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Prevalence of Gingival Overgrowth in Patients Taking Amlodipine

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ABSTRACT

Introduction: Hypertension and cardiovascular diseases affect a large number of adult populations worldwide including Nepal. Amlodipine is a third generation Calcium channel antagonist that is commonly used as antihypertensive. Drug induced gingival overgrowth is an important adverse effect noted with various drugs including amlodipine. The number of patients under amlodipine therapy appears to be steadily increasing largely due to the preference of this drug over other antihypertensive drugs.

Objective: To determine the prevalence of amlodipine-induced gingival overgrowth.

Methods: A cross-sectional study was carried out among patients taking amlodipine and attending the outpatient department (OPD) of Cardiology Unit, National Academy of Medical Sciences (NAMS) Bir Hospital, from 2013 May to 2013 December. Basic demographic information were collected in Cardiology Unit and patients with gingival overgrowth were recalled in the Periodontology and Oral Implantology Unit of Dental OPD for intraoral examination. The data collected were analysed statistically using SPSS software version 17.

Results: Among 73 patients examined, 20 (27.4%) had gingival overgrowth. Thus, the prevalence of gingival overgrowth was 27.4% and it was found to be higher in males as compared to females. The prevalence of gingival overgrowth was found to be related to the degree of oral hygiene and gingival inflammation.

Conclusions: From this study, it can be concluded that there exists an association between use of amlodipine and gingival overgrowth. Therefore, a closer collaboration between medical and dental clinical team is necessary for the joint management of people taking amlodipine.

Keywords: Amlodipine; drug induced gingival overgrowth; hypertension.

INTRODUCTION

Gingival overgrowth (GO) comprises any clinical condition in which an increase in size of gingiva is observed. Drug induced gingival overgrowth (DIGO) occurs as a side effect of certain drugs such as anticonvulsants, immunosuppressants, and calcium channel blockers (CCBs), the intended target organ of which is not the gingival tissue.[1] The mechanism by which these drugs induce gingival enlargement is not well understood. However, these drugs can create an imbalance in the production and degradation of collagen leading to accumulation of collagenous components in gingival connective tissue.[2] Amlodipine is a widely accepted[3] third generation calcium channel antagonist that is commonly prescribed to treat hypertension, arrhthymias, and angina.[4]

Any gingival enlargement in patients taking above drugs should be a concern for clinicians as it may affect mastication, aesthetics, and interfere with speech and oral hygiene maintenance.[5] The DIGO can be effectively managed with non-surgical periodontal therapy, substitution of the offending drug, and surgical periodontal therapy.[1]

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Even though many patients under amlodipine therapy present with GO to the dental practitioners, the prevalence of amlodipine induced gingival overgrowth is yet unknown in context of Nepal. Therefore, the purpose of this study was to evaluate the prevalence of GO in patients taking amlodipine in Nepal.

METHODS

A hospital-based analytical cross-sectional study was conducted in Periodontology and Oral Implantology Unit, Dental Outpatient Department (OPD) of National Academy of Medical Sciences (NAMS), Bir Hospital from May 2013 to December 2013. The participants in this study were selected from the patients undergoing treatment in Cardiology OPD (NAMS, Bir Hospital) and taking amlodipine.

Ethical approval was obtained from the Institutional Review Board of NAMS and written permission to conduct the study in Cardiology Unit was obtained from Unit III of Cardiology Unit, Bir Hospital. This study adheres to the tenets of the Declaration of Helsinki and Good Clinical Practice guidelines. A written informed consent was taken from each participant before beginning the study.

All patients with at least 16 natural teeth aged 35 years and above, taking amlodipine for at least a period of three months were included in this study. Patients taking any other medication besides amlodipine that can induce GO, those who had undergone periodontal therapy in the last six months, those who had taken antibiotics within past six months, those having systemic diseases such as diabetes mellitus, which can significantly affect periodontal condition, pregnant females and smokers or tobacco users in any form were excluded from this study.

Sample size was calculated by using the data from the study by Karnik et al. in 2012[6] and was determined to be 73. Convenience (non-probability) sampling was done that is those who met the inclusion criteria were included in the study.

