

Prevalence of Gingival Hyperplasia induced by Calcium Channel Blockers (CCBs) – Pharmacist Perspective

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ABSTRACT: Background: Calcium channel blockers are widely prescribed for hypertension are associated with high incidence of gingival hyperplasia. Identifying and understanding the prevalence of gingival hyperplasia can be guided by the health care professionals to make decisions on treatment to potential side effect, thereby improving patient treatment outcomes. Aim: This study is aimed to assess the Incidence of CCB induced gingival hyperplasia in hypertensive patients. Results: CCB treatment about 58% were males and 42 % were females, whereas in non-CCB treatment group 71.02% and 28.98 % were males and females respectively. From this 60% of patients experienced gingival hyperplasia with Nifedipine in an average dose of 110 ± 75.4 mg and duration of 18.5 ± 8.75 months followed by 33.33% of patients with amlodipine in a dose of 7.5 ± 3.53 mg and duration of 25.3 ± 4.76 months. Average dose and duration of antihypertensive drugs other than CCB, that induced Gingival hyperplasia among 4 patients. Propranolol (30%) and Metoprolol (6.66%) were the common drugs associated with Gingival hyperplasia among which propranolol in dose of 10.15 ± 5.25 mg with duration of 17.5 ± 0.70 . Conclusion: The present study concludes that calcium channel blockers, particularly Nifedipine and Amlodipine, exhibit a higher propensity for causing gingival hyperplasia when compared to other Antihypertensive drugs.

KEYWORDS: Calcium channel blockers; Gingival hyperplasia; Gingival overgrowth; Amlodipine

I. INTRODUCTION

The term "GINGIVAL OVERGROWTH" represents the histological gum enlargement diagnosis and has many possible causes. The

extracellular matrix collagenous components which build within the gingival connective tissue leads to Gingival Overgrowth [1 2]. One of the most frequent offender is drug use, their effect has been linked to a patient underlying genetic makeup [3]. This disorder impairs aesthetic, mastication, speaking, and oral hygiene practices, causing periodontal disease to worsen [4]. Hormonal changes, such as those associated with pregnancy and puberty, might increase this gingival growth [5].

Based on the etiological factors and pathological changes, the Gingival enlargement is classified as a) Inflammatory enlargement, b) Drug-induced enlargement, c) Enlargement associated with disease condition, d) Neoplastic enlargement, e) false enlargement.[6].

There are many drugs which cause drug induced gingival hyperplasia in which three class of drugs (immunosuppressive drugs, anticonvulsant and anti- hypertensive drugs) are more associated with gingival overgrowth [3]. Drug induced gingival hyperplasia is a frequent side effect of immunosuppressants, calcium channel blockers, with ranging from 13% to 50% [7]. The calcium channel blockers show exhilarated response by the gingival tissues to various changes between the host and environment [8,9].

Different prevalence has been noted for the illness; those for nifedipine-induced GO range from 20% to 83%, [10]. Additional research showed that the prevalence of GO was 74%,3.3%, and 21% respectively, in connection to other calcium channel blockers such diltiazem, amlodipine, and verapamil [10,11] Although the pathogenesis of GO –Induced by calcium channel blockers is unclear, It has shown that drug factors (dosage and duration),age, sex,

oral hygiene, genetics, and pre-existing gingival inflammation affect DIGO [12].

Patients who are at risk of developing DIGE or who have the condition need close dental care, there both surgical and non-surgical options

II. MATERIALS AND METHODS:

2.1. Materials

A separate data collection form and ADR assessment scale (Naranjo scale) is used to record patient details and adverse effects (Patient case history, Diagnosis, Medication order sheets, Interviewer-administered questionnaires, visual observation and Gingival index) were recorded.

The Gingival index criteria used is summarized as follows:

Grade 0: Absence of inflammation or normal gingival

Grade 1: Mild inflammation: slight change in colour, slight edema; no bleeding on probing

Grade 2: Moderate inflammation: moderate glazing, redness, edema and hypertrophy, bleeding on probing

Grade 3: Severe inflammation: marked redness and hypertrophy, ulceration, tendency to spontaneous bleeding

2.2 Methods:

This was a Prospective observational study conducted among 214 hypertensive patients (107 CCB and 107 with other antihypertensive drugs using hypertensive patients visiting in and outpatient department of cardiology in Sudha Institute of Medical Science, Erode, Tamil Nadu. Data were analysed Chi-square test was used to compare the study groups and Linear regression statistics were carried out to analyse the incidence of CCB and NON-CCB induced gingival hyperplasia with association of average use (in months) and average dose (in mg/day) of antihypertensive drugs.

used in DIGE management strategies [13], the most successful treatment for drug-related gingival hyperplasia is medication withdrawal or substitution. [13-15]

