European Journal of Research in Dentistry 2022; 6 (1): 1-7
DOI: http://dx.doi.org/10.29228/erd.18

ORIGINAL ARTICLE / ARAŞTIRMA MAKALESİ

Periodontal Treatment Approach for Dihydropyridine Induced Gingival Overgrowth with or without Drug Substitution

Dihidropridine Bağlı Dişeti Büyümesinde Farklı İlaç Rejimlerinde Periodontal Tedavi Yaklaşımı

Onur EROĞLU[1], Ece YETİŞ[2], Hafize ÖZTÜRK ÖZENER[3], Leyla KURU[4]

ABSTRACT

Objectives: The aim of this study is to evaluate clinical effectiveness of nonsurgical periodontal treatment (NSPT) in patients with drug induced gingival overgrowth (DIGO) with or without drug substitution in comparison with patients presenting inflammatory gingival overgrowth (GO).

Material and Methods: A total of 17 patients with generalized GO were included in this clinical trial. Based on the medical physicians consultation, DIGO patients who continued using dihydropyridine were allocated to the Group 1 (n=6), whereas patients whose drug substitution was carried out were allocated to the Group 2 (n=5). Group 3 (n=6) subjects had inflammatory GO. All study groups received NSPT for 4 sessions. At baseline and 6 weeks after NSPT, plaque index, gingival index, bleeding on probing (BOP), probing depth (PD) and, plaster model and photographic GO scores were measured.

Results: NSPT resulted in significant decreases in periodontal clinical parameters in all groups ($p<0.05$). Intergroup comparisons of baseline measurements revealed no statistically significant differences ($p>0.05$) except PD value which was higher in the Group 1 compared to the Group 2 ($p<0.05$). Comparisons of post-NSPT data among groups exhibited statistically significant difference only between Groups 1 and 2 in the model and photographic GO scores ($p<0.05$).

Conclusions: After the 6-week evaluation period, NSPT was found to be an effective method in reducing the severity of inflammation and size of overgrown gingival tissues in patients with DIGO and inflamatory GO. Substitution of drug causing GO provided further contribution to NSPT regarding the size of overgrown gingiva in the patients with DIGO.

Keywords: Gingival overgrowth, hypertension, antihypertension agents, root planing, drug substitution

ÖZ

Amaç: Bu çalışmanın amacı, ilaca bağlı dişeti büyümesi (İBDB) gösteren ve ilaç değişimi yapılan ve yapılmayan hastalarda cerrahi olmayan periodontal tedavinin (COPT) klinik etkinliğini değerlendirmek ve enflamatuvar dişeti büyümesi (EDB) gösteren hastalarla karşılaştırmaktır.

Gereç ve Yöntemler: Ağızda generalize dişeti büyümesi görülen toplam 17 hasta araştırmaya dahil edildi. Dihidropiridine bağlı dişeti büyümesi olan hastalardan hekim konsültasyon sonucu ilacına devam edenler Grup 1 (n=6), ilaç değişimi yapılan hastalar ise Grup 2 (n=5) olarak ayrıldı. EDB görülen hastalar Grup 3'e (n=6) dahil edildi. Tüm çalışma gruplarına 4 seans COPT uygulandı. Başlangıçta ve COPT'den 6 hafta sonra plak indeks, gingival indeks, sondalamada kanama , sondalama derinliği (SD) ile alçı model ve fotoğrafik dişeti büyümesi skorları ölçüldü.

Bulgular: Tüm hasta gruplarında COPT sonrası tüm klinik parametrelerde azalma gözlendi ($p<0.05$). Başlangıç ölçümlerinin gruplar arası karşılaştırmasında, Grup 1'de Grup 2'ye göre daha yüksek olan SD değeri ($p<0.05$) dışında anlamlı bir fark görülmedi ($p>0.05$). COPT sonrası verilerin gruplar arasında karşılaştırılmasında, yalnızca Grup 1 ve 2 arasında model ve fotoğrafik dişeti büyümesi değerlerinde istatistiksel olarak anlamlı fark bulundu ($p<0.05$).

Sonuçlar: COPT'nin İBDB ve EDB görülen hastalarda 6 haftalık süreçte enflamasyonun şiddetinin ve büyümüş dişeti dokularının boyutlarının azaltmasında etkili bir yöntem olduğu sonucuna varıldı. Dişeti büyümesini indükleyen ilacın değişimi, İBDB hastalarında büyümüş dişetinin boyutlarının azaltılmasında COPT'ye ek katkıda bulunduğu belirlendi.

