

Changes in Inflammatory Markers in Bacterial- and Nifedipine-Induced Gingival Inflammation

Anitha George¹, Sanil P George², Sajil John³, Nebu George⁴, Sheena Joe⁵, Riju Mathew⁶

Contribution

¹Professor, Consultant (Oral Medicine and Radiology), Cochin, Dental Centre, Kakkanad, Cochin, Kerala, India; ²Professor & Head, Department of Periodontics, Mahe Institute of Dental Sciences, Chalakkara, Mahe, Kerala, India; ³Professor & Head, Department of Periodontics, Al-Azhar Dental College, Thodupuzha, Thiruvananthapuram, Kerala, India; ⁴Reader, Pushpagiri College of Dental Sciences, Tiruvalla, Kerala, India; ⁵Research Scholar, Mahatma University, Chennai; ⁶Lab Manager, Believers Church Medical College Hospital, Thiruvalla.

Correspondence:

Dr. Anitha George, Consultant (Oral Medicine and Radiology), Cochin Dental Centre, Kakkanad, Cochin, Kerala, India. Email: anitha19470@gmail.com

How to cite the article:

George A, George SP, John S, George N, Joe S, Mathew R. Changes in inflammatory markers in bacterial- and nifedipine-induced gingival inflammation. J Int Oral Health 2015;7(Suppl 2):64-67.

Abstract:

Background: Inflammatory gingival enlargement is a common observation in routine dental practice. Drugs like nifedipine, used for hypertension and *Porphyromonas gingivalis* infection-induced gingival enlargement is of a major concern. The current study aims to identify the inflammatory response of the gingival enlargement by measuring the major inflammatory markers fibrinogen and C-reactive protein (CRP).

Materials and Methods: Thirty-two patients with nifedipine-induced gingival enlargement, twelve with *P. gingivalis* infection, and seven with both drug and bacterial infection formed the test group and 16 age- and sex-matched healthy subjects formed the control. Gingival status was assessed, and the gingival index is noted. Fibrinogen and CRP were measured in venous blood. Results of the test and controls were compared using *t*-test and Pearson correlation.

Results: It was found that the changes in the inflammatory markers were statically significant in both fibrinogen levels and the CRP. The inflammation was more pronounced in subjects exposed to the drug and bacterial infection. The gingival index was found directly correlating with both the fibrinogen and the CRP levels.

Conclusion: The quantitative estimation of both fibrinogen and CRP are good markers for the quantification of inflammation and hence evaluating the risk of coronary heart disease (CHD). Substituting the drug and reducing the bacterial load will help in improving the outcome of the treatment and thereby reducing the risk of CHD.

Key Words: C-reactive protein, fibrinogen, gingivitis, gingival hyperplasia, gingival inflammation, nifedipine, *Porphyromonas gingivalis*

Introduction

Inflammatory gingival enlargement is commonly observed in routine dental practice. Many drugs that induce gingival enlargement were reported in the literature. Anticonvulsants such as phenytoin, sodium valproate, phenobarbitone, vigabatrin, and carbamazepine; immunosuppressants like cyclosporine and calcium channel blockers like nifedipine, isradipine, felodipine, amlodipine, verapamil, and diltiazem are some among them.¹⁻³ The pathogenesis of gingival hyperplasia-induced by drugs is still not completely understood even after extensive studies. Age, demographic variables, genetic factors, oral hygiene, etc., were implicated in gingival hyperplasia. These drugs are believed to cause cellular proliferation of gingiva by affecting the hormones like testosterone.⁴ The dose of the drug and the duration of therapy are correlating well with the degree of gingival hyperplasia. The incidence and degree of gingival hyperplasia increase with the concomitant use of drugs, although controversy still exists.³ Kataoka *et al.* had reported the direct effect of drugs like cyclosporine, phenytoin, and nifedipine on gingival cell activity.¹ Cells growth enhancement and collagens protein production has been observed in cultures of human gingival cells directly stimulated with these drugs.²