III. RESULTS AND DISCUSSION:

Table 1 showed the study population were grouped into two, based on the treatment options i.e., hypertensive patients who were on calcium channel blockers treatment and hypertensive patients who were on other antihypertensive drug therapy. Among the patients who were on CCB treatment about 58% and 42% were males and females respectively, whereas in non-CCB treatment group 71.02% were males and 28.98% were females. It was observed that male patients were tend to be higher in both the study groups which can be attributable to lifestyle changes, occupational stress and comorbid conditions among the such participants (Fig.1a). It also indicated the age wise distribution of patients among two groups, and it was found that 61.68% were in the age group of 55-75 years followed by age group of 45-55 years 17.75% among ccb treatment group and non ccb treatment group 65.40% were in the age group of 55-75 years followed by 19.63% of patients the age group of 45-55 years (Fig 1b). Similar study reported by supratim datta et al.,(2017). The prospective, cross sectional observational study was conducted in the Department of Medicine, Kasturba Medical College and Hospital, Manipal, Karnataka showed that utilization pattern of antihypertensive drugs on the basis of gender. CCBs and ACE inhibitors/ARBs were prescribed mostly in males and beta blockers mostly prescribed in females and on the basis of age showed that the mean age group of male patients is 56.5 ± 15.9 which is higher than mean age group of female patients is 53 ± 19.3 . CCBs and beta blockers mostly used in the age group of 18-64 years than in patients greater than 65 years and also ACE inhibitors and diuretics mostly used in the age group of greater than 65 years than 18 – 64 yrs. which is similar to our study. [16]

Figure 1a: Gender wise distribution of patients on CCB (n=107) and patients on other antihypertensive drugs (n=107).

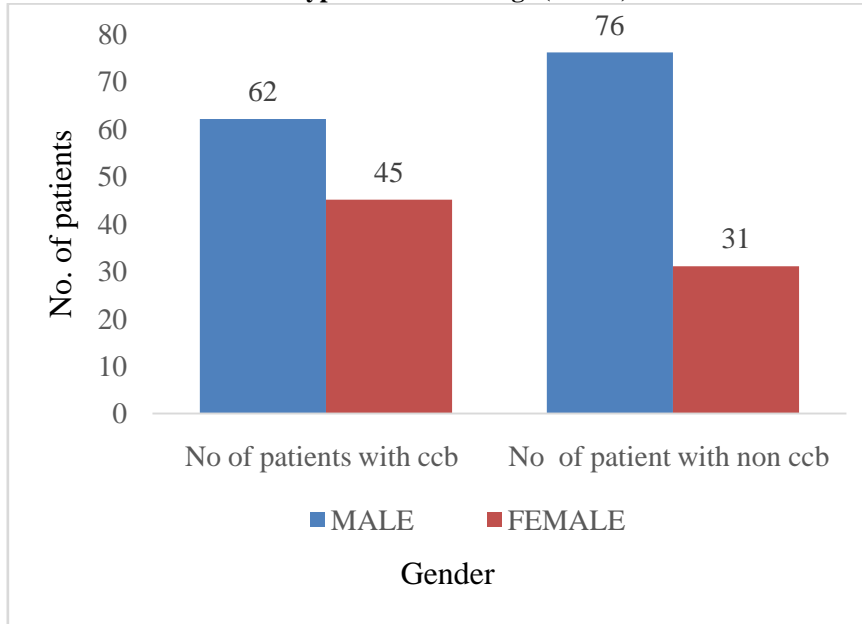


Figure 1b: Age wise distribution of patients on CCB (n=107) and patients on other antihypertensive drugs (n=107).

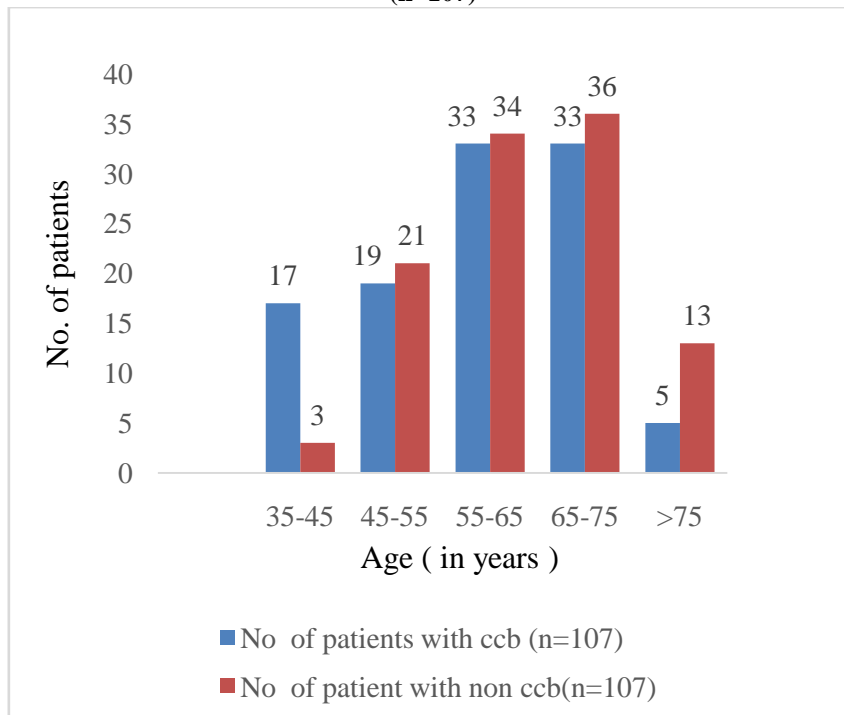


TABLE 1a: GENDER WISE DISTRIBUTION OF PATIENTS ON CCB (n=107) AND PATIENTS ON OTHER ANTIHYPERTENSIVE DRUGS (n=107)