Anahtar kelimeler: Diş eti aşırı büyümesi, hipertansiyon, antihipertansifler, kökü düzleştirme, ilaç ikamesi

Leyla Kuru (✉)
DDS, PhD., Department of Periodontology, Faculty of Dentistry, Marmara University Basıbuyuk, Maltepe, Istanbul, Turkey
e-mail: lkuru@marmara.edu.tr

Onur Eroglu
Department of Periodontology, Faculty of Dentistry, Marmara University, Istanbul, Turkey

Ece Yetis
Department of Periodontology, Faculty of Dentistry, Marmara University, Istanbul, Turkey.

Hafize Öztürk Özener
Department of Periodontology, Faculty of Dentistry, Marmara University, Istanbul, Turkey.

Submitted / Gönderilme: 14.05.2022 **Accepted/Kabul:** 31.05.2022

INTRODUCTION

Gingival overgrowth (GO) is a pathological alteration in the dimensions of gingival tissues. Clinical characteristics

of this pathology may vary among individuals. There is a number of etiological factors that can cause GO such as gingival inflammation, medications, genetic factors, systemic diseases and conditions. Microbial dental plaque induced inflammatory GO is the oral manifestation of gingivitis without any accompanying systemic disease. Another common form of overgrowth is defined as drug induced GO (DIGO) caused by certain medications as an adverse effect (Kantarci et al., 2019). The first scientific publication on DIGO, following the therapy of epileptics with one of anticonvulsant derivatives phenytoin was in 1939 by Kimball (Kimball, 1939). Since then, DIGO has been also linked to immunosuppressives and calcium channel blockers (CCB) (Rateitschak-Plüss et al., 1983; Ramon et al., 1984). The gingival overgrowth side effect of CCB drugs was first reported in 1984 in patients using nifedipine, a dihydropyridine (DHP) group of CCBs (Ramon et al., 1984). So far, various DHPs including amlodipine, felodipine, nitrendipine and isradipine have been linked to this undesirable effect (Pieper, 1996; Livada& Shiloah, 2014). The incidence of GO induced by nifedipine and amlodipine was reported as 6% and 3.3%, respectively (Jorgensen, 1997; Ellis et al., 1999). Signs and symptoms usually appear within 1 to 3 months following the consumption of the drugs and begin as a bead-like, localized, tight, nodular growth at the interdental papilla extending along the facial and lingual surfaces (Dongari-Bagtzoglou, 2004; Sanz, 2013). In cases where DIGO is secondarily infected by pathogen microorganisms, the size of gingival tissues increases with additional characteristic features of inflammatory GO (Sanz, 2013).

The mechanism of DIGO has not been fully understood while several investigators suggested non-inflammatory and inflammatory theories. Reduction in collagenase activity due to increased folic acid uptake (Brown et al., 1991), blocking of aldosterone production in the adrenal cortex with a feedback rise in adrenocorticotropic hormone levels (Nyska et al., 1994), or up-regulation of keratinocyte growth factor (Das & Olsen, 2000) are all proposed in the non-inflammatory theory. In the presence of inflammation, it has been reported that there is a change in the levels of Tranforming growth factor-1, basic fibroblast growth factor, connective tissue growth factor, platelet derived growth factor, vascular endotelial growth factor , interleukin-1, and interleukin-6 in the tissues with DIGO (Sato et al, 2005; Gong et al., 2014; Becerik et al., 2016; Köse et al., 2020). Although the relationship between dental plaque and DIGO was investigated extensively in clinical studies, it has not been clarified yet whether plaque accumulation is the cause or the result of gingival changes (Tavassoli et al.; 1998; Aimetti et al.; 2005; Pundir et al., 2014). Many factors such as age, genetics and oral hygiene level make the pathogenesis even more complex as they affect the severity of DIGO (Smith et al., 2006). Even though improved oral hygiene level reduces the degree of GO, no agreement has been established in literature about the effect of plaque control. Several authors have observed a positive association between nonsurgical periodontal therapy (NSPT) and recovery of DIGO (Aimetti et al., 2005; Kantarci et al., 1999; Somacarrera et al., 1997), while others do not support this concept (Seymour & Smith, 1999; Pernu et al., 1993). NSPT alone may be sufficient in the treatment of inflammatory GO without fibrotic component (Livada & Shiloah, 2014; Carranza & Hogan, 2015). On the other hand, regulation of the drug regimen in addition to NSPT is another important factor to be considered. Instead of discontinuation of the growth-inducing drug, replacing it with an equivalent drug is usually the preferred option (Nakib & Ashrafi, 2011; Pundir et al.,2014). Drug substitution can be challenging in hypertensive patients for regulation of blood pressure level, on the other hand, it is the only approach for inhibition of GO recurrence. However, at present no consensus has been reached on the regulation of the drug regimen in the treatment of DIGO (Kantarci et al., 2019). So far, effectiveness of NSPT alone or with drug substitution in patients with DIGO has not been investigated. Therefore, the aim of this study was to evaluate the effect of NSPT in patients having DIGO with or without drug substitution on clinical parameters in comparison with patients having inflammatory GO.

