DOI: https://doi.org/10.54393/pjhs.v5i06.1649

PAKISTAN JOURNAL OF HEALTH SCIENCES
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 6 (June 2024)

Original Article

Gingival Overgrowth in Patients Induced by Calcium Channel Blockers

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ARTICLE INFO

Keywords:
Cardiac Patients, Calcium Channel Blockers, Gingival Overgrowth, Amlodipine

How to Cite:
Panhwar, M. A., Unar, J., Panhwar, I., Shaikh, T. H., Bhutto, S.-U.-U., Sehito, M. A., & Kandhro, R. (2024). Gingival Overgrowth In Patients Induced By Calcium Channel Blockers: Gingival Overgrowth and Calcium Channel Blockers. Pakistan Journal of Health Sciences, 5(06). https://doi.org/10.54393/pjhs.v5i06.1649

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Received Date: 2nd May, 2024
Acceptance Date: 19th June, 2024
Published Date: 30th June, 2024

ABSTRACT

Gingival enlargement can be caused by a number of factors, including inflammatory conditions and the side effects of certain medications. Gingival overgrowth is one of the frequent features of gingival diseases. **Objectives:** To find out frequency of calcium channel blockers causing gingival overgrowth. **Methods:** A descriptive cross-sectional study was conducted among cardiac patients visiting the cardiology department at Liaquat University Hospital, Hyderabad by convenience sampling technique for a time duration of six months. SPSS version 23.0, was used for data analysis. Chi-square test was applied with a significance level of P-value <0.05. **Results:** The most commonly used calcium channel blockers were amlodipine and diltiazem at 31.3% and 26.7% respectively, while 15.6% of cases were using nifedipine, 14.4% were on verapamil and 11.9% were on calcium channel blocker drug of bepridil. The severity of gingival overgrowth was significantly correlated with the male gender (p value= 0.001). **Conclusions:** After administration of calcium channel blockers, there is a potential that adverse consequences may occur such as gingival overgrowth, will become more common by prolong use of such drugs as indicated in this study.

INTRODUCTION

An expansion of the gingiva (gums) is known as gingival enlargement. Several disorders, including inflammatory ones and the adverse effects of certain drugs, can lead to gingival expansion. This increase can be minor to exceedingly severe, localized, or generalized and it can be upsetting to the patient's look and function [1]. The term "hypertrophy" describes a rise in the size of individual cells, gingival enlargement is a more appropriate phrase to use since these identifications are not possible with a clinical examination and tissue assessment. The etiology of gingival enlargement has been divided into five broad categories: neoplastic enlargement, drug-induced enlargement, inflammatory enlargement, enlargement linked to systemic illnesses, and fake enlargement [2, 3]. Gingival hyperplasia can be caused by a variety of reasons, including medicines, periodontal variables and plaque management. Gingival enlargements are now linked to about 20 medications mostly anticonvulsants (like phenytoin), immunosuppressants (like cyclosporine A), and different calcium channel blockers (like nifedipine, verapamil, and diltiazem) [4]. Gingival enlargement is often significantly linked to dihydropyridine calcium channel

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blockers, such as nifedipine and felodipine" [5]. There are published statistics about the occurrence of Gingival Overgrowth (GO) in patients using nifedipine, even though the majority of the literature consists of case reports. Studies have shown that the incidence of this illness varies, with 20% to 83% observed for nifedipine-induced GO. Additional investigations showed that the prevalence of GO was 74%, 3.3%, and 21%, respectively, among amlodipine and verapamil calcium channel blockers diltiazem [6, 7]. Drugs known as calcium channel blockers treated heart-related disorders. Even while Calcium Channel Blockers (CCB) treatment is widely accepted in the medical world and is popular, its oral impact is rarely acknowledged or discussed. As a collective, CCBs have been repeatedly identified as a contributing component to a prevalent oral ailment observed in individuals undergoing dental cure: medication induced growth or expansion of the gingiva. There have been reports of varying prevalence rates (20% to 50%) for GO produced by CCB for nifedipine induced GO, whereas 3.3% was found for GO induced by amlodipine [8-10]. An increase in gingival mass and volume, which can be modest to severely severe, is its defining feature. The formation of an extracellular matrix in the gingival connective tissue, or CCB-induced gingivitis, usually starts within the first month of medication therapy [11]. Speech, mastication, tooth eruption, and aesthetics can all be negatively impacted by the abnormalities. These drugs frequently cause disfiguring gingival overgrowth, which makes it easier to have mouth infections, cavities, and periodontal disease [12-15].

