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The Impact of Topically Applied 0.5% Nifedipine Gel in Nonsurgical Treatment of Periodontitis

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Abstract
Background: *Periodontitis is a condition that affects the supporting tissues of the teeth and is increasing more common worldwide,*
Aim: *To evaluate the clinical, radiographic and biochemical efficacy of 0.5% Nifedipine gel as a local delivery following the non-surgical periodontal therapy in periodontitis patients (Stage II, Grade A),*
Patients and methods: *The present study was designed as a split-mouth randomized controlled clinical, radiographic, and Immunohistochemical study carried out on 20 patients of both sexes at Oral Medicine and Periodontology Department, Faculty of Dental Medicine, Al-Azhar University, Assiut Branch. They were diagnosed by recording the case history and performing extra oral and intraoral clinical examinations as well as radiographic evaluation,*
Results: *There was no significant difference between Group I and Group II regarding plaque index baseline, gingival index baseline, probing pocket depth baseline, BFGF baseline, and marginal bone level baseline $p>0.05$. However, significant differences were observed after one, three, and six months $p<0.05$, with no significant difference between Group I and Group II regarding BFGF after two weeks and one month,*
Conclusion: *We concluded that the use of a 0.5% in situ gel of nifedipine, when applied topically, can effectively reduce probing pocket depth and increase attachment level in patients with stage II grade A periodontitis, and improve radiographic marginal bone level more effectively than non-surgical periodontal treatment alone.*
Key words: *Impact; Topically Applied 0.5% Nifedipine Gel; Periodontitis.*

Introduction

Periodontitis is a condition that affects the supporting tissues of the teeth and is increasing more common worldwide. In fact, almost 40% of people in developed countries exhibit clinical symptoms of periodontal disease, making it the eleventh most prevalent disease worldwide, according to the Global Burden of Disease Study.1

Nonsurgical periodontal therapy is critical in the treatment of periodontal disease and consists of removing the main etiological factors, namely supra- and subgingival biofilm and bacterial toxins, with the goal of reducing gingival inflammation, bleeding on probing, and probing depth.2 Both manual and ultrasonic instruments can be used for periodontal debridement.3

In an effort to improve treatment outcomes, local drug delivery agents have developed as adjuncts to mechanical debridement. Mechanisms of action include antibacterial activities, anti-inflammatory qualities, controlled release kinetics, and synergistic effects with adjunct therapies. Local drug delivery has evolved to enable targeted and personalised therapy, addressing microbial pathogens and host immunological responses.4

Nifedipine is used to treat peripheral vascular problems, angina, and cardiovascular conditions such as

hypertension. It has also been shown to have anti-oxidative, anti-inflammatory, anti-atherosclerotic, bone-remodeling, and immunomodulating capabilities.5

Nifedipine-induced gingival overgrowth is a typical adverse effect of systemic Nifedipine medication. It has been found to be the most common form of drug-induced gingival growth, with an incidence ranging from 14% to 83%.6

Basic fibroblast growth factor (bFGF) is a member of the fibroblast growth factor (FGF)family, which controls cell migration, proliferation, and differentiation.7 It has been linked to a number of physiological processes, including the formation of extracellular matrix, angiogenesis, chondrocyte proliferation, and embryonic induction mesoderm.8

This study aimed to evaluate the clinical, radiographic and biochemical efficacy of 0.5% Nifedipine gel as a local delivery following the non-surgical periodontal therapy in periodontitis patients (Stage II, Grade A).

Patient and method:

The present study was designed as a split-mouth randomized controlled clinical, radiographic, and Immunohistochemical study carried out on 20 patients of both sexes at Oral Medicine and Periodontology Department, Faculty of Dental Medicine, Al-Azhar University, Assiut Branch. They were diagnosed by recording the case history and performing extra oral and intraoral clinical examinations as well as radiographic evaluation.