Gender	No of patients with CCB	Percentage (%)	No of patient with non CCB	Percentage (%)	P Value
MALE	62	58	76	71.02	<0.001
FEMALE	45	42	31	28.98	
TOTAL	107	100	107	100.00	

TABLE 1b: AGE WISE DISTRIBUTION OF PATIENTS ON CCB (n=107) AND PATIENTS ON OTHER ANTIHYPERTENSIVE DRUGS (n=107)

Age(in years)	No of patients with CCB	Percentage (%)	No of patient with non CCB	Percentage (%)	P Value
35-45	17	15.88	3	2.81	<0.001
45-55	19	17.75	21	19.63	
55-65	33	30.84	34	31.76	
65-75	33	30.84	36	33.65	
>75	5	5	13	12.15	
TOTAL	107	100.00	107	100.00	

Table 2 showed the list of the patients based on the treatment that they receiving for hypertension. It was found that calcium channel blockers (49.89%), beta blockers (25.61%) and ACE inhibitors (21.01%) were the common drug classifications employed for the treatment for the patients. CCBs were the common class of drugs used in the treatment of hypertension in which amlodipine (24.29%) was highly prescribed followed by nifedipine (15.80%), clinidipine (7%)

and verapamil (2.80%) (Fig.2). The study conducted by, supratim datta et al. (2017). The Prospective, Cross sectional observational study was conducted in the department of pharmacology and medicines, kasturba medical college and hospital, Manipal, Karnataka showed that Mostly 72.3% of CCBs drugs prescribed by hypertensive patients followed by 34.9% of ACE inhibitors /ARBs and 31.1% of beta blockers which is similar to our study. [16]

Figure 2: Distribution of patients (n=214) with percentage who were prescribed with antihypertensive drugs

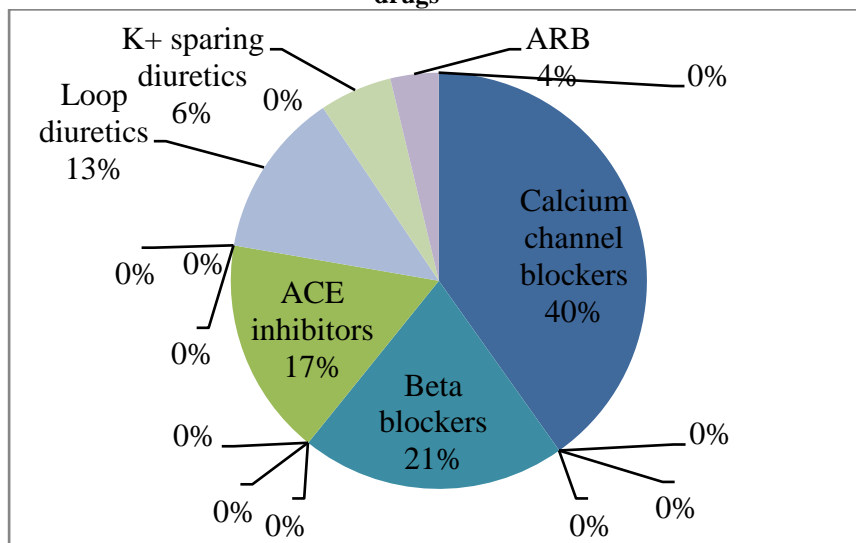


TABLE 2: DISTRIBUTION OF PATIENTS (n=214) WHO WERE PRESCRIBED WITH ANTIHYPERTENSIVE DRUGS

Class of antihypertensive drugs	Drugs	No of patients based on their use of drugs	Percentage of patients (%)	Total no of patients for each class of drug use (%)
Calcium channel blockers	Amlodipine	52	24.29	49.89
	Clinidipine	15	7	
	Nifedipine	34	15.80	
	Verapamil	6	2.80	
Beta blockers	Propranolol	13	6	25.61
	Carvedilol	15	7	
	Metoprolol	25	11.68	
	Atenolol	2	0.93	
ACE inhibitors	Enalapril	16	7.47	21.01
	Ramipril	22	10.28	
	Lisinopril	3	1.40	
	Captopril	4	1.86	
Loop diuretics	Torsemide	15	7	16
	Furosemide	20	9.34	
Potassium sparing diuretics	Spironolactone	15	7.00	7.00
ARB	Olmesartan	2	0.93	4.66
	Telmisartan	8	3.73	
TOTAL		265	124.51	124.17

Table 3 indicated the prevalence of gingival hyperplasia among two study groups. It was found that 29.90% of patients among CCB treatment group were experienced GH, whereas in non CCB treatment group 9.34% of patients were experienced gingival hyperplasia. It showed that, CCB treatment group is more prone to gingival hyperplasia when compared with NON-CCB treatment group(Fig.3). Similar study conducted by, Kehinde Adesola et al., (2017) There was a significant correlation between drug-induced

gingival overgrowth and the type of antihypertensive medication used, according to a hospital-based, cross-sectional study that was approved by the health research and ethics committee of the Lagos University Teaching Hospital in Nigeria. Participants on CCB had a higher prevalence of drug-induced gingival overgrowth (DIGO) (36.2%) than those who were not on CCB (17.2%). which is similar to our present study.[5]

