The Effect of Cyclosporine with and without Nifedipine on Gingival Overgrowth in Renal Transplant Patients

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Abstract

Purpose: *This investigation was performed to evaluate the effect of cyclosporine alone and in combination with nifedipine on gingival overgrowth.*

Methods: *One hundred and nineteen patients who had undergone renal transplantation at least 12 months previously were selected for the study. The patients were divided into 2 groups according to whether they had received cyclosporine alone (group 1,* n *= 98) or cyclosporine with nifedipine (group 2,* n *= 21). Periodontal and pharmacological characteristics were assessed for all patients.*

Results: *Marked gingival overgrowth was seen in 11 (52%) of the patients in group 2 but just 6 (6%) of those in group 1. In addition, the gingival overgrowth index was significantly greater for patients who had received both nifedipine and cyclosporine (Mann–Whitney* U*-test,* p *< 0.001). However, there were no significant differences between groups with higher and lower gingival overgrowth index in terms of age, sex, cyclosporine dose, nifedipine dose or level of cyclosporine in the serum.*

Conclusion: *The combination of cyclosporine and nifedipine may increase the incidence as well as the severity of gingival overgrowth in renal transplant patients. Among patients who had received both drugs, there was a clear relationship between gingival overgrowth and duration of cyclosporine and nifedipine use.*

MeSH Key Words: *calcium channel blockers/adverse effects; gingival overgrowth; immunosuppressive agents/adverse effects; kidney transplantation*

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Cyclosporine is the first-choice immunosupressant for preventing allograft rejection in patients who have received organ transplants. This drug has reportedly also been used for treatment of pemphigus, psoriasis, type 1 diabetes mellitus and rheumatoid arthritis.[1] However, cyclosporine can cause side effects, and gingival overgrowth is one of the most important problems associated with the use of this drug.[2] The hypertension that typically occurs in renal transplant patients is routinely treated with calcium-channel blockers. For patients receiving cyclosporine, nifedipine is the most frequently used calcium-channel blocker because of its direct effect on hypertension as well as its effects in reducing cyclosporine-induced nephrotoxicity.[3]

The aim of this study was to compare the effects of cyclosporine alone and in combination with nifedipine on the gingival tissue of patients who had previously undergone renal transplantation.

Materials and Methods

This study involved a clinical oral examination of patients referred to the Renal Transplant Unit at Labafi Nejad Hospital, Tehran, Iran, during the year 2000. Patients who had undergone renal transplantation at least 12 months earlier and who had received either cyclosporine

alone or cyclosporine in combination with nifedipine throughout the intervening period were considered for inclusion. Pregnant women were excluded, to avoid any changes caused by hormonal effects. None of the patients reported any systemic disease (e.g., diabetes, cardiovascular disease or epilepsy) that would affect their gingival status. Patients were also checked to ensure that they did not have any dental caries, crowns, fixed or removable partial dentures or crowding (any of which could lead to plaque retention) or any periodontal disease. At least 10 teeth in each arch (4 anterior teeth and 3 teeth on each side of the posterior segment) were checked and examined.

Of 317 potential patients who were examined, 119 met the inclusion requirements. Patients were divided into 2 groups: those who had taken cyclosporine alone (group 1, $n = 98$) and those who had taken cyclosporine and nifedipine (group 2, $n = 21$). One dentist, who had been calibrated for his periodontal assessment skills, performed all of the examinations. The examiner was not aware of what type of medicine the patients had taken.

A whole-blood sample was obtained from each patient on the day of the dental examination, before the morning dose of cyclosporine. A radioimmunoassay technique[4] using a Diasorin kit (DiaSorin S.A., Antony, France) was employed to assess the cyclosporine level in serum.