Nifedipine used for treating the hypertension is one of the leading causes of the drug-induced gingival enlargement that was first reported three decades back⁵ and still under investigation.⁶ Many factors like poor oral hygiene, high dose of the drugs, genetic factors, individual susceptibility, and drug its metabolites interaction with the fibroblasts of gingiva were attributed to the overgrowth of gingiva in nifedipine-induced hyperplasia.^{2,7} In-depth mechanism of the process were studied by many investigators.¹

Porphyromonas gingivalis is periodontal pathogen reported to be present in the majority of subjects with periodontal diseases and scanty seen in subjects with good periodontal health. Evidence relating the pathogenic role of these bacteria is available in the literature; however, the molecular and physiological mechanism remains unexplained. The prevalence of coronary heart disease (CHD) is reported to be higher in patients with periodontitis. The role of the inflammatory markers, which predisposes an individual to CHD, was not investigated in any of these studies. Hence, in the present study, an attempt is being made to evaluate the impact of drug-induced and bacterial gingivitis on the inflammatory markers, which intern increase the risk of CHD.

Fibrinogen is a protein synthesized by the liver and is intimately involved in blood clotting and inflammation management. It is a soluble protein, which gets converted into a solid fibrous protein that becomes the blood clot. Besides this, fibrinogen functions as a messenger molecule that coordinates and regulates our bodies' response to inflammation. C-reactive protein (CRP) is acute phase protein, the level of which will help to assess the degree of inflammation, and hence the risk of CHD. Our current study aims to correlate the effect of the drug-induced and bacterial gingivitis to the levels of the inflammatory markers.

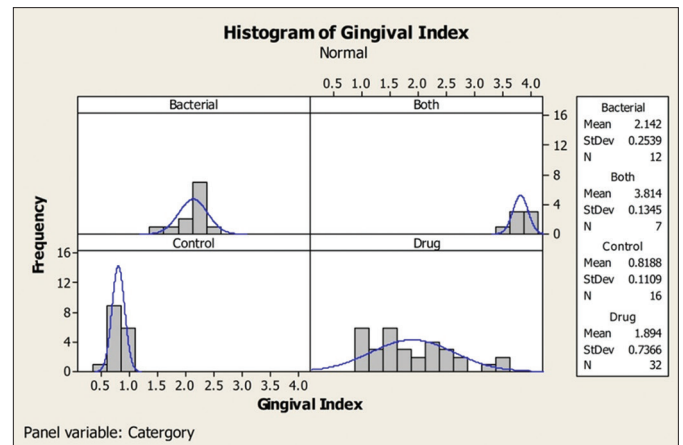
Materials and Methods

Thirty-two patients with gingival enlargement due to nifedipine and twelve patients with gingival inflammation due to *P. gingivalis* infection and seven with *P. gingivalis* infection and nifedipine-induced gingival inflammation were identified by the physicians and referred to the dental clinic formed the test group. The diagnosis was confirmed by the dentist based on clinical assessment by comprehensive periodontal examination. The detailed examination consists of a visual examination, radiographs, probing of the gingiva to measure the extent of gingival damage and by laboratory investigation. *P. gingivalis* was identified by anaerobic culture technique. Gingival status was assessed based on tools of of Loe and Silness.⁸ Fibrinogen concentration was measured in heparinized plasma and CRP in serum by nephelometric method in BN ProSpec (Siemens) analyzer. The values were compared with 16 age and sex matched controls. The comparison is done using the one-way ANOVA test, and Pearson correlation is done using the SPSS 17 software and the minitab 15 software. A $P \leq 0.05$ was considered as statistically significant.