Examining the gingival overgrowth was brought on by various calcium channel blockers that aimed for this study. It was beneficial for the knowledge of patients' cardiac practitioners regarding drugs of those calcium channel blockers that will be associated with gingival overgrowth to reduce morbidity.

METHODS

After approval of the study by the Institutional Research Ethics Committee LUMHS Jamshoro, a descriptive cross-sectional study was carried out at the cardiology department at Liaquat University Hospital Hyderabad using a non-probability convenience sampling approach during six months' duration was 1st June to 30th November 2018, (NO. LUMHS/REC/-681) dated 31-05-2018. All patients provided informed consent prior to their participation in the study. Patients visiting cardiac OPD and were using calcium blockers for more than 1 year were included in this study while pregnant women, patients with malignant disorders, and disabled persons were expelled from the study. The sample calculation was done using the Raosoft software, by using the proportion (20% of patients on calcium channel blockers are affected by gingival overgrowth) [12]. Margin of error was taken 5% and 95% confidence of interval, the sample size counted was 243. Miller and Damm classification of gingival overgrowth was used for describing the severity of gingival over growth was classified into four Categories as: Grade 0 = no gingival overgrowth, Grade 1 = mild over growth, blunting of marginal gingiva, Grade 2 = moderate overgrowth and Grade 3 = severe over growth bearing two-thirds of the tooth crown or where the whole attached gingiva affected. Based on a clinical examination, gingival overgrowth was confirmatively diagnosed. The SPSS version 23.was used for data analysis. Frequency calculations were performed for various variables and categorical factors, such as gender. The Chi-square test was applied to seek out the associations of different variables where P-value<0.05 was considered as significant.

RESULTS

Table 1 displays the participant's demographic information. Among a total of 243 participants, 159 (65.4%) were male and 84 (34.6%) were females, with ages between 40 and 60 years old where most of the subjects belonged to age 51-55 years (38.7%).

Table 1: Demographic Information of Study Subjects

Variables	(Mean ± SD) / N (%)
Mean Age	49.71 ± 5.25
Age (Years)	
40-45	60 (24.7)
46-50	55 (22.6)
51-55	94 (38.7)
56-60	34 (14.0)
Gender	
Male	159 (65.4)
Female	84 (34.6)

Patients were categorized as per duration of calcium channel blocker usage duration, most of the cases 43.6% were using it for more than 24 months, 30.5% were using calcium blockers from 19 to 24 months and 25.9% were using this medicine from 12 to 18 months as indicated in table 2.

Table 2: Duration, Type and Severity of Calcium Channel Blockers Use

Duration	N (%)
12-18 months	63 (25.9)
19-24 months	74 (30.5)
More than 24 months	106 (43.6)
Types of Calcium Channel Blockers	
Nifedipine	38 (15.6)
Amlodipine	76 (31.3)
Diltiazem	65 (26.7)
Verapamil	35 (14.4)
Bepridil	23 (11.9)

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Severity of Gingival Overgrowth	
Non/Grade 0	37 (15.2)
Mild/Grade 1	99 (40.7)
Moderate/Grade 2	78 (32.1)
Severe/Grade 3	29 (11.9)

As indicated in table 3, according to the type of the calcium channel blockers, the most commonly used calcium channel blockers were Amlodipine and Diltiazem 31.3% and 26.7% respectively, while 15.6% cases were using Nifedipine, 14.4% were on Verapamil and 11.9% were on the calcium channel blocker drug of Bepridil. As per evaluation of the severity of gingival overgrowth, the majority of the cases 40.7% and 32.1% had mild and moderate gingival overgrowth respectively, followed by 11.9% had severe gingival overgrowth and only 15.2% had no gingival overgrowth. The severity of gingival overgrowth was significantly correlated with male gender (p-value 0.001) as compared to females (p-value 0.014).

Table 3: Severity of Disease According To Drug and Gender

Calcium Channel Blocker	Severity of Disease N (%)				Total	p-Value
	Non	Mid	Moderate	Severe		
Nifedipine	28 (11.5%)	24 (9.9%)	7 (2.9%)	1 (0.4%)	60 (24.7%)	0.001
Amlodipine	5 (2.1%)	32 (13.2%)	15 (6.2%)	3 (1.2%)	55 (22.6%)	
Dilitiaem	4 (1.6%)	35 (14.4%)	44 (18.1%)	11 (4.5%)	94 (38.7%)	
Verapamil	0 (0.0%)	8 (3.3%)	12 (4.9%)	14 (5.8%)	34(14.0%)	
Bepridil	4 (1.6%)	12 (4.9%)	7 (2.9%)	6 (2.5%)	29 (11.9%)	
Gender						
Male	18 (7.4%)	60 (24.7%)	59 (24.3%)	22 (9.15%)	159 (65.4%)	0.001
Female	19 (7.8%)	39 (16.0%)	19 (7.8%)	7 (2.8%)	84 (34.6%)	0.014