Periodontal Assessment

The lingual and labial surfaces of all teeth were scored according to the Turesky–Gilmore–Glickman modification of the Quigley–Hein plaque index.[5] Gingival overgrowth was evaluated according to the gingival overgrowth index of McGaw and others.[6] A score for gingival overgrowth (ranging from 0 to 3; Table 1) was assigned for all of the upper and lower buccal and lingual gingival units, each of which ranged from the buccal or lingual midpoint of the mesial papilla to the midpoint of the distal papilla of every tooth. For further classification of patients, each group was divided into 2 subgroups on the basis of gingival overgrowth: patients with heavy gingival overgrowth (HGO) were those with at least 1 tooth with a score of 3 (Table 1) or with more than 2 teeth with a score of 2 and patients with minimal gingival overgrowth (MGO) were those who had no gingival overgrowth (score = 0 and score = 1) or 2 teeth or less with a score of 2.

Mean values for gingival overgrowth score were obtained for each sextant of the mouth (sextant I = teeth 18 to 14, sextant II = teeth 13 to 23, sextant III = teeth 24 to 28, sextant IV = teeth 38 to 34, sextant V = teeth 33 to 43 and sextant VI = teeth 44 to 48).

Statistical Analysis

The Kolmogorov–Smirnov test was employed to assess the normal distribution of results for each group. Student's *t*-test was used in cases where a normal distribution was confirmed, and the Mann–Whitney *U*-test was employed for other comparisons. Differences were considered significant at $p < 0.05$.

Table 1 Criteria for gingival overgrowth index[a]

Score	Criteria
0	No overgrowth, feather-edged gingival margin
1	Blunting of gingival margin; only interdental papilla involved
2	Moderate gingival overgrowth (< 1/3 of crown length)
3	Marked gingival overgrowth (> 1/3 of crown length)

[a] *Reprinted from McGaw and others[6] with permission from Elsevier.*

Table 2 Demographic and pharmacotherapy characteristics for 119 renal transplant patients

Characteristic	Group; median (and range)[a] Cyclosporine only ($n = 98$)	Cyclosporine and nifedipine ($n = 21$)
Sex (ratio males:females)	62:36	13:8
Age (years)	21.2 (16–58)	21.6 (16–54)
Cyclosporine therapy		
Dose (mg/kg)	3.6 (1.62–5.72)	2.6 (2.11–4.76)
Duration (months)	56.0 (14–124)	57.0 (14–111)
Nifedipine therapy		
Dose (mg/kg)	NA	0.36 (0.15–0.60)
Duration (months)	NA	41.0 (13–111)

[a] *Except where indicated otherwise.*

Results

The demographic characteristics and pharmacotherapy history of the 119 patients who participated in this periodontal screening are shown in Table 2. There was no statistically significant difference between the 2 groups in terms of sex ratio ($p = 0.90$). Gingival overgrowth index showed no significant differences between male and female patients ($p = 0.64$). Similarly, there was no statistically significant difference in mean age between HGO and MGO patients within group 1 ($p = 0.13$) (Table 3) or within group 2 ($p = 0.97$) (Table 4). There were no significances in age between groups 1 and 2 ($p = 0.85$) (Table 5) or between all HGO patients and all MGO patients ($p = 0.44$) (Table 6).

Gingival overgrowth appeared in 55 (56%) of the 98 patients in group 1 (cyclosporine only) and 19 (90%) of the 21 patients in group 2 (cyclosporine and nifedipine), for a total of 74 (62%) of the entire study population. Marked gingival overgrowth (HGO patients) was observed in 6 (6%) of group 1 and 11 (52%) of group 2 ($p < 0.001$), for a total of 17 (14%) of all patients.