Figure 3: Distribution of gingival hyperplasia among study participants

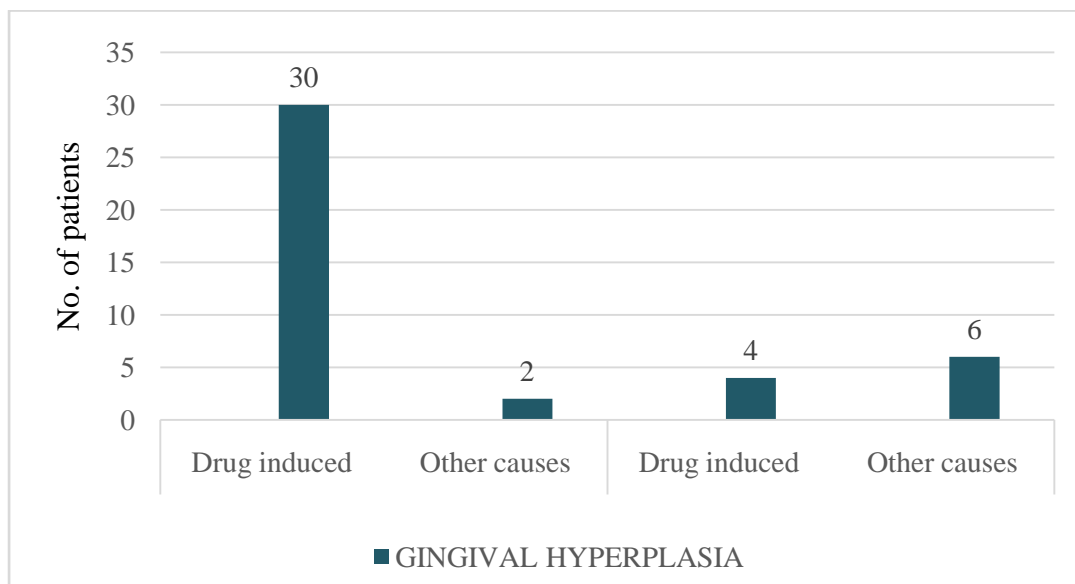


TABLE 3: DISTRIBUTION OF GINGIVAL HYPERPLASIA AMONG STUDY PARTICIPANTS (n=214)

Adverse reaction	Patients with CCB (n=107)		Percentage (%)	Patient with other antihypertensive drugs(n=107)		Percentage (%)
	Drug induced	Other causes		Drug induced	Other causes	
GINGIVAL HYPERPLASIA	30	2	29.9	4	6	9.34

Table 4 explained the clinical characteristics of gingival hyperplasia among study groups. Out of 32 patients who were on CCB treatment, experienced almost all the characteristics symptoms of gingival hyperplasia, including pain (93.3%), red gums (90%), plaque buildup (90%), bad breath (86.6%) and bleeding gums (86.6%). The patients in the non-ccb treatment group with gingival hyperplasia, also experienced symptoms of pain (40%), bad breath (40%), red gums (30%), plaque buildup (30%) and bleeding gums (20%). It

showed that CCB group who were more prone to gingival hyperplasia are more associated with symptoms of G.H compared to NON-CCB treatment group (Fig.4). The hypertensive patient who were taking CCB experienced GH symptoms highly (p value <0.001-significant) when compared with patients who were on other antihypertensive drugs. The significant difference among were two group analysed by using chi-square test.

Figure 4: Clinical characteristics of patients who were taking CCB and other antihypertensive drugs

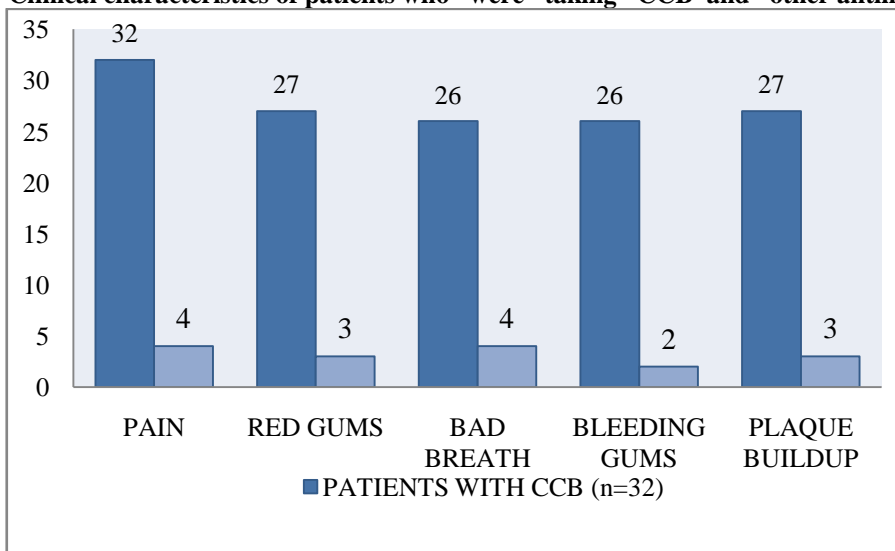


TABLE 4: CLINICAL CHARACTERISTICS OF PATIENTS WHO WERE TAKING CCB AND OTHER ANTIHYPERTENSIVE DRUGS

Clinical characteristics	Patients with ccb (n=32)	Percentage (%)	Patients with other antihypertensive drugs(n=10)	Percentage(%)	P Value
PAIN	32	100	4	40	<0.001
RED GUMS	27	90	3	30	
BAD BREATH	26	86.6	4	40	
BLEEDING GUMS	26	86.6	2	20	
PLAQUE BUILDUP	27	90	3	30	