Ethical consideration

The study protocol was approved by the ethical committee, Faculty of Dental medicine, Al-Azhar University. NO: AUAREC20220007-5. All patients were fully informed about the study's nature and the possible risks of the study procedures; they signed the consent form before the work.

Inclusion criteria: All patients were free from any systemic diseases according to the American dental academy general guidelines for referring dental patients to specialists and other settings for care 9 and Patients with Stage II, Grade A periodontitis. Patient with CAL 3 to 4mm with no tooth loss and probing depth ≤5 mm. Grade A: no evidence of CAL or bone loss over 5 years.

Exclusion criteria: Patients with previous periodontal treatment including scaling and root planing or periodontal surgery in the last 3 and 6 months, respectively, Patients received antibiotics and non-steroidal anti-inflammatory for at least 3 months before sample collection, Patients with sensitivity to the medication used in the study, Patients under antihypertensive, immune suppressants and anticonvulsant drugs which could affect their periodontium, Pregnant or lactating women and smokers patients.

Sample size calculation

Based on Salatein et al (2023) 1 and Using G power statistical power Analysis program (version 3.1.9.4) for sample size determination 2, A total sample size (n=20; subdivided to 10 in each group), will be sufficient to detect a large effect size (d) =1.35, with an actual power (1-β error) of 0.8 (80%) and a significance level (α error) 0.05 (5%) for two-sided hypothesis test.

Methods

All patients were subjected to the following:

Periodontal intervention

All patients were received Phase I therapy included: Patient education and motivation, mechanical plaque control, correction of restorative and prosthetic irritational factor, Eexcavation of caries and a temporary restoration,diet changes/ modification, full-mouth scaling was performed in one or two visit without the use of adjunct disinfectants for each patient. These procedures were carried out with hand instruments and ultrasonic devices to remove local deposits such as plaque, calculus, endotoxins, and other plaque-retentive local factors. Afterwards, the tooth surfaces were polished with paste and a rubber brush.

Intra-pocket application of 0.5% Nifedipine in-situ gel:

Firstly, areas of application were isolated by the cotton roll, the application was accomplished by inserting the needle into the base of the periodontal pocket firstly and then injecting the gel while working the way up, until the gel appeared from gingival margin, the treated sites were covered with periodontal dressing to achieve retention of the product into the pocket and avoid carry-across effects, Patients were instructed to stop eating, spitting, and drinking for 1 hour after application, teeth brushing and flossing for 4 hours after application. Also

were instructed for plaque control regimen, and the oral hygiene instructions were provided at each appointment.

Evaluation of periodontal status

Clinical evaluation: The periodontal conditions were evaluated clinically for all patients at baseline, 3 and 6 months after treatment using the following parameters: Plaque index (PI), Gingival index (GI), Probing pocket depth (PPD) and Clinical attachment level (CAL).10-13

Radiographic assessment

The marginal bone level (MBL) was assessed for all patients at baseline, 6 months after treatment. Cone Beam Computed Tomography (CBCT) scans were obtained using a Dentsply Sirona®, serial no. 12060, and processed with Sidex4 software. The scans were acquired with a Field of View (FOV) of 8cm, using parameters of 85 kVp and 10 mA. Radiographic measurements were performed on CBCT multiplanar images, and the height of the intrabony defect was determined from the cementoenamel junction (CEJ) to the alveolar crest. The gain or loss of Marginal Bone Level (MBL) was calculated by comparing the MBL at a 6-month interval with the baseline value, using addition or subtraction accordingly.

Biochemical evaluation: Basic fibroblast growth factor levels in gingival crevicular fluid samples were measured using enzyme-linked immunosorbent assay (ELISA) at baseline, 2 and 4 weeks in both groups.

