

Amlodipine induced Gingival Overgrowth in Patients at a Tertiary Level Hospital of Nepal

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ABSTRACT

Background: Amlodipine is a commonly prescribed anti-hypertensive in clinical practice. Gingival overgrowth is a rare side effect of this drug; with a reported prevalence of 1.7-3.3% in literature. Gingival overgrowth can cause aesthetic and functional problems as well as cause hindrance to maintain proper oral hygiene, thereby deteriorating the periodontal condition of the patient. The prevalence of Amlodipine induced gingival overgrowth is poorly defined in our country.

Aim: This study aims to assess Amlodipine induced gingival overgrowth in a tertiary level referral hospital of Nepal Army.

Materials and Methods: This study was conducted on hypertensive patients with amlodipine therapy under regular follow up in the Department of Internal Medicine of Shree Birendra Hospital from September to December 2017. The data from record keeping was used for the study. Ethical clearance from Institutional Review committee of Nepal Army Institute of Health Sciences was obtained before conducting the study.

Results: Out of 507 patients taking amlodipine, 240 were eligible for study and six (2.5%) were found to have amlodipine induced gingival overgrowth. These patients were on a dose of 5-10 mg over six months to 25 years. The gingival overgrowth was correlated with dose and duration which was statistically significant ($p < 0.05$).

Conclusion: Low prevalence of amlodipine induced gingival overgrowth and correlation with dose and duration was seen in this short-term study. However further large-scale follow-up studies may be required to assess the severity of the problem.

Keywords: Amlodipine; drug induced gingival overgrowth; Nepal.

INTRODUCTION

Calcium channel blockers (CCBs) are commonly prescribed anti-hypertensive medication with some notable adverse effects like headache, dizziness, facial flushing, oedema.¹ Drug induced gingival overgrowth (DIGO) is commonly seen with Nifedipine with a reported prevalence between 14.7% to 83%.² DIGO is a rare finding with amlodipine with an

incidence of 1.7-3.3%.^{1,3,4} It was first reported by Ellis et al in 1993.⁵

DIGO is the proliferation of gingival epithelial cells as well as connective tissue cells and extracellular matrix. DIGO can cause aesthetic and functional problems deteriorating the periodontal condition of the patient.⁶ Male predominance⁵ has been reported but it is not clear. DIGO is mostly seen in anterior labial dentulous region⁶ and the effect of dose, duration and pathogenesis is still not clear.⁷⁻⁹ The pathogenesis of gingival overgrowth (GO) is presumed to be mediated via non-inflammatory and inflammatory pathways^{4,7-9} which cause defective collagenase activity, fibroblasts proliferation and upregulation of inflammatory cytokines.

Since the prevalence of DIGO by amlodipine is poorly defined in our context and has not been reported in Nepal, this study was done in a tertiary level hospital of Nepal Army to assess the prevalence of Amlodipine induced GO.

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MATERIALS AND METHODS

This single centered cross-sectional study was done based on data recorded in record system of the patients presenting to Medical out-patient department (OPD) in tertiary level hospital in Nepal Army i.e. Shree Birendra Hospital. All hypertensive patients under amlodipine visiting the OPD of Department of Internal Medicine for follow up from September to December 2017 were enrolled in the study. This is the only tertiary referral hospital of Nepal Army and such study has not been done in the past. Patients under amlodipine therapy for more than six months were included in this study. Patients with concomitant uses of other drugs known to cause DIGO such as phenytoin, cyclosporine, nifedipine, diltiazem, verapamil etc., patients below 19 years or over 60 years of age; edentulous patients or patients missing more than three anterior teeth or presence of total 20 teeth; patients with known conditions or diseases that can cause GO (pregnancy, leukemia, sarcoidosis) and patients who had discontinued using amlodipine for more than 1 month prior to the study were excluded.

Ethical clearance from Institutional Ethical Review committee (IRC) of Nepalese Army Institute of Health Sciences (NAIHS) was obtained for conducting the study. The medical history of all cases to elaborate demographic data, dose and duration of drug was taken, and the medical charts and records were maintained. The GO was clinically diagnosed as DIGO if there was a clinical presentation of firm fibrotic beadlike growth of interdental papilla or GO of interdental papilla extending to the marginal gingiva causing blunting of the margins or progressing to the attached gingiva which may cover the crown.⁶ All cases were treated with non-surgical periodontal therapy.

The collected data was entered and analyzed using SPSS version 22 and inference was taken using Chi-square test. The statistical significance was interpreted based on confidence interval of 95% with 5% standard error.

RESULTS

Out of 507 patients under amlodipine, 240 met the inclusion criteria for the study. Mean age was 49.69 ± 8.1 years. Among total cases, 45% were females and rest being males (Figure 1). There were some comorbidities in 85 (35.4%), rest 155 did not present any comorbidities other than hypertension.

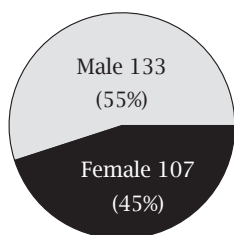


Figure 1: Gender distribution among cases of amlodipine.

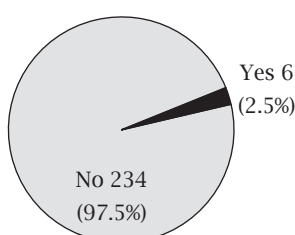


Figure 2: Prevalence of gingival overgrowth.

Table 1: Comorbidities among amlodipine users.

