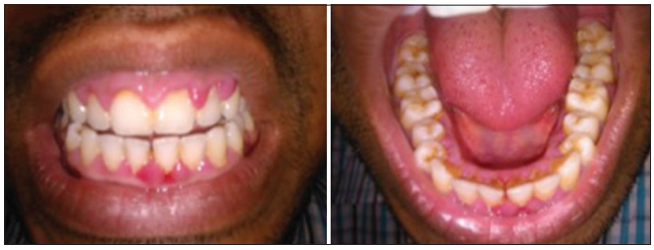

Figure 1: Moderate gingival enlargement, with prominent interdental papillary involvement on buccal and lingual aspect.

Table 3: Correlation of various grades of gingival enlargements with dosage of Amlodipine.

Gingival enlargement	Amlodipine dosage per day			Total
	2.5 mg	5 mg	10 mg	
Grade-1	0	4	0	4
Grade-2	15	71	1	87
Grade-3	8	48	4	60
Grade-4	0	1	1	2
Total	23	124	6	153
	Pearson Chi-square value	15.56	6	0.016*

*Significant <0.05

Table 4: Distribution of gingival index scores among subjects.

Gingival index score	No. of patients	Percentage
0	0	0
1 (mild inflammation)	71	46.4
2 (moderate inflammation)	79	51.6
3 (severe inflammation)	3	2

Effect of dose on gingival enlargement amlodipine has been associated with GE even in doses as low as 2.5 mg/day taken over a longer duration of time.[11] In general, DIGE is observed at an average of three months after the commencement of the drug regime.[12] The condition usually sets in as a nodule in the interdental papilla, which gradually enlarges, involving the facial and palatal/lingual margins. This is followed by the coalescing of interdental papillae, eventually with the enlarged gingival margins, and may result in a massive tissue fold over the tooth surfaces, impeding masticatory function and/or speech.[9] The gingival enlargement in the early stages may be painless, but in advanced cases, it can cause substantial discomfort during mastication.

The results of the present study are like the other studies.[13-16] Disfiguring gingival overgrowth triggered by amlodipine is not only esthetically displeasing but often impairs nutrition and access to oral hygiene, especially when the ensued enlargement is associated with pain. This may, in turn, result in an increased susceptibility to oral infection, caries, and periodontal diseases. The management of DIGE includes considering the systemic stability of the underlying condition and evaluation of local factors, as local factors may assist in the progress of the ensuing gingival enlargement. The initial nonsurgical phase of treatment should include strict plaque control measures. When oral hygiene and pharmacotherapeutic measures turn out to be inadequate, in complete resolution of DIGE, periodontal surgery may become indispensable to re-establish the original gingival architecture to reinstate function and esthetics. If the gingival enlargement is not addressed at the right time, it may influence the health-related quality of life and psychological status of patients. Hence, the earlier the treatment approaches for these patients; the better would be the treatment prognosis of the condition. Furthermore, efforts can be made to enhance awareness among patients by means of virtual health programs or the use of telemedicine between various healthcare providers to tackle the problems by bridging the healthcare gaps in the system.[17]

Table 5: Relationship of grades of gingival enlargement and duration of intake of amlodipine.

Gingival enlargement	>1 month–1 year	1–5 year	5–10 year	10–15 year	>15 year
Grade-1	0	1	1	2	0
Grade-2	15	**44**	14	5	9
Grade-3	11	18	19	9	3
Grade-4	1	0	0	1	0
Total	27	**63**	34	17	12
	Pearson Chi-square	24.038[a]	12	0.020*	

*p<0.05, Bold: Maximum number of subjects with Grade 2 gingival enlargement had a history of ingestion of amlodepine for a period of 1-5 years, [a]Chi square value

CONCLUSION

The sensitive balance between oral health and general health can be maintained only when one is abreast with interrelated aspects of the systemic disease. It is also necessary for patients to be made aware of the ensuing side effects before the start of treatment, emphasizing the fact that marinating periodontal health is of utmost significance to prevent the extent of adverse effects of treatment. Even a minimal dose of amlodipine may lead to significant gingival enlargement, as observed in the present study. Physicians need to be aware that regular follow-ups with suitable dental referrals for evaluating gingival and periodontal status become imminent. Furthermore, future studies can assess the psychological and functional impact of DIGE to address this condition with the utmost care. Furthermore, dental professionals need to identify and guide the patient to seek the necessary medical intervention for a change of medications if surgical management fails to address the problem.

Ethical approval

Ethical approval was obtained from institutional Ethical Committee 2015/P/OM/27.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflict of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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