There was no statistically significant difference between groups 1 and 2 in terms of dental plaque index ($p = 0.55$) (Table 5). Similarly, the difference in dental plaque index

Table 3 **Differences in medical, periodontal and pharmacological variables between patients with heavy gingival overgrowth (HGO) and those with minimal overgrowth (MGO) within group 1 (cyclosporine only)**

	Group; mean ± SD[a]		
Variable	**HGO (*n* = 6)**	**MGO (*n* = 92)**	***p* value**
Sex (ratio males:females)	3:3	59:33	
Age (years)	26.33 ± 8.20	31.55 ± 8.32	0.13[b]
Dose of cyclosporine (mg/kg)	4.14 ± 0.86	3.61 ± 0.81	0.14[c]
Duration of cyclosporine therapy (months)	45.33 ± 28.04	56.76 ± 37.31	0.56[c]
Plaque index	2.21 ± 0.87	2.07 ± 0.92	0.62[c]
Overgrowth index	0.33 ± 0.10	0.07 ± 0.10	< 0.001[c]

SD = standard deviation.
[a]*Except where indicated otherwise.*
[b]*Student's* t*-test.*
[c]*Mann–Whitney* U*-test.*

Table 4 **Differences in medical, periodontal and pharmacological variables between patients with heavy gingival overgrowth (HGO) and those with minimal overgrowth (MGO) within group 2 (cyclosporine and nifedipine)**

	Group; mean ± SD[a]		
Variable	**MGO (*n* = 11)**	**HGO (*n* = 10)**	***p* value**
Sex (ratio males:females)	6:5	7:3	
Age (years)	31.69 ± 10.57	31.53 ± 10.66	0.97[b]
Dose of cyclocporin (mg/kg)	3.54 ± 0.86	3.63 ± 0.59	0.94[c]
Duration of cyclosporine therapy (months)	86.27 ± 27.07	25.84 ± 11.07	0.001[c]
Plaque index	13.24 ± 34.42	2.18 ± 0.82	0.13[c]
Overgrowth index	0.65 ± 0.29	0.13 ± 0.10	0.001[c]
Dose of nifedipine (mg/kg)	0.33 ± 0.79	0.41 ± 0.14	0.95[b]
Duration of nifedipine therapy (months)	59.54 ± 30.72	21.66 ± 6.95	< 0.01[b]

SD = standard deviation.
[a]*Except where indicated otherwise.*
[b]*Student's* t*-test.*
[c]*Mann–Whitney* U*-test.*

between HGO and MGO patients within group 1 ($p = 0.62$) (Table 3) and within group 2 ($p = 0.13$) (Table 4) was not significant. However, among all 119 patients, the difference in dental plaque index between HGO and MGO patients was significant ($p = 0.03$) (Table 6).

With regard to duration of cyclosporine therapy, there was no significant difference between HGO and MGO patients within group 1 ($p = 0.56$) (Table 3) or overall ($p = 0.30$) (Table 6), but the difference was significant within group 2 ($p = 0.001$) (Table 4).

The dose of cyclosporine was not significantly different between groups 1 and 2 ($p = 0.87$) (Table 5). Similarly, the differences in cyclosporine dose between HGO and MGO patients were not significant within group 1 ($p = 0.14$) (Table 3) or group 2 ($p = 0.94$) (Table 4).

There was a significant difference between HGO and MGO patients within group 2 in terms of duration of nifedipine therapy ($p < 0.01$) (Table 4), but the dose of this drug did not differ between these subgroups ($p = 0.95$) (Table 4). The level of cyclosporine in the serum did not differ significantly between HGO and MGO patients in the whole population ($p = 0.46$) (Table 6).

The distribution by sextant of the mean values (± standard deviation) for gingival overgrowth score in the HGO patients was as follows: sextant I, 0.4 ± 0.49; sextant II, 0.9 ± 0.55; sextant III, 0.3 ± 0.53; sextant IV, 0.3 ± 0.59; sextant V, 0.9 ± 0.46; sextant VI, 0.4 ± 0.64. Among these sextants, the highest scores occurred in sextants II and V. The gingival overgrowth score in sextant V was higher on the labial surface than the lingual surface (data not shown). The differences among sextants in the gingival overgrowth score were highly significant ($p < 0.002$).