Comorbidities	Frequency	Percent
None	155	64.6
Diabetes Mellitus (DM)	52	21.7
Cerebrovascular diseases (CVD)	5	2.1
Coronary Artery Disease (CAD)	1	0.4
Chronic Obstructive Airway Diseases	5	2.1
Dyslipidemia	8	3.3
Hyperthyroidism	10	4.2
DM+CAD	2	0.8
Chronic Kidney Diseases	2	0.8
Total	240	100.0

The commonest comorbidity was diabetes mellitus (Table 1). Gingival overgrowth was present in 6 (2.5%) of the hypertensive cases under amlodipine while the rest 234 (97.5%) cases did not present with gingival overgrowth (Figure 2). GO was not significantly associated with gender whereas there was a significant association with the dose and duration of amlodipine ($p < 0.05$, $OR > 1$) (Table 2).



Figure 3: DIGO in a 32-year-old male patient under 10 mg amlodipine for 2 years.

Table 2: Association of gender and amlodipine use with gingival overgrowth.

Variables		Gingival Over-growth		Total	p-value	OR (95% CI)
		No	Yes			
Sex	Male	129	4	133	.574	0.614 (0.11-3.42)
	Female	105	2	107		
Dose	5 mg or Less	219	4	223	.011	7.30 (1.23-43.12)
	More than 5	15	2	17		
Duration	5 Years or less	178	2	180	.017	6.35 (1.13-35.63)
	More than 5 Years	56	4	60		

DISCUSSION

The prevalence of amlodipine induced gingival overgrowth was 2.5% in this study which is comparable to those reported in literature of 1.3%,¹ 1.4%,³ 3.3%,⁸ 3.4%.¹⁰ All patients in this study were under amlodipine for six months or more. Drug duration and dosage were significantly associated with DIGO

in this study. Similarly, Jorgensen et al in 1997¹ reported in an observational study, no GO occurred with a low dose of amlodipine of 5 mg/day for at least six months. Seymour et al in 1994¹¹ reported that GO began two to three months after starting the medication at low levels of 5-10 mg/day. There are contradictory findings correlating the relation between dose and overgrowth.⁷ The wide range of prevalence of DIGO may be attributed to various risk factors, according to Seymour et al,¹² who proposed a multifactorial risk model. GO has been attributed to age, genetic predisposition, pharmacokinetic variables, plaque-induced inflammatory and immunological changes and activation of growth factors.

CCB drugs inhibit the intracellular Calcium influx and cause defective collagenase activity,^{2,7,9,12} which is further aggravated by reduced uptake of folic acid. They stimulate the proliferation of a subpopulation of fibroblasts.⁹ The inflammatory mechanism involves the stimulation of the production of inflammatory cytokines like Interleukin (IL)-2 by T cells,^{4,9} IL-6 and production of growth factors like transforming growth factor beta (TGF β), basic fibroblast growth factor (β FGF) which enhances proliferation of connective tissue fibroblasts and collagen and glycosaminoglycans of the lamina propria.^{7,9,12} There is reduced collagenolytic effect due to reduction in Calcium ion influx and consequent increase in extracellular matrix (ECM) collagen.^{2,7,9} Drugs tend to deposit within the gingival epithelium and have a greater effect.⁹ Another mechanism involves mast cells in inflammation which stimulates fibroblast proliferation, ECM synthesis and degradation.¹⁴ Histologically epithelial and mesenchymal interaction that leads to greater ECM deposition.¹⁴

However, these theories do not explain why only some patient develop GO. Only some individuals respond to the drug and cause GO. Even the responders have a variable pattern in the extent and severity of GO among themselves. A study by Banthia et al¹⁴ in 2015 reported that the degree of GO is affected by periodontal status. GO only occurs in dentulous area where plaque is present. Drug induced gingival hyperplasia has been now classified under plaque-induced gingival diseases¹⁵ and plaque accumulation can increase or be a consequent of the gingival overgrowth. Histologically, there is presence of sparse to moderate inflammatory cell infiltrate

correlated to inflammatory condition. A recent study stated that it is not clear whether plaque is a cause or a result of GO.¹⁶

Another reason why some patients have greater cellular proliferation and collagen synthesis may be attributed to the variation in the differential subpopulations of fibroblasts in the individuals. A recent study by Csiszar et al¹⁷ has reported that there is a distinct molecular composition of increased levels of integrin α v β 6, type I procollagen, fibronectin, tenascin-C, TGF- β , connective tissue growth factor (CTGF), and the signaling molecule (SOS)-1 in the interdental papilla of the gingiva which is responsible for healing and upregulation of ECM components. Pathogenesis of DIGO is not clear in literature and newer molecular approaches are needed to establish the pathogenesis.¹⁸

Treatment of DIGO involves consultation with the treating physician, baseline periodontal evaluation and non-surgical periodontal therapy with or without adjunctive chlorhexidine mouthwash followed by alternative drug therapy and surgical removal (scalpel or laser gingivectomy or partial internal bevel incision) in severe cases with notification to the patient of chances of recurrence.^{19,20} Further research in large scale studies should be done to correlate with the dosage and histologic changes if possible. All patients were treated accordingly. The GO did not reduce after scaling in these patients, hence alternative anti-hypertensive drug was given.

The limitations of the study include short duration of the study with a small sample size. The grading of the GO was not done due to a small prevalence and was insignificant. Further large-scale studies should be done with histopathologic analysis and possible molecular approach to clearly understand the pathogenesis of DIGO.

CONCLUSION

In this small study, the prevalence of amlodipine induced gingival overgrowth was low. Nevertheless, DIGO due to amlodipine was significantly associated with dose and duration of amlodipine use. So, the patients prescribed with the drug should be monitored regularly and treated when the GO occurs. Therefore, regular follow up and assessment of GO must be done in patients taking amlodipine.

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