MATERIALS AND METHODS

This clinical trial was carried out by the approval of Ethical Committee of Marmara University, Faculty of Medicine (Approval date: 06.12.2019. ID number: 09.2019.1078).

Study Population

This prospective study was conducted in patients who admitted to the Department of Periodontology, Dental Faculty, Marmara University, Istanbul, Turkey between September 2019 and March 2020. The signed informed consent was obtained from included participants.

The inclusion criteria for all participants were as follows: nonsmoker, not received any periodontal treatment within last 3 months, not consumed antibiotics and antiinflammatory drugs within last 3 months, not being pregnant or in lactation period and consent to participate in the study. For DIGO patients additional inclusion criteria were comsumption of DHP for at least 6 months and not using another drug that may cause GO. A total of 17 selected patients were allocated into 3 groups as:

Group 1 (n=6): DIGO patients, whose medications were not allowed to be replaced by an expert consult.

Group 2 (n=5): DIGO patients, whose medications were replaced by an expert consult.

Group 3 (n=6): Systemically healhty individuals who were diagnosed as inflammatory GO and not using any medication known to induce GO.

Clinical Parameters

At baseline examination, the periodontal evaluation included assessment of plaque index (PI) (Silness & Loe, 1964), gingival index (GI) (Loe & Silness, 1963), probing depth (PD) and bleeding on probing (BOP) by means of a UNC probe (*University of North Carolina, PCPUNC15,* Hu-Friedy Ins Co, ABD) at six sites of per tooth. The degree of GO was measured on plaster study models using the scoring method described by Seymour et al. (Seymour, 1985). The photographic evaluation for GO was also performed as described by Ellis and Seymour (Ellis & Seymour, 2001). The measurements of all parameters were performed by a nonblinded single researcher (OE) and repeated 6 weeks after NSPT (Figure 1).

Non-surgical Periodontal Therapy

The medical physicians of the DIGO patients were consulted for the replacement of GO inducing medication to another drug that is known not to cause GO. According to the recommendation of the expert consultation, 6 patients who were advised to continue DHP were allocated to Group 1 whereas 5 patients who were allowed to replace DHP were allocated to Group 2. Following baseline assesment, all patients received NSPT consisting of oral hygiene instruction, whole mouth supra and subgingival scaling and root planing applied with ultrasonic scaler (Woodpecker A-Led) and hand instruments (Gracey; Hu-Friedy Ins. Co) in a total of 4 sessions under local anesthesia.

Statistical Analysis

The statistical analysis was performed with SPSS v22 (SPSS Corporation, Chicago). The Wilcoxon signed rank test was used to analyze repeated measurements of periodontal clinical parameters. The Kruskal-Wallis test was used for intergroup multiple comparisons. Moreover, in case of significant difference, the Mann-Whitney U test was used to compare two groups by Bonferroni correction. A p value <0.05 was considered as statistically significant.

RESULTS

Demographic data are displayed in Table 1. The mean ages of patients in the Groups 1, 2 and 3 were 53.00±9.63 years, 50.00±16.04 years and 31.33±6.88 years, respectively. The mean durations of drug usage in the Group 1 and 2 were 44.40±47.16 months and 64.00±87.06 months, respectively (Table 1). Multiple comparison of patients' age revealed statistically significant differences among groups ($p<0.05$), the mean age of the Group 1 (53.00±9.63) was significantly higher than the Group 3 (31.33±6.88) ($p<0.05$). There was no difference between Groups 1 and 2 in terms of duration of drug consumption ($p>0.05$).

