An Investigation on Gingival Hyperplasia Induced by Nifedipine

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Statement of Problem: In recent years, numerous reports have been presented in the literature, about gingival overgrowth induced by Nifedipine- a calcium antagonist- prescribed for hypertension and certain types of angina.

Purpose: The purpose of the present study was to investigate the prevalence rate of Nifedipine induced gingival hyperplasia in patients and its probable relationship with age, gender, plaque score and drug consumption period.

Materials and Methods: The study was on 200 patients with heart disease. The gingival condition of 100 patients under Nifedipine treatment was compared with 100 controls treated with other hypertension drugs. Comparison of variables in study and control groups and also between patients with and without gingival hyperplasia was done using χ^2 and t-student tests.

Results: The prevalence rate of Nifedipine- induced gingival hyperplasia, among experimental patients, was 17%, while it was not observed among control ones. Oral examination revealed gingival overgrowth as a lobular or nodular enlargement on interdental papilla located on anterior interproximal regions.

Conclusion: In this study, there was a significant relationship between gingival inflammation resulting from dental plaque and drug dosage, with hyperplasia.

Key words: Hyperplasia- Gingival overgrowth induced by Nifedipine- Gingival hyperplasia

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Nifedipine is a calcium channel blocker, prescribed for the treatment of hypertension and some forms of angina. The main function of Nifedipine is vascular dilation associated with a decrease in peripheral resistance and blood pressure.

The most common side effects of this drug are dizziness, flushing, headache, hypotension, and peripheral edema.(1)

Nifedipine's importance, in dentistry, is due to its effect on gingival tissues, as it causes gingival hyperplasia in some patients. The relationship between using Nifedipine and gingival changes was first reported in 1984 and confirmed later. Other calcium channel blockers such as Verapamile,(2) Diltiazem(3) and Nitrinedepine(4) were also reported to cause gingival hyperplasia. Despite different reports regarding the effects of Nifedipine on gingival hyperplasia, there is little information about its

pathogenesis and prevalence.[5-10]

The aims of this study were:

1- To investigate the prevalence of gingival hyperplasia in patients treated with Nifedipine.

2- To evaluate the probable relationship between sex, age, plaque score, Nifedipine dosage and its period of consumption with gingival hyperplasia in patients under Nifedipine treatment.

Materials and Methods:

The present study was an observational case-control one. The investigation was carried out in heart department of Shariati hospital on 200 patients (98 male, 102 females) suffered from cardiovascular diseases. All patients were subdivided into 2 groups:

- One hundred patients under Nifedipine treatment (51 male, 49 female) were classified as study group.
- One hundred patients as control subjects, (47 male, 53 female) treated with other hypertension drugs.

The inclusion criteria for patients treated with Nifedipine were as follows:

- A minimum of 3- month period for Nifedipine consumption.
- The presence of at least 6 anterior or posterior teeth.

The following criteria excluded the subjects from the study:

1- Edentulous patients

2- Patients with complete or partial dentures

Exclusion criteria were applied for both main groups.

In order to investigate plaque score and gingival inflammation in study and control groups, Silness and Loes' "plaque index" (PI) and "gingival index" (GI) methods were used. Therefore, a questionnaire including personal information, dosage and type of consumed drugs, plaque and gingival indices coding and methods for oral hygiene preservation, was prepared and completed by all patients.

During the study, a histopathologic sample of a patient who was treated with Nifedipine for 15 months and did not have any other drug was prepared from the areas of $\overline{2\ 1|1\ 2}$ and $\underline{|1\text{-}5}$. The histological samples were immediately fixed in 10% formalin and stained with hematoxilyne and eosine. Infiltration of inflammatory cells, especially mast cells was confirmed by special staining. Comparison of the gingivitis prevalence between study and control groups was performed using χ^2 test. Also, χ^2 test was used to compare the disease type in Nifedipine group between patients with enlargement. Age, drug consumption period, average dosage of drug and PI was compared using t- student test between patients with and without gingival hyperplasia.

Results:

In the study group, 17% was affected with gingival hyperplasia (52.94% female and 47.05% male). Gingival hyperplasia was not observed in any of the control patients.

The highest prevalence of gingival enlargement was in the 4^{th} decade of life.

The severity of gingivitis and gingival index level was greater in Nifedipine (study) group as compared to the control group, but the difference wasn't statistically significant ($P>0.05$) (Tables II).

Plaque index of study and control groups has been showed in Table III.

In this study, there was a statistically significant relationship between plaque index (PI) and drug dosage with gingival changes. Hyperplasia was not related to factors such as: age, type of disease, and the duration of Nifedipine consumption.

Clinical observation in patients with gingival overgrowth, showed a lobular or nodular enlargement of interdental papilla in the anterior region.

Gingival consistency was spongy congested, and hemorrhagic. These changes were limited to the attached gingiva. Generally, gingival overgrowth was more obvious in the anterior

region, especially in the lower jaw. Edentulous regions did not show hyperplasia. Despite long-term Nifedipine consumption, In patients with a good oral hygiene, no gingival changes were seen.

