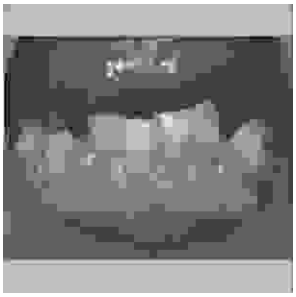
ORIGINAL PROF-982

GINGIVAL HYPERPLASIA;
DURING VERAPAMIL THERAPY IN HYPERTENSIVE PATIENTS.



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ABSTRACT... dr_mnwr@yahoo.com **Objective:** Calcium ion plays an important role in gingival hyperplasia due to its effects on hemostatic balance of epithelial differentiation and apoptosis. It is hypothesized that non inflamed gingival fibroblasts are less active and do not respond to circulating drugs. While the fibroblasts within inflamed tissue are in an active state. Hence a study was conducted to investigate and assess the relationship between oral hygiene and severity of gingival hyperplasia in hypertensive patients receiving verapamil. **Design of study :** In the present comparative investigation, clinical periodontal parameters were determined. **Material & Methods:** Thirty hypertensive patients who were taking verapamil 240 mg/day in divided doses selected randomly. Subjects were divided in to HEL groups. A gingival enlargement score was assessed for each patient by using hyper plastic index, while using plaque index assessed the oral hygiene status. **Results:** There were highly significant differences between test groups E and L, when they were compared with group H (Healthy group). Mean plaque index and hyper plastic index varied between test groups H, E and L. The differences showed statistical high significance. **Conclusions:** Oral hygiene plays a decisive role in the development of gingival hyperplasia and the incidence can be controlled successfully by meticulous professional and individual oral hygiene.

Key words: Gingival hyperplasia, verapamil, and calcium channel blockers.

INTRODUCTION

Gingival hyperplasia secondary to drugs was first reported in the early 1960s in institutionalized epileptic patients who were receiving therapy with phenytoin for the treatment of seizers[1,2]. Recently numerous calcium channel blocker agents especially verapamil have been associated with gingival hyperplasia, when used in hypertensive patients[3,4].

Verapamil is frequently prescribed to hypertensive patients and thus an additive effect on the gingival tissues is usually observed. It is known that calcium

channel blocker verapamil inhibit Ca^{+2} uptake on gingival fibroblasts that correlates with the rate of fibroblast proliferation. There is also evidence that verapamil inhibits both adherence and lipopolysacchride stimulated macrophage induced death of fibroblasts, which results in gingival overgrowth[5]. Several mechanisms have been suggested for drug induced gingival hyperplasia. Inhibition of apoptosis and resultant epithelial hyperplasia has been reported[6].

The epithelium consists of keratinocytes, which emerge from the proliferation compartment in the basal cell layer and move upward through various layers of the stratified squamous epithelium, progressively under going differentiation, then finally cell death[7,8]. To maintain the normal architecture of gingival epithelium, the serial events of growth, differentiation, and death are strictly modulated. This homeostatic balance undoubtedly involves integration of epithelial differentiation and apoptosis. The mode of cell death at the end of differentiation of the gingival epithelium is apoptosis. Apoptosis plays an important role in the control of tissue overgrowth, and suppression of apoptosis may lead to an increase in the growth rate of gingival tissue[9,10.11].

Nuclear and cytoplasmic condensation, membrane budding, formation of apoptotic bodies, and non-random fragmentation of DNA characterize apoptosis. The importance of Ca^{2+} signals for triggering apoptosis has been demonstrated in many experimental systems. A sustained elevation of Ca^{2+} can activate degradative enzymes such as Ca^{2+} dependent protease like calpain and endonucleases responsible for DNA fragmentation. Apoptosis in gingival keratinocytes is inhibited under low Ca^{2+} culture conditions so the calcium channel blockers like verapamil are reported to inhibit apoptosis[12,13].

Because not all patients on verapamil develop gingival hyperplasia, identifying patients at risk is important in order to take the necessary measures to minimize the onset and severity of this condition.

It is hypothesized that non-inflamed gingival fibroblasts are less active or even quiescent and do not respond to circulating drugs. While the fibroblasts within inflamed tissue are in an active state as a result of inflammatory mediators and endogenous growth factors[14,15]. Hence a study was conducted to investigate and assess the relationship between oral hygiene and severity of gingival hyperplasia in hypertensive patients receiving verapamil.