Gingival crevicular fluid samples collection: GCF samples were collected from patients with high probing depth and CAL scores, avoiding food, drinking, brushing, or mouthwash two hours before collection. Teeth were isolated, supra gingival plaque removed, and crevicular site dried. Samples were transferred to vials containing 100 µL phosphate buffer saline and frozen at -80°C for assaying for bFGF.

bFGF analysis: The samples were assayed for bFGF levels using commercially available (Human FGF basic/FGF2/bFGF Immunoassay) kit. A highly sensitive ELISA reader was used to detect the bFGF level in ng/ml in the sample of GCF. The assays were conducted according to the manufacturer's instructions. Assay procedures: The process involved determining the wells for diluted standard, blank, and sample. Each well was filled with 100µL of each standard, blank, and sample dilution, and then incubated for 90 minutes at 37°C. The liquid was then decanted and washed. Next, 100µL of biotinylated detection antibody working solution was added to each well, and incubated for 1 hour at 37°C. The solution was then washed with 350µL of wash buffer, HRP Conjugate working solution, and Substrate Reagent. The plate was then protected from light and 50µL of stop solution was added to each well. The optical density value of each well was determined using a microplate reader set to 450 nm.

Calculation of results: The duplicate readings average for each standard and samples were determined, then the average zero standard optical density was subtracted. A four-parameter logistic curve on log-log graph paper, with standard concentration on the x-axis and optical density values on the y-axis was plotted. The actual concentration was calculated by multiplying the calculated concentration by the dilution factor.

Statistical Analysis

All data were subjected to revision and validation then description and analysis on IBM-compatible PC by using SPSS (Statistical Package for the Social Science) program version 26.0.0, Microsoft Office Excel 2010, and GraphPad Prism 6. The level of significance was calculated according to the following probability (P) values: $P > 0.05$ = non-significant (NS), $P < 0.05$ = significant (S) and $P < 0.001$ = highly significant (HS).

Results:

There were 11 cases Female and 9 cases Male. The age ranged from 29 to 59 years with mean 41.55 years. (Table 1).

Table 1 Descriptive data according to Sex and Age

		No. = 20
Sex	Female	11 (55.0%)
	Male	9 (45.0%)
Age	Mean ± SD	41.55 ± 9.62
	Range	29 – 59

There were no statistical significant between Group I and Group II regarding plaque index baseline p>0.05, while there were statistical significant between Group I and Group II regarding plaque index after one month and three months, while there were highly statistical significant after six monthsp<0.05. (Table 2)

Table 2 Showing comparison between Group I and Group II regarding plaque index score at the different intervals

Plaque index		Group I **No. = 20**	Group II **No. = 20**	Test value•	P-value	Sig.
Baseline	Mean ± SD	2.23 ± 0.36	2.28 ± 0.37	-0.426	0.673	NS
	Range	1.3 – 2.62	1.5 – 3			
After one month	Mean ± SD	0.65 ± 0.17	0.52 ± 0.15	2.508	0.017	S
	Range	0.34 – 0.89	0.29 – 0.88			
After three months	Mean ± SD	0.84 ± 0.14	0.73 ± 0.14	2.483	0.018	S
	Range	0.58 – 0.97	0.5 – 0.95			
After six months	Mean ± SD	1.07 ± 0.17	0.92 ± 0.12	3.107	0.004	HS
	Range	0.81 – 1.31	0.75 – 1.13			

There were no statistical significant between Group I and Group II regarding gingival index baseline p>0.05, while there were highly statistical significant between Group I and Group II after one and three months, while there were highly statistical significant after six months p=0.006. (Table 3)

Table 3 Showing comparison between Group I and Group II regarding gingival index score at the different intervals

Gingival index		Group I **No. = 20**	Group II **No. = 20**	Test value•	P-value	Sig.
Baseline	Mean ± SD	2.44 ± 0.34	2.33 ± 0.33	1.023	0.313	NS
	Range	1.83 – 2.93	1.88 – 2.88			
After one month	Mean ± SD	0.81 ± 0.11	0.69 ± 0.15	2.743	0.009	HS
	Range	0.47 – 0.92	0.39 – 0.86			
After three months	Mean ± SD	0.94 ± 0.15	0.82 ± 0.15	2.675	0.011	S
	Range	0.65 – 1.22	0.52 – 0.98			
After six months	Mean ± SD	1.12 ± 0.15	0.97 ± 0.15	2.893	0.006	HS
	Range	0.82 – 1.35	0.72 – 1.23			