The periodontal clinical parameters of all groups at baseline and 6 weeks after treatment are shown in Table 2. PI, GI, PD and BOP decreased statistically significantly at post-treatment 6 weeks compared with their respective baseline values ($p<0.05$).

Table 1. Demographic data of patients

	GROUP 1 Mean±SD	GROUP 2 Mean±SD	GROUP 3 Mean±SD	P* 1-2-3	P+ 1-2	P+ 1-3	P+ 2-3
Gender (F/M)	3/3	3/2	3/3	-	-	-	-
Age (years) **min-max**	53.00 ± 9.63 44-64	50.00 ± 16.04 30-67	31.33 ± 6.88 22-41	**0.013**	1.00	**0.02**	0.07
Duration of drug consumption (months) **min-max**	64.00±87.06 6-240	44.40±47.16 6-120	-	-	0.713	-	-

*Kruskal-Wallis test, +Mann-Whitney U test, $p<0.05$.

Table 2. Clinical periodontal parameters of all groups before and after NSPT

		GROUP 1	GROUP 2	GROUP 3	P			
CLINICAL PARAMETERS		**Mean±SD**	**Mean±SD**	**Mean±SD**	**GROUP1-2-3[#]**	**GROUP1-2[§]**	**GROUP1-3[§]**	**GROUP2-3[§]**
PI	Baseline	2.60±0.29	2.25±0.47	2.5±0.41	0.503	-	-	-
	6 weeks	0.54±0.17	0.46 ±0.22	0.43±0.14	0.530	-	-	-
P*		**0.028**	**0.043**	**0.027**				
GI	Baseline	1.86±0.18	1.90±0.49	1.89±0.13	0.690	-	-	-
	6 weeks	0.90±0.46	0.51 ±0.5	0.29 ±0.09	0.058	-	-	-
P*		**0.028**	**0.043**	**0.028**				
PD (mm)	Baseline	5.19±0.76	4.06±0.95	3.75 ±0.55	**0.035**	0.238	**0.036**	1.000
	6 weeks	3.58±1,22	3.00 ±0.86	2.76 ±0.52	0.501	-	-	-
P*		**0.028**	**0.043**	**0.028**				
BOP (%)	Baseline	89.81±13.83	75.99±34.13	87.05±17.14	0.860	-	-	-
	6 weeks	28.63±14.46	11.96±10.10	14.33 ±5.07	**0.037**	0.077	0.088	1.000
P*		**0.027**	**0.043**	**0.028**				
Model GO Score (%)	Baseline	75.00±7.62	72.00±5.40	58.00±12,06	0.264	-	-	-
	6 weeks	38.66±5.33	14.8±6.01	24.33±14.82	**0.043**	**0.038**	0.476	0.754
P*		**0.028**	**0.042**	**0.027**				
Photographic GO Score (%)	Baseline	71.10± 8.9	79.99± 7.70	67.66±22.22	0.591	-	-	-
	6 weeks	36.66±2.72	12.66±13.41	25.53±14.09	**0.015**	**0.012**	0.256	0.661
P*		**0.028**	**0.042**	**0.028**				

*Wilcoxon signed rank test, [#]Kruskal-Wallis test, [§]Mann-Whitney U test, $p < 0.05$.
PI: plaque index, GI: gingival index, PD: probing depth; BOP: bleeding on probing GO: gingival overgrowth index, SD: standard deviation.

Multiple comparison revealed no significant differences among the groups in PI, GI and BOP values at baseline. On the other hand, statistically significant difference was found in the baseline PD measurement among the groups (p<0,05); the Group 1 presented significantly higher PD (5.19±0.76 mm) than the Group 2 (PD=3.75±0.55 mm) (p<0.05). There were no statistical differences in PI, GI and PD values among groups at 6 weeks after NSPT (p>0.05). Although multiple comparison of BOP values revealed significant difference (p<0.05), further statistical analysis demonstrated no difference between any of the groups (p>0.05).