*P value <0.05 which is considered to be significant

Table 5 distributed patients of two study groups on severity level of gingival hyperplasia based on gingival index, It was found that, in CCB treatment group 76.6% of patients were assessed with severe inflammation, followed by 73.3% of patients were assessed with moderate inflammation, 63.3% of patients were assessed with mid inflammation and 43.3% of patients were assessed with normal gingival. In non ccb treatment group, It was found that 80% of patients were assessed with severe inflammation, followed by 90% of patients were assessed with moderate inflammation, 100% of patients were assessed with mild inflammation and normal gingival. When

assessing severity with gingival index, It was observed that patients in ccb treatment group were severely affected when compared with patients in non – ccb treatment group (Fig.5). Compared to other study conducted by, Muhammad annuridin sabaruddin et al., (2021) At the outpatient clinic of the Hospital University Sains Malaysia (USM), a cross-sectional study involving hypertensive patients who had been taking anti-hypertensive medications for at least six months was carried out. Despite of them, being in low severity (grade 1), ccb-induced gingival overgrowth appeared to be rather common in those patients taking the drug. this study is contrasted with our study.[4]

Figure 5: Severity assessment of gingival hyperplasia among patients on ccb and patients on other antihypertensive drugs

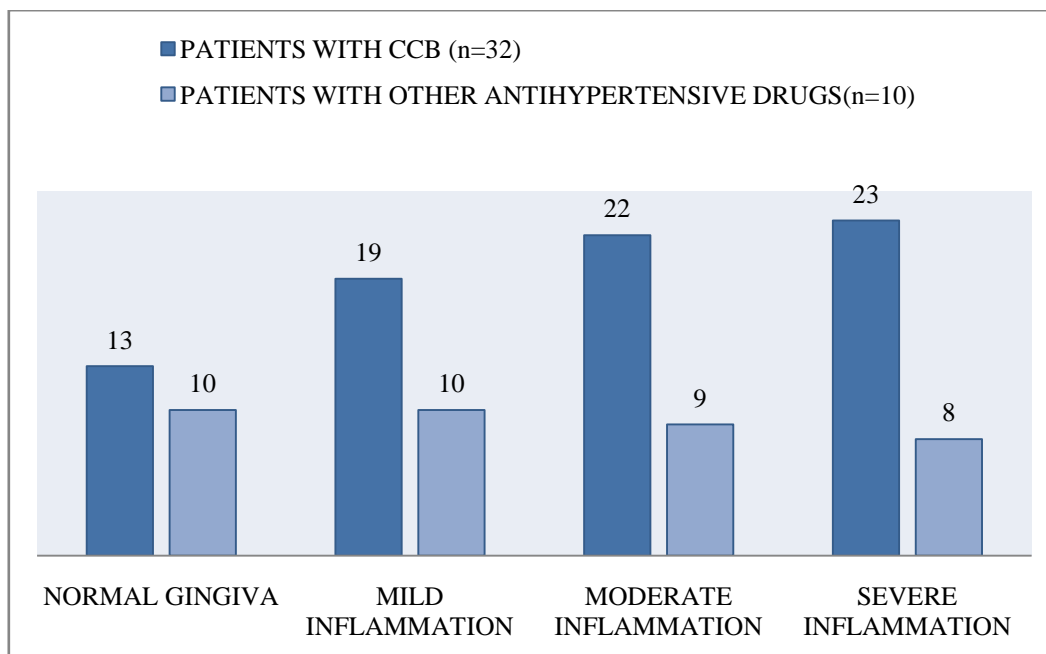


TABLE 5: SEVERITY ASSESSMENT OF GINGIVAL HYPERPLASIA AMONG PATIENTS ON CCB AND PATIENTS ON OTHER ANTIHYPERTENSIVE DRUGS

Severity assessment of G.H	Patients with ccb (n=32)	Percentage(%)	Patients with other antihypertensive drugs(n=10)	Percentage(%)	P Value
Normal gingiva	13	43.3	10	100	<0.001
Mild inflammation	19	63.3	10	100	
Moderate inflammation	22	73.3	9	90	
Severe inflammation	23	76.6	8	80	
TOTAL	77	256.5	37	370	

*P value <0.05 which is considered to be significant

Table 6 analysed the average duration and dose of CCBs among patients experienced gingival hyperplasia. Out of 30 patients 60 % of patients experienced gingival hyperplasia with Nifedipine in a average dose of 110 ± 75.4 mg for a average duration of 18.5 ± 8.75 months followed by 33.33% of patients with amlodipine in a dose of 7.5 ± 3.53 mg for average duration of 25.3 ± 4.76 months. It was clear that most of the experienced Gingival hyperplasia in long term treatment with CCB includes Nifedipine, Amlodipine, Clinidipine and Verapamil. (Fig.6). Similar study conducted by

, kishore kumar katuri et al., In the department of periodontics at the Sibar Institute of Dental Sciences in Guntur, Andhra Pradesh, India, a cross-sectional study was conducted. The study, which was done between September 2020 and February 2020, revealed that it measured the degree of gingival overgrowth in individuals with hypertension who were taking 3 different ccbs (nifedipine, amlodipine, and felodipine). Patient on nifedipine and amlodipine had higher rates of gingival overgrowth than those receiving felodipine. which is similar to our study. [2]