Discussion

Gingival overgrowth is a proven side effect induced by the combination of cyclosporine and nifedipine. In this study, mean gingival overgrowth score in group 2, which had received both cyclosporine and nifedipine (0.40 ± 0.34), was significantly higher than the corresponding score for group 1,

Table 5 **Differences in medical, periodontal and pharmacological variables for the 2 study groups**

Variable	Group; mean ± SD[a] Cyclosporine only (*n* = 98)	Cyclosporine and nifedipine (*n* = 21)	*p* value
Sex (ratio males:females)	62:36	13:8	0.90[b]
Age (years)	31.23 ± 8.36	31.61 ± 10.34	0.85[c]
Dose of cyclosporine (mg/kg)	3.64 ± 0.82	3.57 ± 1.73	0.87[d]
Duration of cyclosporine therapy (months)	56.06 ± 36.79	48.04 ± 29.9	0.32[d]
Plaque index	2.08 ± 0.91	7.98 ± 2.54	0.55[d]
Overgrowth index	0.09 ± 0.12	0.40 ± 0.34	< 0.001[d]

SD = standard deviation.
[a]*Except where indicated otherwise.*
[b]*Chi-square test.*
[c]*Student's* t*-test.*
[d]*Mann–Whitney* U*-test.*

Table 6 **Differences in medical, periodontal and pharmacological variables between patients with heavy overgrowth (HGO) and those with minimal overgrowth (MGO)**

Variable	Group; mean ± SD[a] HGO (*n* = 17)	MGO (*n* = 102)	*p* value
Sex (ratio males:females)	9:8	66:36	
Age (years)	29.81 ± 9.89	31.55 ± 8.51	0.44[b]
Dose of cyclosporine (mg/kg)	3.75 ± 0.88	3.61 ± 0.79	0.42[c]
Duration of cyclosporine therapy (months)	60.17 ± 28.73	53.72 ± 36.75	0.30[c]
Plaque index	9.35 ± 27.75	2.08 ± 0.91	0.03[c]
Overgrowth index	0.54 ± 0.28	0.08 ± 0.1	0.001[c]
Serum level of cyclosporine (ng/mL)	179.20 ± 92.52	194.10 ± 75.22	0.46[b]

SD = standard deviation.
[a]*Except where indicated otherwise.*
[b]*Student's* t*-test.*
[c]*Mann–Whitney* U*-test.*

which had received cyclosporine only (0.09 ± 0.12) ($p < 0.001$). According to previous reports, gingival overgrowth occurs in about 30% of cyclosporine-treated patients,[5] with prevalence ranging from 6% to 81%.[7,8] The combination of cyclosporine with nifedipine is accompanied by greater gingival overgrowth, with a reported prevalence of 48% to 60%.[3,9] Thus, gingival overgrowth is more frequent and more severe when cyclosporine and nifedipine are combined.[3,9,10]

It is believed that the pharmacodynamics of cyclosporine and nifedipine is based on calcium regulation, as well as the synthesis and release of collagenase. Other metalloproteinases are derived from fibroblasts, a process that depends on calcium level.[9] Any changes in the synthesis or release of collagenase from fibroblasts may lead to destruction of collagen. Lack of balance in the production and destruction of collagen is one of the main mechanisms of gingival overgrowth.[9] The combination of cyclosporine and nifedipine has a more disruptive effect on collagen degradation because it is accompanied by the increasingly inhibitory effects of both drugs on collagenase (which is calcium dependent). The collagen level in the connective tissue may then rise, which in turn leads to more severe gingival overgrowth.