NSPT resulted in the significant decreases in both model and photographic GO scores in all groups (p<0.05). Baseline GO assessment on both plaster models and intraoral photographs showed similar values among the groups (p>0.05). However, 6 weeks after NSPT the model and photographic GO scores were statistically significantly different among the groups (p<0.05) (Table 2). The DIGO patients with drug substitution (Group 2) demonstrated significantly lower gingival enlargement than the DIGO patients without drug replacement (Group 1) at 6 weeks after NSPT (p<0.05). Individual model and photographic GO scores of the patients in all groups at 6 weeks following NSPT are listed in Table 3. At 6 weeks after NSPT, Model score values varied for group 1, 2 and 3 between 18-58%, 0-34% and %8-52, respectively. At 6 week following NSPT, Photographic score values varied for group 1, 2 and 3 between 30,00-46,66%, 0-26,66% and 13,33-50,00%, respectively. At the reevaluation phase performed 6 weeks after completion of NSPT, all patients were examined and assessed in terms of surgical treatment requirement. Periodontal surgery was planned for all patients in the Group 1; 3 out of 5 patients in the Group 2; and all patients in the Group 3. When the model and photographic scores of two patients who did not need periodontal surgery were 4% and 0%, and 0% and 0%, respectively.

Table 3. Individual GO scores of all patients after NSPT

	Model Score (%)			Photographic Score (%)		
Patient No	**Group 1**	**Group 2**	**Group 3**	**Group 1**	**Group 2**	**Group 3**
1	40.00	34.00	20.00	43.33	26.66	23.33
2	38.00	18.00	26.00	33.33	10.00	33.33
3	18.00	18.00	18.00	30.00	26.66	13.33
4	34.00	4.00	52.00	33.33	0	50.00
5	44.00	0	22.00	46.66	0	20.00
6	58.00	-	8.00	33.33	-	13.33

DISCUSSION

DIGO is a side effect of specific drugs such as anticonvulsants, immunosuppressants and CCBs used in the treatment of certain systemic diseases. The enlarged gingival tissue characteristics may be fibrotic or both inflammatory and fibrotic at the same time (Kantarci et al., 2019). Therefore, treatment approach of this pathology depends on the gingival tissue features. Previous studies reported that gingival inflammation is positively correlated with DIGO (Barclay et al., 1992; Harel-Raviv et al., 1995; Keglevich et al., 1999). Within the scope of NSPT, scaling and root planing procedures have positive effect on reducing the size of DIGO by eliminating the inflammatory component of overgrown gingiva (Livada & Shiloah, 2014). This non-invasive conservative method generally minimizes the need for surgical intervention, and is the first step in the treatment of DIGO as well as any periodontal therapy strategy (Aimetti et al., 2005). However, contradictory results have been published by studies investigating NSPT in patients with DIGO. Some researchers concluded that nonsurgical approach comprising supra – and subgingival scaling and root planing is adequate in the management of DIGO (Hancock & Swan,1992; Aimetti et al., 2005), while others stated that oral hygiene programs and NSPT are beneficial for the patient although they are unable to prevent or resolve DIGO entirely (Seymour & Smith,1991; Pernu et al., 1993). When the gingiva does not present the physiological form, contour and size after NSPT, surgical periodontal treatment needs to be applied in order to remove excess gingival tissues, eliminate periodontal pockets, restore the function of the periodontium, and correct the gingival form. Several studies have reported nonsurgical and surgical management of GO induced by certain drugs (Montebugnoli et al., 1996; Kantarci et al., 1999; Naidoo & Stephen, 1999; Aimetti et al., 2005; Mavrogiannis et al., 2006), however, there is no study assessing the effect of drug replacement together with NSPT in patients with DIGO. This clinical trial is the first study to evaluate the short-term effectiveness of NSPT in the management of DIGO with or without drug substitution in comparison with inflammatory GO.

Seymour (Seymour, 2006) reported that age is not a risk factor for DIGO, due to the high prevalence of cardiovascular diseases in individuals using CCB and the limited information regarding age in individuals with DIGO. In our study, the mean age of the DIGO patients in the Groups 1 and 2 (53.00±9.63 years and 50.00±16.04 years, respectively) were higher than the patients with inflammatory GO in the Group 3 (31.33±6.88 years), as expected.

The importance of bacterial biofilm in the etiology of DIGO has been extensively studied and no correlation was found between gingival inflammation and DIGO (Pundir et al., 2014; Aimetti et al., 2005; Pernu et al., 1993). DIGO is affected not only by the severity of inflammation, but also by other factors such as duration of drug usage, drug dose, drug type and genetics. In previous studies, the relationship between the dose and tissue concentration of drugs and DIGO formation were investigated in order to find out the threshold value that triggered this pathology (Modeer et al., 1992; Ellis et al., 1993; Thomason et al., 1995; Seymour et al., 2000). However, the half-life, tissue distribution and concentration, peaking and elimination time of drugs that cause DIGO show differences amoung individuals. That's why studies examining the relationship between DIGO and drug variables including drug dosage and drug concentration in saliva, gingival crevicular fluid and plasma have not revealed a common consensus about threshold value of occurence of DIGO (Modeer et al., 1992; Ellis et al., 1993; Thomason et al., 1995).