Figure 6: Average use and dose of CCB among study participants who were affected with gingival hyperplasia(n=30)

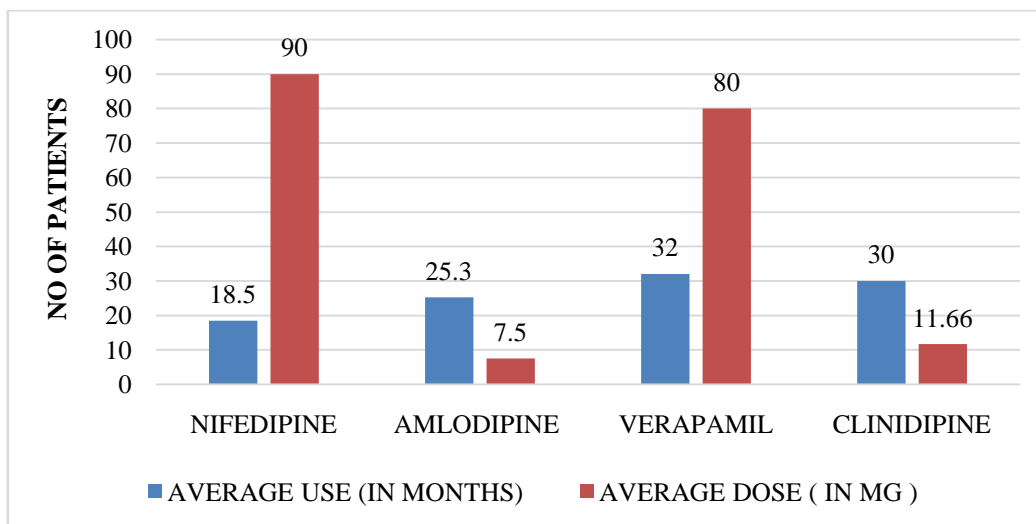


TABLE 6: AVERAGE USE AND DOSE OF CCB AMONG STUDY PARTICIPANTS WHO WERE AFFECTED WITH GINGIVAL HYPERPLASIA(n=30)

SUSPECTED DRUG	CALCIUM CHANNEL BLOCKERS				NO OF PATIENTS(n=30)	PERCENTAGE(%)
	AVERAGE USE±S.D (IN MONTHS)	P value	AVERAGE DOSE ±S.D (IN MG)	P value		
NIFEDIPINE	18.5±8.75	<0.003	90±75.4	<0.054	18	60
AMLODIPINE	25.3±4.76		7.5±3.53		10	33.33
VERAPAMIL	32±0		80±40		1	3.33
CLINIDIPINE	30±0		11.66±7.63		1	3.33
			TOTAL			30

Table 7 explained average dose and duration of antihypertensive drugs other than CCB, that induced Gingival hyperplasia among 4 patients. Propranolol (30%) and Metoprolol (6.66%) were the common drugs associated with Gingival hyperplasia among which propranolol in dose of 10.15 ± 5.25 mg with duration of 17.5 ± 0.70 . Metoprolol was highly induced Gingival Hyperplasia compared with Propranolol. It was

indicated that Beta blocker also induced Gingival hyperplasia in patients when compared to other antihypertensive drug classes, other than CCB(Fig.7). The study conducted by, Saumiya gopal et al., (2015) showed that 4 patients who were taking combination therapy of amlodipine and metoprolol, out of them one presented with gingival overgrowth which is similar to our study. [17]

Figure 7: Average use and dose of other antihypertensive drug among study participants who were affected with gingival hyperplasia

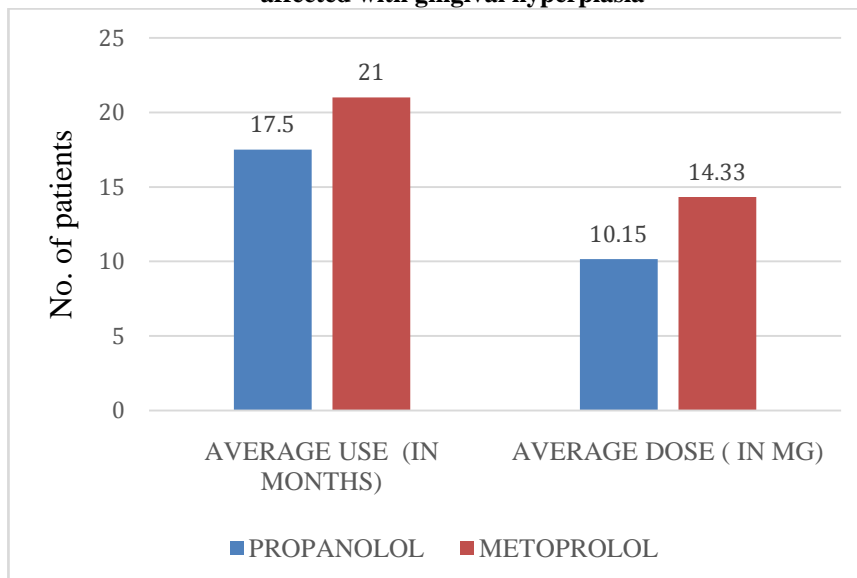


TABLE 7: AVERAGE USE AND DOSE OF OTHER ANTIHYPERTENSIVE DRUG AMONG STUDY PARTICIPANTS WHO WERE AFFECTED WITH GINGIVAL HYPERPLASIA (n=10)