In a recent study, nifedipine-treated men were 3 times more likely to experience gingival overgrowth than women.[11] However, several other studies have shown no correlation between sex and gingival overgrowth.[7,12] In the present study, there was no significant difference in gingival overgrowth index between men and women, although there was a higher incidence of gingival overgrowth in women. This result could be due to the difference in measuring methods or devices for the HGO patients and the effect of individual predispositions in fibroblastic function.[6]

Some authors have stated that gingival overgrowth is dependent on drug dose.[3,8] In animal studies, the dose of nifedipine alone had a clear effect on gingival overgrowth, but this was not the case when nifedipine and cyclosporine were used together.[13] The results of the current investigation agree with those of other authors[14–16] in not supporting a role for dose dependency of the drugs alone or together.

It has been stated that dental plaque has a fundamental role in gingival overgrowth induced by cyclosporine intake,[17] and other studies have reported a significant correlation between plaque or gingivitis and the prevalence and severity of gingival overgrowth.[7,9] In contrast, some researchers have found no correlation between plaque or gingivitis and gingival overgrowth.[8] A recent study showed

that dental plaque had no role in gingival overgrowth, but that gingivitis might have a predisposing effect.[18] In the study reported here, the role of dental plaque was assessed among patients with marked and less significant gingival overgrowth. There was no significant difference within group 1 (cyclosporine only; Table 3) or group 2 (cyclosporine and nifedipine; Table 4), but the difference *was* significant when the results for all patients were analyzed together (p = 0.03) (Table 6). This analysis suggests that dental plaque has a predisposing role in gingival overgrowth, such that when this factor was considered in groups 1 and 2 separately, it was overshadowed by other factors, such as drug dose or duration of drug therapy, and no significant correlation could be seen. However, when the larger population was evaluated, the effect of plaque on gingival overgrowth could be detected more easily, and the correlation was statistically significant. The plaque index was higher in patients with marked gingival overgrowth. Therefore, poor oral hygiene due to gingival overgrowth may be the main cause of plaque accumulation, and increasing plaque index is secondary to severe gingival overgrowth. However, it would appear that dental plaque, even if necessary, is not sufficient to account for development of the gingival response in patients receiving cyclosporine. In the present study, several patients in the MGO group exhibited a high dental plaque score but displayed no evidence of gingival overgrowth. Data from cross-sectional studies such as these, however, should be evaluated with caution, and further long-term studies are necessary to clarify this issue. The role of local and pharmacological parameters in the pathogenesis of cyclosporine-induced gingival overgrowth remains unclear.

A significant inverse correlation between the duration of cyclosporine therapy and gingival overgrowth was reported for a group of cardiac transplant patients.[19] Some authors have reported a relationship between gingival overgrowth and duration of nifedipine intake.[20] Animal studies have shown that cyclosporine-induced, nifedipine-induced and phenytoin-induced gingival overgrowth is related to the duration of drug therapy.[12] However, other authors have reported no significant correlation between the duration of therapy and gingival overgrowth.[6,7] Comparison of the HGO and MGO patients within group 2 of this investigation showed a significant correlation between gingival overgrowth and duration of cyclosporine and nifedipine therapy (Table 4). Individual susceptibility could be considered the cause, as the reaction of gingival fibroblasts to the overgrowth inducers might vary according to ethnic background.[9] Other factors, including mean duration of therapy, dose of drug and measuring techniques, could also account for differences in results that have been reported in the literature. Further investigations are suggested to define different types of gingival fibroblasts and differential responses of these cells to drugs that induce gingival overgrowth to clarify the correlation between duration of therapy and gingival overgrowth.

In conclusion, the combination of cyclosporine and nifedipine may increase the incidence as well as the severity of gingival overgrowth. Dental plaque does not play a major role in gingival overgrowth during therapy with cyclosporine or cyclosporine combined with nifedipine. However, the role of other factors in predisposition or exacerbation of tissue overgrowth cannot be ruled out by the results of the present study. There was a relationship between gingival overgrowth and duration of cyclosporine and nifedipine intake in the group taking both of these drugs. Individual variations in cyclosporine metabolism or response of the gingival fibroblast subpopulation to cyclosporine or its metabolites might also be important causative factors. ◆

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