Time-related effectiveness of NSPT in GO is also controversial (Kantarci et al., 1999; Montebugnoli et al., 1996; Aimetti et al., 2005). Although the time periods for evaluation were different, it has been observed that NSPT resulted in a decrease in the size of the overgrown gingiva by eliminating the gingival inflammation. There is no established protocol for reevaluation time of DIGO. The consensus report of American Academy of Periodontology World Workshop (Segelnick & Weinberg, 2006) concluded that between 4 to 6 weeks posttreatment period is usually sufficient for assessing the response to therapy. In the light of this information, the clinical effectiveness of NSPT were evaluated at 6 weeks in our study.

Our findings demonstrated that combining a self-performed plaque control program with professional supra and subgingival instrumentation is beneficial in treating both DIGO and inflammatory GO. All clinical periodontal parameters revealed significant reductions 6 weeks after NSPTin all patients. The decrease in PI scores indicated improved oral hygiene level of all patients. Preventing plaque accumulation resulted in significant elimination of inflammation in gingival tissues, followed by decreases in GI and BOP scores. Since all types of GO include inflammatory component at different levels, this finding was in correlation with previous studies (Pernu et al., 1993; Kantarci et al., 1999; Aimetti et al., 2005; Carvalho et al., 2010; Pundir et al., 2014). The PD values were reduced significantly

compared to baseline as a consequence of elimination of inflammation and apical recession of the gingival margin. However, there were no significant differences among the study groups.

Pharmacologic strategy in the management of DIGO involves the substitution of causative drug with an equivalent one (Camargo et al., 2001; Carvalho et al., 2010; Kato et al., 2015). However, creating alternative approach for controlling blood pressure in severe hypertension patients can be challenging for physicians. From this point of view, the decision of replacing the GO inducing drug, needs strong collaboration between dentists and medical doctors. On the other hand, it is contraversial between researchers whether creating alternative pharmacological strategy for the management of hypertension makes any difference in the treatment of GO or not (Morisaki et al., 2001; Fang & Tan, 2021). Considering the change in GO scores in comparison with the baseline values in this study, the modification of DIGO group's medications had additional impact in the 6-week early recovery period after treatment. From this point of view, 6 weeks initial response time interval may be sufficient to evaluate the effectiveness of drug regimen adjustment with NSPT in the treatment of DIGO.

CONCLUSIONS

The severity of GO and inflammation were shown to be reduced after a 6-week recovery period following NSPT in this study . The replacement of the causative drug in the treatment of DIGO made an additional contribution to NSPT in the 6-week period. The combination of NSPT and drug substitution can be considered a treatment option in the management of DIGO patients. This non-invasive approach provides advantages by means of comfortable chairside treatment both for patients suffering from DIGO and for dentists.

Acknowledgement

This study was supported by Marmara University Scientific Research Project Department with the number SAG-C-DRP-241.018.0576.

Conflicts of interest

No potential conflict of interest was reported by any of the authors in this study.