There were non statistical significant between Group I and Group II regarding probing pocket depth baseline p>0.05, while there were highly statistical significant after one, three and six months p=0.0001. (Table 4)

Table 4 Showing comparison between Group I and Group II regarding probing pocket depth in mm at the different intervals

Probing depth		Group I **No. = 20**	Group II **No. = 20**	Test value•	P-value	Sig.
Baseline	Mean ± SD	4.50 ± 0.51	4.40 ± 0.50	0.623	0.537	NS
	Range	4 – 5	4 – 5			
After one month	Mean ± SD	3.15 ± 0.59	2.35 ± 0.49	4.681	0.000	HS
	Range	2 – 4	2 – 3			
After three months	Mean ± SD	2.53 ± 0.51	1.42 ± 0.51	6.678	0.000	HS
	Range	2 – 3	1 – 2			
After six months	Mean ± SD	3.26 ± 0.73	1.79 ± 0.71	6.278	0.000	HS
	Range	2 – 4	1 – 3			

There was highly statistical significant between Group I and Group II regarding after one, three and six months p=0.0001. (Table 5)

Table 5 Showing comparison between Group I and Group II regarding CAL in mm at the different intervals

CAL		Group I	Group II	Test value•	P-value	Sig.
		No. = 20	**No. = 20**			
Baseline	Mean ± SD	3.70 ± 0.47	3.20 ± 0.41	3.583	0.051	NS
	Range	3 − 4	3 − 4			
After one month	Mean ± SD	2.65 ± 0.49	1.95 ± 0.22	5.818	0.000	HS
	Range	2 − 3	1 − 2			
After three months	Mean ± SD	2.32 ± 0.67	1.11 ± 0.32	7.117	0.000	HS
	Range	1 − 3	1 − 2			
After six months	Mean ± SD	2.79 ± 0.63	1.21 ± 0.54	8.321	0.000	HS
	Range	2 − 4	1 − 3			

There were no statistical significant between Group I and Group II regarding BFGF baseline, after two weeks and one-month p>0.05. (Table 6)

Table 6 Comparative analysis among Group I and Group II according to MDA level at GCF in nanogram at different intervals

BFGF		Group I	Group II	Test value•	P-value	Sig.
		No. = 20	**No. = 20**			
Baseline	Mean ± SD	801.27 ± 189.11	692.51 ± 130.13	2.119	0.062	NS
	Range	523.89 − 1281.1	535.86 − 896.07			
After two weeks	Mean ± SD	917.32 ± 94.54	943.34 ± 153.59	-0.645	0.523	NS
	Range	762.74 − 1130.52	688.82 − 1212.54			
After one month	Mean ± SD	859.91 ± 117.92	880.65 ± 154.15	-0.478	0.636	NS
	Range	674.3 − 1048.15	638.04 − 1140.73			

There were no statistical significant between Group I and Group II regarding marginal bone level Baseline p>0.05, while there were highly statistical significant between Group I and Group II after six months p=0.000. (Table 7)

Table 7 Showing comparison between Group I and Group II regarding Marginal bone level in mm

Marginal bone level		Group I	Group II	Test value	P-value	Sig.
		No. = 20	**No. = 20**			
Baseline	Mean ± SD	2.67 ± 0.27	2.54 ± 0.39	1.183	0.244	NS
	Range	2.33 − 3.2	2 − 3.12			
After six months	Mean ± SD	2.55 ± 0.27	2.01 ± 0.47	4.286	0.000	HS
	Range	2.1 − 3	1.23 − 2.65			