Basic demographic information were collected in Cardiology Unit and patients with gingival overgrowth were recalled in the Dental OPD for intraoral examination. Intraoral examination was performed using a mouth mirror and a University of North Carolina-15 (UNC-15) periodontal probe. Assessment of oral hygiene was done using Plaque Index (PI) of Silness and Loe 1964.[7] Gingival inflammation was assessed by using Gingival Index (GI) of Loe and Silness 1963.[8] Scoring of gingival enlargement was done using Bokenkamp et al. index 1994.[1] All clinical examinations were performed by a single examiner.

The data were entered in SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, Ill., USA). Results were analysed using appropriate statistical methods. Chi-square test was performed for qualitative or categorical variables. Independent t-test was used for quantitative analysis.

RESULTS

Of the 73 patients examined, gingival overgrowth was seen in 20 (27.4%) patients; therefore, the prevalence of gingival overgrowth in patients taking amlodipine was 27.4%. Out of 20 patients with gingival overgrowth, 16 (80%) individuals had grade I severity and four (20%) individuals had grade II severity.

Out of the 73 participants in the study, 42 (57.5%) were males and 31 (42.5%) were females. Most of the individuals in this study were between 50 years and 60 years with minimum age of 35 years and maximum age of 82 years. The mean age of study population with gingival overgrowth was 61.25±10.31 years whereas with no gingival overgrowth was 52.57±10.71 years. Age and sex was found to be statistically significant in association with overgrowth (Table 1). However, the severity of gingival overgrowth was not statistically significant in relation to age and sex.

Three patients (4.1%) in this study were taking 10 mg of amlodipine. Fifty-five (75.34%) patients were taking 5 mg of amlodipine, and 15 (20.54%) patients were taking 2.5 mg of amlodipine (Table 2). Even though the overgrowth was present in two (66.7%) patients of those taking 10 mg amlodipine, the results were not statistically significant. Using Chi-square test, relationship was not found to be statistically significant in terms of severity of GO and the dose.

Five (6.8%) patients had taken the drug for less than six months. Six (8.2%) patients had taken the drug for 6-12 months, 40 (54.8%) had taken the drug for 1-5

Table 1: Relationship of gingival overgrowth and its severity with age and sex, n (%).

Demographic characteristics		Severity of gingival overgrowth			Without gingival overgrowth n (%)	Total n (%)	p-value
		Grade I severity n (%)	Grade II severity n (%)	p-value			
Sex	Male	12 (28.57)	4 (9.5)	0.675	26 (61.9)	42 (100)	0.017
	Female	4 (12.9)	-		27 (87.09)	31 (100)	
Age (years)	35-53	4 (16)	1 (4)	0.675	20 (80)	25 (100)	0.003
	>53	12 (24.94)	3 (6.25)		33 (68.75)	48 (100)	

Table 2: Relationship of gingival overgrowth and its severity with drug dose, n (%).

Drug dose	Severity of gingival overgrowth			Without gingival overgrowth n (%)	Total n (%)	p-value
	Grade I severity n (%)	Grade II severity n (%)	p-value			
2.5 mg	2 (13.33)	-	0.624	13 (86.67)	15 (100)	0.135
5 mg	13 (23.63)	3 (5.45)		39 (70.9)	55 (100)	
10 mg	1 (33.33)	1 (33.33)		1 (33.33)	3 (100)	

years, 17 (23.3%) had taken the drug for 6-10 years, and five (6.8%) had taken the drug for more than 10 years. Those taking the drug for less than six months had no GO. Duration of drug intake was not found to be related to the severity of gingival overgrowth (Table 3).

In this study, all patients had some degree of gingival inflammation: 31 (41.5%) had mild inflammation, whereas 42 (57.5%) had moderate inflammation. Even though gingival overgrowth was statistically significant with inflammation, its severity was not significant with degree of inflammation (Table 4).

None of the patients had excellent oral hygiene. Six (8.2%) patients had good oral hygiene and they showed no gingival overgrowth. Among 48 (65.85%) patients with fair oral hygiene, eight had gingival overgrowth and among 19 (26%) patients with poor oral hygiene, 12 had gingival overgrowth. Gingival overgrowth was statistically significant with plaque score. Comparing the severity of overgrowth between the individuals with poor and fair oral hygiene, statistical significance was not found (Table 5). However, it can be emphasised that individuals with good oral hygiene did not have gingival overgrowth.