REFERENCES

1. Aimetti M, Romano F, Debernardi C. Effectiveness of periodontal therapy on the severity of cyclosporin A-induced gingival overgrowth. J Clin Periodontol. 2005;32(8):846-50.
2. Barclay S, Thomason JM, Idle JR, Seymour RA. The incidence and severity of nifedipine-induced gingival overgrowth. J Clin Periodontol. 1992;19(5):311-14.
3. Becerik S, Celec P, Gurkan A, Ozturk VO, Kamodyova N, Atilla G. Gingival crevicular fluid and plasma levels of transglutaminase-2 and oxidative stress markers in cyclosporin a-induced gingival overgrowth. J Periodontol. 2016;87(12):1508-16.
4. Brown RS, Beaver WT, Bottomley WK. On the mechanism of drug-induced gingival hyperplasia. J Oral Pathol Med. 1991;20(5):201-9.
5. Camargo PM, Melnick PR, Pirih FQ, Lagos R, Takei HH. Treatment of drug-induced gingival enlargement: aesthetic and functional considerations. Periodontol 2000. 2001;27:131-138.
6. Carranza FA, Hogan EL. Gingival Enlargement. Newman MG, Takei HH, Klokkevold PR, Carranza FA, editors. Carranza's Clinical Periodontology 12th Ed. USA: Elsevier; 2015 .p. 232-33.
7. Carvalho FB, Cabral PA, Gusmao ES, Jamelli SR, Cimoes R. Non-surgical treatment of gingival overgrowth induced by nifedipine: a case report on an elderly patient. Gerodontology. 2010; 27(1):76-80.
8. Das SJ, Olsen I. Keratinocyte growth factor is upregulated by the hyperplasia-inducing drug nifedipine. Cytokine. 2000;12(10):1566-69.
9. Dongari-Bagtzoglou A. Drug-associated gingival enlargement. J Periodontol. 2004;75(10):1424-31.
10. Ellis JS, Seymour RA, Monkman S, Idle JR. Disposition of nifedipine in plasma and gingival crevicular fluid in relation to drug-induced gingival overgrowth. J Periodontal Res. 1993;28(5):373-78.
11. Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ, Thomason JM. Prevalence of gingival overgrowth induced by calcium channel blockers: a community-based study. J Periodontol. 1999;70(1):63-7.
12. Fang L, Tan BC. Clinical presentation and management of drug-induced gingival overgrowth: A case series. World J Clin Cases. 2021;9(32):9926-34.
13. Gong Y, Lu J, Ding X, Yu Y. Effect of adjunctive roxithromycin therapy on interleukin-1β, transforming growth factor-β1 and vascular endothelial growth factor in gingival crevicular fluid of cyclosporine A-treated patients with gingival overgrowth. J Periodontal Res. 2014; 49(4):448-57.
14. Hancock RH, Swan RH. Nifedipine-induced gingival overgrowth. Report of a case treated by controlling plaque. J Clin Periodontol. 1992;19(1):12-14.
15. Harel-Raviv M, Eckler M, Lalani K, Raviv E, Gornitsky M. Nifedipine-induced gingival hyperplasia. A comprehensive review and analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;79(6):715-22.
16. Jorgensen MG. Prevalence of amlodipine-related gingival hyperplasia. J Periodontol. 1997;68(7):676-68.