SUSPECTED DRUG	NON CCB DRUGS				NO OF PATIENT S(n=10)	PERCENT AGE (%)
	AVERAGE USE ± S.D (IN MONTHS)	P value	AVERAGE DOSE±S.D (IN MG)	P value		
PROPRANOLOL	17.5±0.70	<0.545	10.15±5.25	<0.043	2	30%
METOPROLOL	21±8.48		14.33±5.01		2	6.66%
			TOTAL			4

Table 8&9, analysed the study groups for causality assessment by employing Naranjo scale (ADR probability scale) includes questions to evaluate the dose response relationship between the drug and adverse event. In patients on CCB treatment (n=30), when employing causality assessment, it was found that, All the drugs have a probable time relationship with drug intake and reaction occurrence. Among the causality assessment with Naranjo score of 7 was identified

among patients prescribed with nifedipine and amlodipine which is followed by Naranjo score of 6 for clindipine and verapamil prescribed patients (Fig.8). In patients on NON-CCB treatment (n=10), propranolol have a Naranjo score of 6 which belongs to probable time relationship with drug intake and reaction occurrence whereas metoprolol have a Naranjo score of 2 which belongs to possible time relationship with drug intake and reaction occurrence(Fig.9).

Figure 8: causality assessment of CCB drugs with Naranjo scale among patients on CCB treatment

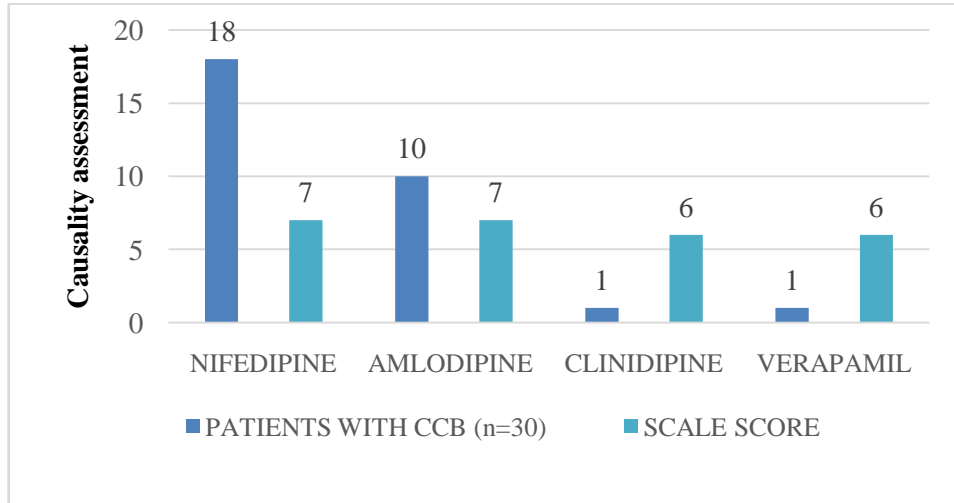


TABLE 8: CAUSALITY ASSESSMENT OF CCB DRUGS WITH NARANJO SCALE AMONG PATIENTS ON CCB TREATMENT

Suspected drug	Patients with ccb (n=30)	Scale score	Causality assessment
NIFEDIPINE	18	7	PROBABLE
AMLODIPINE	10	7	PROBABLE
CLINIDIPINE	1	6	PROBABLE
VERAPAMIL	1	6	PROBABLE

Figure 9: Causality assessment of non CCB drugs with Naranjo scale among patients on other antihypertensive drugs treatment

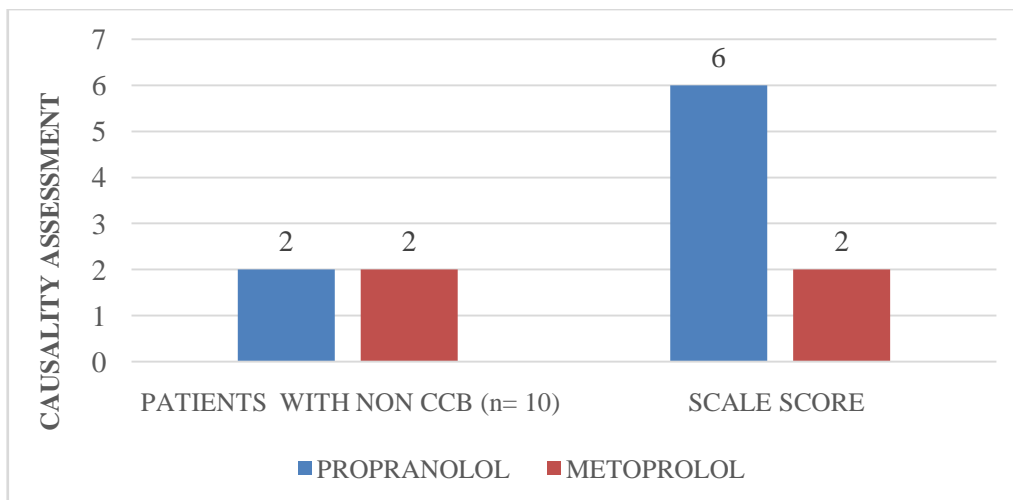


TABLE 9: CAUSALITY ASSESSMENT OF NON CCB DRUGS WITH NARANJO SCALE AMONG PATIENTS ON OTHER ANTIHYPERTENSIVE DRUGS TREATMENT