Table 3: Relationship of gingival overgrowth and its severity with duration of drug intake, n (%).

Duration of drug intake	Severity of gingival overgrowth			p-value
	Grade I severity	Grade II severity	Total	
6-12 months	2 (100)	-	2 (100)	0.864
1-5 years	3 (75)	1 (25)	4 (100)	
6-10 years	8 (72.7)	3 (27.3)	11 (100)	
>10 years	3 (100)	-	3 (100)	

Table 4: Relationship of gingival overgrowth and its severity with inflammation.

Inflammation	Severity of gingival overgrowth			Without gingival overgrowth n (%)	Total n (%)	p-value
	Grade I severity n (%)	Grade II severity n (%)	p-value			
Mild inflammation	2 (6.4)	-	0.632	29 (93.5)	31 (100)	0.001
Moderate inflammation	14 (33.33)	4 (9.5)		24 (57.14)	42 (100)	

Table 5: Relationship of gingival overgrowth and its severity with plaque score.

Plaque score	Severity of gingival overgrowth			Without gingival overgrowth n (%)	Total n (%)	p-value
	Grade I severity n (%)	Grade II severity n (%)	p-value			
Fair	7 (14.5)	1 (2.08)	0.909	40 (83.33)	48 (100)	0.001
Poor	9 (47.3)	3 (15.7)		7 (36.8)	19 (100)	

DISCUSSION

Gingival overgrowth is one of the most important clinical features of gingival pathology. It has multifactorial aetiologies and has been frequently associated with inflammatory changes in the gingiva. Other factors related to this condition are hereditary (familial), malignancies, and those resulting from adverse effects associated with systemic administration of certain drugs.

Drug induced gingival overgrowth is a side effect associated principally with three major groups according to their therapeutic actions, namely, anticonvulsants, immunosuppressants, and calcium channel blockers. It is still unknown why drugs with such different pharmacological actions induce similar gingival changes.

Although the pharmacologic effect of each of these drugs is different and directed towards various primary target tissues, all of them seem to act similarly on a secondary target tissue, that is, the gingival connective tissue causing common clinical and histopathological findings. 'Gingival overgrowth' or 'gingival enlargement' is the preferred term for many of these medication related gingival conditions previously labeled as gingival hyperplasia or gingival hypertrophy.[9]

Clinical manifestations of gingival enlargement frequently appear within one to three months after initiation of treatment with the associated medications. It normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces. Gradually, gingival lobulations are formed that may appear inflamed or fibrotic in nature depending on the degree of local factor induced inflammation. The fibrotic enlargement is normally confined to the attached gingiva, but may extend coronally causing the extensive disfigurement of gingiva.[1]

Disfiguring gingival overgrowth triggered by these medications is not only aesthetically displeasing but also impairs nutrition and access for oral hygiene resulting in an increased susceptibility to oral infection, caries and periodontal diseases. Therefore, drug induced gingival overgrowth remains a significant problem for the dental clinicians and the periodontists.

Amlodipine is a third generation dihydropyridine calcium antagonist, which has a unique physiochemical profile characterised by near complete absorption, late peak plasma concentrations, high bioavailability and slow hepatic biodegradation. The associated slow elimination of amlodipine with resulting long duration of its action means that only a single daily dose is required that in turn results in better patient compliance.

While the mechanism of drug induced gingival overgrowth is considered to be multifactorial, the drug/cellular interaction is pivotal in the pathogenesis of this effect. Several factors like age, genetic predisposition, presence of preexisting plaque, and gingival inflammation influence the relationship between the drugs and gingival tissue.[2] Furthermore, within the group of patients that develop this unwanted effect, there appears to be variability in the extent and severity of the gingival changes.[10]

In the present study, the prevalence of gingival overgrowth was found to be 27.4% which is significantly higher than previously reported prevalence of gingival enlargement. This could be attributed to the presence of inflammation as most of the patients had poor oral hygiene. In addition, the prevalence of gingival overgrowth in this study was more in males as compared to females which is in accordance with a study by Barak et al.[11] in 1987 who reported the male predominance of gingival enlargement in 34 patients taking nifedipine. Similarly, Ellis et al.[12] 1999 reported that males were 3.3 times as likely as females to develop gingival enlargement in response to nifedipine which was also supported by studies done by Harrel et al.[13] 1995, Tavassoli et al.[14] 1998, and Ishida et al.[15] 1995.