Discussion

The current work can be regarded as a novel study, and there aren't many clinical results that can be comparable to the current findings. The use of 0.5% nifedipine in-situ gel as local drug delivery in the treatment of stage II, grade A periodontitis has not yet been documented in any studies, with the exception of one in vivo study that examined the impact of NIF on the regeneration of a mouse model of periodontal tissue defect and found that nifedipine seems to be a promising medication that encourages periodontal regeneration.6

According to the study's results, there were no appreciable differences between the two groups during the observation period, but there was a statistically significant decrease in the plaque and gingival index scores of both groups at various intervals when compared to baseline in terms of plaque accumulation and gingival

inflammation severity. These findings could be explained by the fact that, throughout the study's observation period, all patients' motivation was maintained and encouraged, as well as by mechanical debridement and dental cleanliness. Additionally, contributed to the study's design, which removes inter-subject variation.14 this is agreement with asystematic review which showed local host modulators a significant improvement in plaque and ginigival index.15

Comparing the mean probing pocket depth in both groups to the baseline, the current investigation found that the reduction was highly statistically significant at various intervals. At baseline, there was no statistically significant difference between the two groups but there was highly statistically difference in NIF group over control one.

The current research found that, when compared to the baseline, the mean CAL in both groups decreased, and that the decrease was statistically significant at various intervals.

In the study comparison between the two groups, there was a highly statistically significant difference at different intervals. The decrease in CAL and PD associated to nifedipine's vasodilatory properties can enhance blood flow to the gingival tissues. Improved blood flow could facilitate the delivery of nutrients and oxygen to periodontal tissues, which could lead to improved regeneration and healing. Also, Nifedipine can enhance fibroblast function, which is beneficial in periodontal repair, as fibroblasts are essential for producing collagen and extracellular matrix, both critical to maintaining the structural integrity and attachment strength of connective tissue in the periodontium. While studies specifically addressing topical nifedipine are relatively limited, research into other local antibiotic therapies, like tetracycline and minocycline, provides a relevant context. These agents are known to aid in the reduction of PD and support CAL, especially in patients with deep periodontal pockets, by directly delivering active compounds to the affected areas, similar to the effects seen with nifedipine's localized application.16 This is in agreement with the results of another study that reported improvements in similar clinical periodontal markers after using PHT as mucoadhesive paste following SRP.17

The current study reported statistically significant differences in gain of MBL in both groups after 6 months when compared to the baseline. The result consistent with another research which found that Local drug delivery agents can enhance the healing process, stimulate bone regeneration and promote new bone formation when delivered locally.18

When comparing the two groups, the current study reported that group II had significantly higher MBL at six months compared to group I. Research on the topical application of NIF in treating periodontitis indicates its potential to reduce alveolar bone loss through enhance markers related to osteogenesis, leading to significant improvements in bone regeneration. This is consistent with the study found that nifedipine-loaded microspheres significantly improved new alveolar bone formation in an experimental model, enhancing physical parameters associated with periodontal regeneration. Key markers related to bone formation were positively influenced, suggesting that NIF may have therapeutic benefits in managing periodontal tissue defects.6

Between both groups, there were statistical significant between Group I and Group II regarding BFGF baseline, while there were no statistical significant between Group I and Group II after two weeks and one month. This is due to the evidence that NIF has effects on gingival health as its main contribution to periodontitis is connected to its vascular advantages rather than its direct influence on growth factors such as bFGF. However, by preserving tissue perfusion and lowering specific inflammatory mediators, its use may promote periodontal health and establish an environment that is conducive to natural healing processes, even though it indirectly affects growth factors.19 These findings are in agreement with the study which concluded that, the topical application of 1% phenytoin in treatment of periodontitis contributes to increase the level of GCF growth factor before gradually declined at the end of evaluation periods.20.

Conclusion

We concluded that adjunctive use of topically applied 0.5% in situ gel of nifedipine appeared to be has beneficial effect in reduction of probing pocket depth and gain of attachment level in treatment of patients with stage II grade A periodontitis. The adjunctive use of topically applied nifedipine gel exhibits a superior improvement in radiographic marginal bone level over non-surgical periodontal treatment alone.

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