17. Kantarci A, Carranza F, Hogan E. Gingival Enlargement. Newman M, Takei H, Klokkevold P, Carranza F, editors. Newman and Carranza's Clinical Periodontology 13th Edition. USA: Elsevier;2019. p. 256-67.
18. Kantarci A, Cebeci I, Tuncer O, Carin M, Firatli E. Clinical effects of periodontal therapy on the severity of cyclosporin A-induced gingival hyperplasia. J Periodontol. 1999;70(6):587-93.
19. Kato T, Takiuchi H, Yamaguchi M, Naito T. Ca-channel blocker-induced gingival overgrowth that improved with non-surgical therapy during visiting care: a case report. Gerodontology. 32(4):318-20.
20. Keglevich T, Benedek E, Gera I. Clinical experience with the treatment of gingival hyperplasia induced by calcium channel blocking agents. Fogorv Sz. 1999;92(12):363-72.
21. Kimball O. The treatment of epilepsy with sodium diphenyl hydantoinate. J Am Med Assoc. 1939;112(13):1244-45.
22. Kose KN, Yilmaz S, Noyan U, Kuru B, Yildirim HS, Agrali OB. The gingival crevicular fluid levels of growth factors in patients with amlodipine-induced gingival overgrowth: A pilot study. Niger J Clin Pract. 2020;23(4):561-67.
23. Livada R, Shiloah J. Calcium channel blocker-induced gingival enlargement. J Hum Hypertens. 2014;28(1):10-4.
24. Loe H, Silness J. Periodontal Disease in Pregnancy. I. Prevalence and Severity. Acta Odontol Scand. 1963;21:533-51.
25. Mavrogiannis M, Ellis JS, Thomason JM, Seymour RA. The management of drug-induced gingival overgrowth. J Clin Periodontol. 2006;33(6):434-39.
26. Modeer T, Wondimu B, Larsson E, Jonzon B. Levels of cyclosporin-A (CsA) in saliva in children after oral administration of the drug in mixture or in capsule form. Scand J Dent Res. 1992;100(6):366-70.
27. Montebugnoli L, Bernardi F, Magelli C. Cyclosporin-A-induced gingival overgrowth in heart transplant patients. A cross-sectional study. J Clin Periodontol. 1996;23(9):868-72.
28. Morisaki I, Dol S, Ueda K, Amano A, Hayashi M, Mihara J. Amlodipine-induced gingival overgrowth: periodontal responses to stopping and restarting the drug. Spec Care Dentist. 2001;21(2):60-2.
29. Naidoo LC, Stephen LX. Nifedipine-induced gingival hyperplasia: non-surgical management of a patient. Spec Care Dentist. 1999;19(1):29-34.
30. Nakib N, Ashrafi SS. Drug-induced gingival overgrowth. Dis Mon. 2011;57(4):225-30.
31. Nyska A, Shemesh M, Tal H, Dayan D. Gingival hyperplasia induced by calcium channel blockers: mode of action. Med Hypotheses. 1994;43(2):115-18.
32. Pernu HE, Pernu LM, Knuuttila ML. Effect of periodontal treatment on gingival overgrowth among cyclosporine A-treated renal transplant recipients. J Periodontol. 1993;64 (11):1098-100.
33. Pieper JA. Evolving role of calcium channel blockers in heart failure. Pharmacotherapy. 1996;16(2):43-9.
34. Pundir AJ, Pundir S, Yeltiwar RK, Farista S, Gopinath V, Srinivas TS. Treatment of drug-induced gingival overgrowth by full-mouth disinfection: A non-surgical approach. J Indian Soc Periodontol. 2014;18(3):311-15.
35. Ramon Y, Behar S, Kishon Y, Engelberg IS. Gingival hyperplasia caused by nifedipine-a preliminary report. Int J Cardiol. 1984;5(2):195-206.
36. Rateitschak-Plüss EM, Hefti A, Lörtscher R, Thiel G. Initial observation that cyclosporin-A induces gingival enlargement in man. J Clin Periodontol. 1983;10(3):237-46.
37. Sanz M. Gingival Enlargement. Harpenau LA, Kao RT, Lundergan WP, Sanz M, editors. Hall's Critical Decisions in Periodontology and Dental Implantology 5th edition. USA: People's Medical Publishing House. 2013; p. 57-8.
38. Sato N, Matsumoto H, Akimoto Y, Fujii A. The effect of IL-1alpha and nifedipine on cell proliferation and DNA synthesis in cultured human gingival fibroblasts. J Oral Sci. 2005;47(2):105-10.
39. Segelnick SL, Weinberg MA. Reevaluation of initial therapy: when is the appropriate time? J Periodontol. 2006;77(9):1598-1601.
40. Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. J Clin Periodontol. 2000;27(4):217-23.
41. Seymour RA, Smith DG. The effect of a plaque control programme on the incidence and severity of cyclosporin-induced gingival changes. J Clin Periodontol. 1991;18(2):107-10.
42. Seymour RA. Effects of medications on the periodontal tissues in health and disease. Periodontol 2000. 2006;40:120-29.
43. Seymour, R. A., Smith, D. G., & Turnbull, D. N. The effects of phenytoin and sodium valproate on the periodontal health of adult epileptic patients. J Clin Periodontol. 1985;12(6), 413-19.
44. Silness J, Loe H. Periodontal Disease in Pregnancy. Ii. Correlation between Oral Hygiene and Periodontal Condtion. Acta Odontol Scand. 1964;22:121-35.
45. Smith JM, Wong CS, Salamonik EB, Hacker BM, McDonald RA, Mancl LA, et al. Sonic tooth brushing reduces gingival overgrowth in renal transplant recipients. Pediatr Nephrol. 2006;21(11):1753-59.
46. Somacarrera ML, Lucas M, Scully C, Barrios C. Effectiveness of periodontal treatments on cyclosporine-induced gingival overgrowth in transplant patients. Br Dent J. 1997;183(3):89-94.
47. Tavassoli S, Yamalik N, Caglayan F, Caglayan G, Eratalay K. The clinical effects of nifedipine on periodontal status. J Periodontol. 1998;69(2):108-12.
48. Thomason JM, Seymour RA, Ellis JS, Kelly PJ, Parry G, Dark J. Iatrogenic gingival overgrowth in cardiac transplantation. J Periodontol. 1995;66(8):742-46.

How to cite this article: Eroglu O, Yetis E, Özener HÖ, Kuru L. Periodontal treatment approach for dihydropyridine induced gingival overgrowth with or without drug substitution. European Journal of Research in Dentistry, 2022; 6 (1): 1-7. DOI: http://dx.doi.org/10.29228/erd.18