DISCUSSION

A total of 243 patients of calcium channel blocker users were studied to assess the gingival hyperplasia. One of the common characteristics of gingival disorders is gingival overgrowth. However, the doctor finds it difficult to diagnose these entities because of their diverse manifestations. They can be divided into groups according to their location, size, extent, etiopathogenesis etc. According to the severity of gingival hyperplasia, the majority of the cases 40.7% and 32.1% had mild and moderate gingival hyperplasia respectively, followed by11.9% had severegingivalhyperplasiaandonly15.2% had no gingival overgrowth [16]. Since not all CCB patients have GO, it has been hypothesized that a subset of each patient's unique gingival fibroblasts may be the reason why gingival tissues are susceptible to the medications. Moreover, it was suggested that gingival fibroblasts, when subjected to the combined effects of pro-inflammatory cytokines like interleukin-1 β (IL-1β) which are higher in gingival inflammation boost the production of collagenous proteins [17]. Regarding the types of the calcium channel blockers, the most commonly used calcium channel blockers were Amlodipine and Diltiazem as 31.3% and 26.7% respectively, while 15.6% cases were using Nifedipine, 14.4% were on Verapamil and 11.9% were on the calcium channel blocker drug of Bepridil. Consistently Jayanthi R *et al.*, reported that the gingival enlargement occurred in 31% and 50% of the patients taking amlodipine [18, 10]. Increased fibroblastic proliferation and collagen synthesis result from the decreased calcium influx, which also reduces or inhibits the secretory function of the fibroblastic cells in question or collagenase production. The relationship between calcium and fibroblast may be strengthened by inflammatory alterations inside the tissue. On the other hand, Pilloni A *et al.*, reported that the among the calcium channel blocker users, 39 (67.2%) participants were on amlodipine, while 19 (32.8%) were on nifedipine [16]. Previous reports of nifedipine-induced hyperplasia have indicated the presence of an inflammatory response, indicating that strict hygiene protocols may limit the scope of the condition and slow its progression. In this study the severity of gingival overgrowth was significantly correlated with elevated age and male gender (p-0.001) and the severity of gingival overgrowth was significantly associated with the individuals, who were using calcium channel blockers from more than 24 months in contrast to less than 24 months (p-value 0.001) as indicated in table 3 While inconsistently Ganesh PR reported that no significant correlation between the length of time spent using CCBs and the incidence of Drug-Induced Gingival Overgrowth (DIGO) [19]. However, those with DIGO had a mean longer CCB usage history (63.2 ± 69.2) compared to those without DIGO (51.341.2) (P-value 0.416). It has been suggested that the presence of a subpopulation of gingival fibroblasts that are specific to each individual may be related to the gingival tissues' sensitivity to these CCB medications. Vidal F *et al.*, maintaining good dental health and receiving frequent professional prophylaxis are essential for maintaining the gingival tissue in patients with gingival overgrowth in a healthy state [20]. Similarly, Ganesh, P.R *et al.*, suggested that without altering the medications that cause gingival hyper growth, traditional periodontal therapy can produce acceptable clinical results [19]. After analyzing the course of therapy, which included scaling and root planning while under local anesthesia, elimination of any leftover pockets surgically and the installation of bridges to create a good occlusion, he came to this conclusion. Vidal F *et al.*, also mentioned the strong evidence supporting the appropriate management of gingival overgrowth brought on by phenytoin and calcium channel blockers by strict professional and personal dental care [20]. Dentists should be ready to treat patients with gingival overgrowth by focusing on patient education and periodontal care as well as preventative treatment. The damaged gingiva has an uneven and bulbous look, necessitating significant adjustments in the way oral hygiene treatments are provided. Due to the strong link between gingival overgrowth and plaque/gingivitis, dentists are essential in

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the prevention and management of this illness.

CONCLUSIONS

The study found that 43.6% of participants had been using calcium channel blockers, most common of which were Amlodipine (31.3%) and Diltiazem (26.7%). In terms of gingival overgrowth severity, 72.8% of participants experienced mild (40.7%) to moderate (32.1%) overgrowth, while 11.9% had severe overgrowth. Drug induced gingival enlargement is a multifactorial condition, and its risk factors can be grouped as systemic, genetic, drug and local.

Authors Contribution

Conceptualization: RK
Methodology: MAP
Formal analysis: JU
Writing, review and editing: JU, THS, SUUB, MAS, IP, RK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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