MATERIAL AND METHODS

A total of thirty (30) hypertensive out patients of either sex, with their ages between 35-50 years and possessed their six (6) upper and six (6) lower anterior teeth were selected randomly from different cardiac care clinics and enrolled for the study. All patients were examined to assess the periodontal status of their upper and lower teeth. All individuals gave informed consent to participate in the study. All the patients were excluded who were taking anticonvulsants, immunosuppressants or any other medication known to produce gingival enlargement. Clinical examinations were conducted under standardized illumination with plain dental mirror and a periodontal probe. The patients received calcium channel blocker verapamil 80 mg three times a day, at least since six months or longer and were divided in to three groups according to HEL scoring criteria (Table-I). Gingival healthy group (H-Group) made up of those scoring +2 (Excellent) or +1 (Good), Equivocal group (E- Group) made up of those patients scoring (0) and a Less healthy group (L- group) made up of those scoring –2 (very poor) or –1 (poor)[6].

Table-I. HEL Scoring Criteria

Grade	Criteria
+2	Normal gingiva with no plaque or calculus
+1	Clean appearance, good oral hygiene and slight localized inflammatory changes
0	Questionable appearance, difficult to assess a ± score
-1	Poor appearance and oral hygiene, overt gingivitis
-2	Extremely poor appearance & oral hygiene, sever gingivitis
+2=Excellent, +1=Good. 0=Equivocal, -1=Poor, -2=Very poor	

The labial, lingual and inter-proximal surfaces of the 12 anterior teeth were scored according to plaque index

(Table-II)[11]. The degree of gingival enlargement was assessed by using a hyperplastic index, that is comprised of two components, which measures independently the vertical and a horizontal extension of gingival enlargement (Table-III)[4].

Table-II. Plaque Index	
Grade	**Criteria**
0	Neither supra-gingival nor sub-gingival calculus found
1	Calculus obviously present in contact with the gingival margins or detected on probing of sulcus

Table-III. Hyperplastic Index (Vertical component)	
Grade	**Criteria**
0	No gingival hyperplasia
1	Blunting of gingival margins (Mild hyperplasia)
2	Less than half of crown length (Moderate hyperplasia)
3	Greater than half of crown length (Marked hyperplasia)

The vertical component of hyperplastic index measured the degree of gingival enlargement in an apico-coronal direction for a gingival unit by means of 4-point scale (Table-IV)[4].

Each unit was from the buccal or lingual midpoint of a tooth to a midpoint of the adjacent tooth. The horizontal component of the hyperplastic index measured the degree of gingival thickening on both the labial and lingual aspects in a labio-lingual direction for a gingival unit. The vertical and horizontal scores were added, thus giving a hyperplasia score for each gingival unit.

Table-IV. Hyperplastic index (Horizontal component)	
Grade	**Criteria**
0	Normal width of free gingival margin
1	Thickening from the normal up to 2 mm
2	Thickening from the normal > 2 mm

The maximum score obtainable is 5. As twenty gingival units were examined, the degree of hyperplasia around upper and lower teeth was expressed as a percentage (%). Individuals in study groups H, E & L, were further divided in into two subgroups, responders and non-responders according to their hyperplastic index score. Subjects with score greater than 30% were regarded as responders, and subjects with a score less than or equal to 30% were regarded as non-responders.

STATISTICAL ANALYSIS

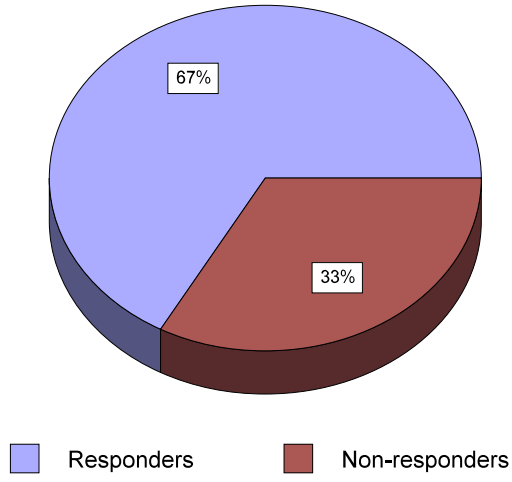
All data were expressed as means. Differences of mean of different periodontal variables in different groups were tested for significance by using the paired student's t-test. For all analyses, P values less than 0.05 was considered significant.