A relationship between androgen metabolism and nifedipine influenced gingival enlargement has been proposed as a possible reason for male predominance. Since CCBs increase the conversion of testosterone to 5α dihydrotestosterone when added to gingival fibroblasts in culture. The active androgen metabolites could target sub-population of gingival fibroblasts and cause either an increase in collagen synthesis and/or a decrease in collagenase activity.[16] Progesterone, a female sex hormone, decreases glycosaminoglycan synthesis by human gingival fibroblasts in vitro. Therefore it is likely that both male and female sex hormones regulate the development of GO. However, in a cross-sectional study by Karnik et al.[6] in 2012, no significant difference in the prevalence between male and female has been reported.

The evidence of the relationship of age to nifedipine-influenced gingival enlargement is equivocal. Some reports indicate no association with age[12, 14, 17, 18] while others indicate that older individuals are more susceptible to gingival enlargement which was explained in the study of Miranda et al.[19] 2001 by the fact that older individuals had cardiovascular disease as compared to the control group. Guncu et al. has reported that age is not an applicable risk factor for the gingival overgrowth induced by CCBs since the use of these drugs is usually confined to the middle aged and older adults.[20]

A certain threshold concentration of the drug or its metabolite is necessary to activate gingival fibroblasts as postulated by Daley et al.[21] 1986. They also suggested that increasing the levels of the drug above this threshold did not increase the severity of the lesion. Relationship with dose has been reported to be controversial by different authors. Barak et al.[11] 1987 has shown that gingival overgrowth was associated with higher doses of nifedipine but others have been unable to do so.[18, 20] This study did not show any relationship between dose and gingival overgrowth.

This study demonstrated that patients taking the drug for less than six months did not have gingival overgrowth. However, there are studies which have stated that DIGO could develop as early as two months in those responding to the drug.[18]

All the patients in this study had either mild or moderate gingival inflammation which may be related to their poor oral hygiene status. Since inflammatory changes are the most frequent cause of gingival overgrowth which could explain the high prevalence of gingival overgrowth in this study. There is considerable epidemiological evidence that plaque-induced gingival inflammation exacerbates the expression of DIGO as stated by Barclay et al.,[22] Bullon et al.,[23] and King et al.[24] With inflammation, there is increased production of inflammatory cytokines that stimulate gingival fibroblast proliferation and affect collagen metabolism of fibroblasts.[2]

Plaque induced inflammatory changes within the gingival tissues enhance the interaction between the drug and gingival fibroblasts. Fu et al.[25] in 1997 has stated plaque accumulation to be strongly associated with the occurrence of gingival overgrowth in animal model of cyclosporine A induced gingival enlargement. This finding has been supported by

the study of Thomas et al.[26] in 2000, in which they reported gingival overgrowth to be related to gingival inflammation and plaque level.

Hancock and Swan[27] reported successful treatment of hyperplasia by controlling plaque. This study showed no statistical significance between plaque and hyperplasia. Although the exact role played by bacterial plaque in DIGO is unclear, there is evidence that elimination of local factors and regular maintenance of good oral hygiene decreases the degree and severity of the gingival enlargement and improve the overall gingival health[28] as supported by Seymour et al.[2]

The association between plaque and GO raises chicken or egg first question as it is difficult to establish whether the high plaque scores observed are the causes or the consequences of DIGO. Overgrown tissue tends to aid plaque accumulation and prevents removal, thus leading to gingival inflammation.

The limitations of this study are small sample size, collection of data from a single point in time does not allow for assessment of disease activity or progression, higher prevalence of GO might be due to inflammatory component and higher prevalence in males might be due to higher enrollment of male patients. In addition, there is possibility of error in the examination of severity of GO due to intraoperator variation.

CONCLUSIONS

Thus it can be concluded that this study further adds to the evidence that amlodipine could induce gingival overgrowth. Therefore, a closer collaboration between medical and dental clinical team is necessary for the joint management of people taking amlodipine and control of drug related GO.

Conflict of interest: None.

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