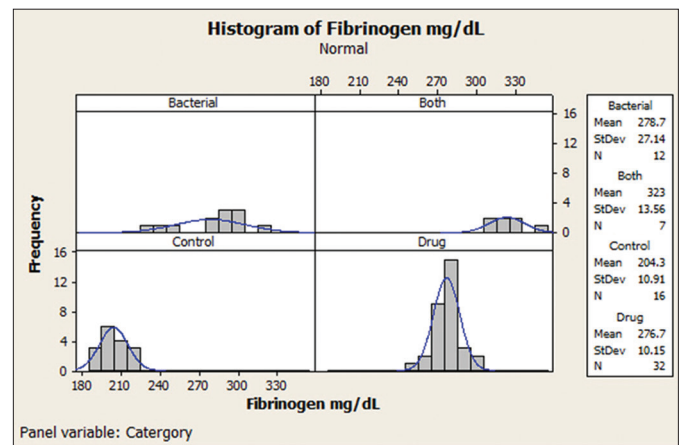
Result

The basic statistics of the study population is given in Table 1. The mean gingival index for the test population was 1.89 ± 0.74 for the gingivitis caused by drug, 2.14 ± 0.25 for gingivitis caused by bacteria and 3.81 ± 0.13 for gingivitis in subjects with drug and bacteria together (Graph 1 and Table 2), which shows that the inflammatory process was well-evident compared to the control population where the gingival index was 0.82 ± 0.11 . The average fibrinogen level for the test population was elevated (drug [276.69 ± 10.15], bacterial [278.67 ± 27.14], and both [323 ± 13.56]) when compared to the control population who had a value of 204.3 ± 10.91

(Graph 2 and Table 2). Fibrinogen level in the test and the control population were statistically of high significance ($P < 0.001$). The CRP was elevated in test cases (drug [2.55 ± 0.58], bacterial [3.08 ± 0.57], and both [4.13 ± 0.81]) than the control population of 0.97 ± 0.24 which was also statistically highly significant (Graph 3 and Table 2). There is a positive



Graph 1: Histogram with distribution curve of gingival index of the test ($n = 51$) and control ($n = 16$), Drug: Nifedipine drug-induced gingivitis group, bacterial: *P. Gingivalis*-induced gingivitis group, Both: Both drug- and bacteria-induced gingivitis group, StDev: Standard deviation.

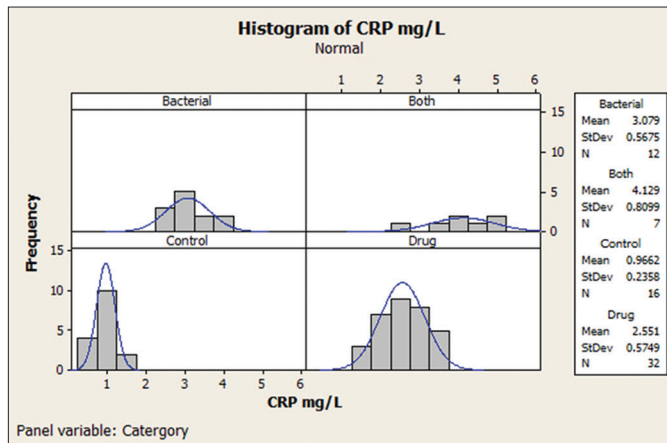


Graph 2: Histogram with distribution curve of fibrinogen levels in mg/dL of the test ($n = 51$) and control ($n = 16$), Drug: Nifedipine drug-induced gingivitis group, Bacterial: *P. Gingivalis*-induced gingivitis group, Both: Both drug- and bacteria-induced gingivitis group, StDev: Standard deviation.

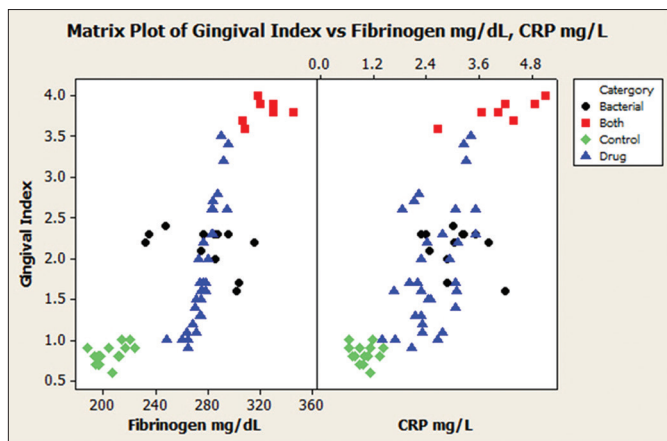
Table 1: Group statistics of the study population.