RESULTS

Table-V. Periodontal variables and the difference between each groups						
Variable	**Groups**			**P Value between groups**		
	H (n=10)	**E (n=10**	**L (n=10)**	**H**	**E**	**L**
Age	40.3±0.2	42.7±.001	41.5±0.4			
Range	35-50	35-50	35-50	NS	NS	NS
Male	5	5	5			
Female	5	5	5			
Plaque index	0.1±0.01	0.4±0.21	0.9±0.2		*	*
Hyperplastic index	13.1±0.49	37.4±0.23	45.1±0.51		*	*
*Results are expressed as mean ± SEM *p <0.001 versus H group (Healthy- Group)*						

Thirty hypertensive patients (15 males and 15 females) as per protocol were enrolled in the study. During the study it was observed that all subjects of either sex ranging in age from 35-50 years (x = 41.5 ± 1.6). They all expressed interest and gave informed consent to join the study. They had a mean of 6.5 months history of verapamil treatment (range 6-9 months).

Figure-1. Difference between Responders and Non-Responders group



Gingival enlargement was more pronounced on the labial aspect of the maxillary gingiva and in between the teeth (interdental papillae area).

Table-VI. Periodontal variables & the difference b/w responders and non responders

Variable	Responder (n=20)	Non responder (n=10)	P value b/w Groups
Plaque index	0.65±0.21	0.1±0.01	P<0.001
Hyperplastic index	41.2±0.69	13.1±0.49	P<0.001

Results are expressed as mean±SEM

There were highly significant differences between test groups E and L, when they were compared with group-H (Healthy Group). Mean plaque index varied between test groups H, E and L (0.1±.01, 0.4±0.2, and 0.9 ±0.2 respectively), the differences showed statistical high significance (p < 0.001). Table-V.

The differences between the responder and non-responder groups are shown in Table-VI. 20 subjects (66.6%) within the test groups H, E, and L (n=30) had a clinically significant gingival enlargement (HI >30%), while there were 10 non-responders (33.3%). Highly significant difference between responder and non-responder groups were found for periodontal variables. Table-VI.

DISCUSSION

Gingival hyperplasia is one of the characteristics of calcium channel blockers, in hypertensive patients and the number of patients with this oral lesion has greatly increased in last three decades. The clinically significant gingival enlargement, was assessed by a quantitative hyperplastic index to evaluate the correlation between drug induced gingival hyperplasia and periodontal parameters[4].

The etiology and pathogenesis of gingival hyperplasia is still not well established, but it could be directly linked to three factors; individual susceptibility, local factors, such as dental plaque, caries, and action of chemical substances and their metabolites[12].

Apoptosis is a process that acts in concert with mitosis to preserve cellular homeostasis or to facilitate tissue remodeling during development. It involves a cascade of biochemical steps, which require a rise in the level of intracellular calcium. Verapamil is well known as a calcium channel blocker and inhibits the calcium influx from extracellular fluid. Blockade of one or more steps in the cascade by verapamil results in a decrease in apoptosis rate. This inhibition of apoptosis in the epithelium leads to cell accumulation, resulting in gingival over growth[13,15].

The results from this study indicated that oral hygiene plays a decisive role in the development of gingival hyperplasia and the incidence can be controlled successfully, even under continues administration of calcium channel blockers, by meticulous professional and

individual oral hygiene. Patients with malpositioned teeth, periodontal disease, and poor oral hygiene are at increased risk of developing gingival hyperplasia[14].

Gingival inflammation and plaque induces a proliferative response in keratinocytes and provides a reservoir for the accumulation of drugs, thus providing local source for gingival epithelial deposition of the drug. The data suggest that the local effects of the drug on gingival tissue account for the suppression of apoptosis in the gingival epithelium[8]. The statistical highly significant difference found in plaque index and hyperplastic index between responder and non-responder groups in the present study suggests that a relationship exists, however not all patients with good oral and dental hygiene were free from gingival over growth.

Consequently our results suggests that prevalence of gingival hyperplasia is more in patients with poor oral hygiene and the number of patients with verapamil-induced gingival hyperplasia decreases significantly with good oral hygiene. This may provide a reasonable option for patients receiving verapamil therapy.

CONCLUSION

The role of oral hygiene and plaque in contributing to gingival hyperplasia cannot be ruled out. Commonly the periodontist receives a patient whose main complaint is gingival bleeding and in clinical examination we notice that the patient has periodontitis associated with hyperplastic gingivitis.

Often times the patient may report in their medical history the use of antihypertensive, antiseizure or antidepressive drugs. The patient may not always be warned of the oral implications of general treatment. We think that it would be advisable for better interaction between dentists and physicians in such cases. Indeed, all health professionals, in one way or another, may have important advice or suggestions to improve the general health of the patient.

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