Patients with hyperplasia, had a poor oral hygiene and a large amounts of plaque and debris were noticeable in their pockets. The histopathologic study of hyperplastic gingiva revealed parakeratosis, acanthosis and thin, long retepegs with a test tube appearance. In addition, moderate infiltration of chronic inflammatory cells such as: plasmocytes and mast cells was observed. In some sites, epithelium was wounded and damaged.

Discussion:

Gingival hyperplasia resulting from using Nifedipine has been established. Like other reports, in this study, a relationship between Nifedipine consumption and gingival hyperplasia was shown.

In this study, the prevalence rate of hyperplasia, was 17%. Previous investigations have shown the following rates: 21.7% (Barclay et al)[11], 47.82% and 21% (Steele et al).[12]

In this study, gingival hyperplasia was related to drug dosage and gingival inflammation caused by dental plaque. It is suggested that bacterial inflammation, resulting from dental plaque, is essential for gingival hyperplasia induced by Nifedipine. Therefore, as expected, in edentulous areas, gingiva didn't show any sign of hyperplasia. On the contrary, the higher the plaque index, the hyperplasia will be more severe. Considering the predominance of lymphoplasmocytes and mast cells in the connective tissue, the significant role of inflammation in the incidence and severity of gingival hyperplasia, will be more obvious.

Most authors have paid attention to the importance of bacterial inflammation. Hancock et al have reported a treated case of gingival hyperplasia (induced by Nifedipine) by scaling and root planning, accompanied by accurate methods of plaque control.[13] In addition, Bullon et al found a positive relationship between the level of hyperplasia and plaque index.[14]

The investigation by Ellis et al on 9 patients, who received Nifedipine showed that in 7 patients, the rate of Nifedipine secretion in GCF (Gingival cervicular fluid) was 15 to 316 times more than that of their plasma. GCF of the two patients, was free of Nifedipine and there was no sign of gingival overgrowth. Ellis et al suggested that Nifedipine was secreted through gingival tissues and its high concentrations

Table I: Date descriptive of patients of study and control groups

Characteristics	Study group (n=100)	Control group (n=100)	Patients affected with gingival hyperplasia
Age spectrum	16-74	14-73	31-74
Average age	49.5	48.4	51.38
Average dosage (mg/day)	27.4	-	28.82
average period of consumption (month)	20	-	19.94

Table II: Gingival Index (based on Loe and Silness gingival Index)

Variables	Severe gingivitis (%)	Moderate g. (%)	Mild g. (%)
Nifedipine group	18.88	48.88	32.22
Control group	0	46.34	52.43
Patients affected with gingival hyperplasia	100	0	0

Table III: Plaque Index (based on Loe and Silness plaque Index) (%)

Variables	(0)	(1)	(2)	(3)
Nifedipine group	12	61	17	10
Control group	18	57	10	15
Patients affected with gingival hyperplasia	0	35.29	52.94	11.76

could make tissues susceptible to enlargement. So, an increase in Nifedipine dosage could increase severity of gingival inflammation.[15,16]

Reports and articles have referred to the role of inflammation and drug dosage on drug induced gingival hyperplasia.[17-20]

Brown et al[17] suggested a functional heterogeneity between subgroups of fibroblasts or mixed subgroups of fibroblasts, in normal tissue.Fujii et al [21] have shown that fibroblasts obtained from hyperplastic tissue synthesize protein approximately two times more than cells of the control groups.

Sooriyamorthy et al[19] concluded that an increase in androgen metabolism is an important factor for gingival overgrowth resulting from Cyclosporine, Nifedipine and Phenytoine. These drugs or their metabolites can probably be cytotoxic for low activity gingival of fibroblasts and consequently facilitate the growth of highly active populations of fibroblasts which are involved in matrix synthesis. In addition, a histochemical study by Lucas et al has shown an increase in the number of fibroblasts containing large amounts of mucopoly- saccharide sulfate in gingival hyperplasia, caused by Nifedipine and Phenytoine.[22]

Fujii et al have shown that gingival fibroblast cultures obtained from patients who react to Nifedipine, display an increase proliferation rate. They also have an accelerated DNA and collagen synthesis in comparison to other patients.[21]

It has also been demonstrated by Satio et al that drugs such as Nifedipine and Phenytoin increase the synthesis of bFGF (basic-fibroblast growth factor), TGF- β (Transforming growth factor- beta) and HSPG (heparan sulphate glycosaminoglycan). These growth factors, in turn, can probably be related to drug induced gingival overgrowth. However, molecular function involved in the gingival hyperplasia due to the synthesis of these growth factors, are not known and required further studies.[23]

Finally, it should be noted that one question still remains ambiguous, that why despite similar conditions concerning plaque and Nifedipine dosage, some of the drug receivers become affected with hyperplasia and others don't? Probably, this can be originated from biological differences among human beings such as the existence of different subgroups of gingival fibroblasts. Therefore, investigating the interactions between factors such as the metabolism of gingival fibroblast subgroups, hormonal effects and growth agents, can be a guide to discover such differences.

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