Parameters	Mean±SD			
	Test population (n=51)			Control (n=16)
	Drug (n=32)	Bacterial (n=12)	Both (n=7)	
Age	44.19±8.13	49±6.32	45.71±6.65	45.44±6.59
Gingival index	1.89±0.74	2.14±0.25	3.81±0.13	0.82±0.11
Fibrinogen mg/dL	276.69±10.15	278.67±27.14	323±13.56	204.25±10.91
CRP mg/L	2.55±0.58	3.08±0.57	4.13±0.81	0.97±0.24

CRP: C-reactive protein, SD: Standard deviation



Graph 3: Histogram with distribution curve of CRP levels of the test ($n = 51$) and control ($n = 16$), Drug: Nifedipine drug-induced gingivitis group, Bacterial: *P. Gingivalis*-induced gingivitis group, Both: Both drug- and bacteria-induced gingivitis group, StDev: Standard deviation, CRP: C-reactive protein.



Graph 4: Scatter diagram of correlation of gingival index to the fibrinogen and CRP, Drug: Nifedipine drug-induced gingivitis group, Bacterial: *P. gingivalis*-induced gingivitis group, Both: Both drug- and bacteria-induced gingivitis group, CRP: C-reactive protein.

Table 2: One-way ANOVA result of the 3 study groups and the control.

Parameter	F value of one-way ANOVA	ANOVA P value
Gingival index	53.07	<0.001
Fibrinogen	132.04	<0.001
CRP	67.89	<0.001

CRP: C-reactive protein

Table 3: Pearson correlation chart of gingival index to the fibrinogen and CRP.

Parameter	Gingival index	
	R value	P value
Fibrinogen mg/dL	0.803	<0.001
CRP mg/L	0.808	<0.001

R: Pearson correlation coefficient, CRP: C-reactive protein

correlation between the gingival index, the fibrinogen and CRP ($r = 0.803$ and $r = 0.808$, respectively) (Table 3 and Graph 4).

Discussion

Epithelial cellular invasion by pathogenic bacteria is well-documented.⁹ Nifedipine causes cellular enlargement by altering hormones like testosterone. When both the causes are present in the same individual, the degree of inflammation is expected to be to be more. It was observed in our study that the gingival inflammation in nifedipine-induced gingivitis and bacterial infection significantly elevated the fibrosis of the gingiva and is evidenced by the significant elevation in the blood levels of fibrinogen and CRP. Similar observation were reported by Trackman *et al.*² and Taylor, *et al.* in drug-induced gingivitis.¹⁰ We have observed elevated levels of inflammatory markers in gingivitis-induced either by the drug or by the bacteria.

The elevation in markers was more pronounced when both the causes were present concurrently. It may be due to the fact that a bacterial infection can cause inflammation, and this may further aggravate the inflammation induced by nifedipine. Studies on the concurrent effect of drug- and bacterial-induced inflammation are scanty, and no such reports are available on the levels of the inflammatory markers and gingivitis. A case-control study with more subjects will help in elucidating the mechanism of inflammation in such subjects.

Even though many etiological factors are attributed to the high prevalence of CHD, reports available on the role of gingivitis or other inflammatory periodontal conditions predisposing an individual to CHD are scanty. In these cases, the risk can be evaluated by measuring the inflammatory markers such as fibrinogen, CRP, etc., in circulation. Once these markers are found to be elevated, the risk of CHD can be reduced by substituting nifedipine and treating for bacterial infection.^{11,12} From our study, it was observed that the level of fibrinogen and CRP may also serve as a marker for gingivitis. Since there is a strong established correlation of elevated fibrinogen and CRP to the cardiovascular disease regular estimation of the fibrinogen and CRP will help in monitoring the patients so that preventive measures can be initiated, thereby the prevalence CHD can be reduced.¹³

Conclusion

The quantitative estimation of both fibrinogen and CRP are good markers of nifedipine-induced gingival enlargement. Due to the direct positive correlation between the gingival index and the markers, these markers can be used to evaluate the extent of gingival inflammation caused by the drugs. The study emphasizes the need for regular assessment of drug-induced gingivitis as the raised inflammatory markers are measurands of coronary artery disease.

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