Other antihypertensive drugs	Patients with non ccb (n= 10)	Scale score	Causality assessment
PROPRANOLOL	2	6	PROBABLE
METOPROLOL	2	2	POSSIBLE

IV. CONCLUSION

The present study concludes that calcium channel blockers, particularly Nifedipine and Amlodipine, exhibit a higher propensity for causing gingival hyperplasia when compared to other Antihypertensive drugs. Notably, Gingival hyperplasia induced by CCB appeared dose-independent and was prominently observed with long-term therapy, whereas the other antihypertensive drugs (Propranolol and Metoprolol) induce a dose-dependent GH reaction irrespective of treatment duration. Crucially, the distressing symptoms of GH would significantly undermine treatment adherence among study patients. This underscores the need for proactive measures, including professional counselling on dental hygiene, advice on regular dental examinations, and implementing management strategies along with all other healthcare professionals.

Future recommendations

Research on evaluating the impact counselling on drug use and gingival hyperplasia among the same study participants. By adding warning label to the tablets.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES:

- [1]. Soroye Modupeoluwa Omotunde and Sorunke Modupeore Eku. Gingival overgrowth and associated factors in a population of Nigerian hypertensives. World Journal of Advanced Research and Reviews 2021;12(3):164-174.
- [2]. Ajay chouksey, Nitin Awasthi, Jayesh Rai, Abhishek Chaudhary. Association of drug- induced gingival enlargement (calcium channel blockers) and local factors: Who is the culprit? International dental and medical, Journal of Advanced Research 2017; 3:1-4.
- [3]. Dorina Lauritano, Marcella Martinelli, Alessandro Baj, et al. Drug- induced Gingival Hyperplasia: An in vitro study using amlodipine and human gingival fibroblasts. Int J Immunopathol Pharmacol 2019; 33:1-7.
- [4]. Haslina Taib, Muhammad Huziq Mohd Radzwan, Muhammad Annuridin Sabaruddin, Wan Majdiah Wan Mohamad and Noraini Mohamad. Prevalence and risk factors of drug induced gingival overgrowth in hypertensive patients. J Dent Indones 2021;28(1):8-14.
- [5]. NW Savage and CG Daly. Gingival enlargements and localized gingival overgrowths. Aust Dent J 2010;55(1):55-60.
- [6]. Book reference: Newman MG, Carranza FA, Perry R et al. Carranza's Clinical Periodontology, 10th edition. Saunders Elsevier 2006-7 :741-777.
- [7]. Moreo G, lauritano D, Limongelli L et al. Drug – induced Gingival overgrowth: A pilot study on the effect of diphenylhydantoin and gabapentin on human gingival fibroblasts. Int J Environ Res Public Health 2020;17(21):8229.
- [8]. Seiji Nishikawa, Hiroko Tada, Akihiro Hamasaki et al. Nifedipine induced gingival hyperplasia: A clinical and in vitro study. J Periodontol 1991;62(1):30-35.
- [9]. Kaur G, Verhamme KM, Dieleman JP et al. Association between calcium channel

- blockers and gingival hyperplasia. *J Clin Periodontol* 2010;37(7):625-30.
- [10]. JS.Ellis, RA Seymour, JG.Steele et al. Prevalence of gingival overgrowth induced by calcium channel blockers: A community- based study. *J Periodontol* 1999;70(1):63-67.
- [11]. RA Seymour, JS Ellis, JM Thomason, Monkman S and Idle JR. Amlodipine induced gingival overgrowth. *J Clin Periodontol* 1994;21(4):281-283.
- [12]. Wetende Andrew, Wagaiyu Evelyn, Macigo Francis, Joshi Mark and Chindia Mark. Pattern of gingival overgrowth among patients on antihypertensive pharmacotherapy at a Nairobi hospital in Kenya. *Open Journal of Stomatology* 2014; 4:169-173.
- [13]. R.Jayanthi, A.Mohammed Kalifa, B.M.Archana, Sindhiya Jayachandran and Flaicy Varghesse. Prevalence and severity of amlodipine induced gingival overgrowth. *International Journal of Contemporary Medical Research* 2017;4(2):377-379.
- [14]. Muhammad Annuridin Sabarudin, Haslina Taib and Wan Mohamed W. Refining the mechanism of drug-influenced gingival enlargement and its management. *Cureus* 2022; 14(5): e25009.
- [15]. Pundir AJ, Pundir S, Yeltiwar RK et al. Treatment of drug-induced gingival overgrowth by full-mouth disinfection: A non-surgical approach. *J Indian Soc Periodontol* 2014;18(3):311-5.
- [16]. Supratim Datta. Utilization study of Antihypertensives in a South Indian Tertiary Care Teaching Hospital and Adherence to Standard Treatment Guidelines. *J Basic Clin Pharma* 2017; 8:33-7.
- [17]. Saumiya Gopal, Rosamma Joseph, Shiny Joseph et al. Prevalence of gingival Overgrowth induced by antihypertensive drugs: A hospital – based study. *J Indian Soc Periodontol* 2015; 9(3):308-311.