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The close association between dental and periodontal treatments and oral ulcer course in Behcet's disease: a prospective clinical study

Umit Karacayli[1], Gonca Mumcu[2], Ismail Simsek[3], Salih Pay[3], Osman Kose[4], Hakan Erdem[3], Haner Direskeneli[5], Yılmaz Gunaydin[1], Ayhan Dinc[3]

[1]*Department of Oral and Maxillofacial Surgery, Gulhane School of Medicine, Ankara, Turkey;* [2]*Department of Health Management, Faculty of Health Sciences, Marmara University, Istanbul, Turkey;* [3]*Department of Rheumatology, Gulhane School of Medicine, Ankara, Turkey;* [4]*Department of Dermatology, Gulhane School of Medicine, Ankara, Turkey;* [5]*Department of Rheumatology, Faculty of Medicine, Marmara University, Istanbul, Turkey*

OBJECTIVE: The aim of the study was to evaluate the influence of dental and periodontal treatments to the course of oral ulcers in patients with Behcet's disease (BD).

METHODS: Fifty-eight consecutive BD patients with oral ulcers were studied. Twenty-nine patients were in the intervention group (F/M: 15/14, mean age: 39.6 ± 6.9 years) and 29 (F/M: 15/14, 39.4 ± 10.6 years) were followed with a conventional treatment approach. In addition to oral hygiene education, dental and periodontal treatments were carried out in the intervention group, whereas the control group was only given oral hygiene education. Patients were evaluated in the pre-treatment observation period (1 month), treatment period (1 month) and 6 months after treatment.

RESULTS: An increase in the number of new oral ulcers (4.1 ± 3.5) was observed within 2 days during the treatment compared with 3–30 days during treatment month (2.3 ± 1.2) ($P = 0.002$). However, 6 months after the treatment, the number of oral ulcers (1.9 ± 1.5) was significantly lower compared with the pre-treatment observation (4.8 ± 3.2) ($P = 0.000$) and treatment periods (6.4 ± 2.3) in the intervention group ($P = 0.05$), whereas a similar oral ulcer presence was observed in the control group (2.8 ± 2.4, 3.7 ± 2.3 and 4.8 ± 4.3, respectively) ($P > 0.05$). Dental and periodontal indices were also better in the intervention group during the 6-month follow-up.

CONCLUSION: Our results suggest that, in BD patients, dental and periodontal therapies could be associated with a flare-up of oral ulcers in the short term, but may decrease their number in longer follow-up. They also lead to a better oral health.

Correspondence: Umit Karacayli, Department of Oral and Maxillofacial Surgery, Gulhane School of Medicine, Ankara, Turkey. Tel: +90 312 3046043, Fax: +90 312 3046020, E-mail: ukaracayli@gmail.com/ukaracayli@gata.edu.tr
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Introduction

Behcet's disease (BD) is a chronic, systemic vasculitic disorder with unknown aetiology. Oral and genital ulcers, ocular, arthritic, vascular, gastro-intestinal and central nervous system manifestations are in the clinical spectrum of BD. Infection-related factors including *Streptococcus* spp. and herpes simplex virus, genetic background such as human leucocyte antigen-B51, and a dysregulated innate immune response are among the mechanisms associated with the etiopathogenesis of BD (1–5).

Infections may be an important part of the pathogenesis as they could both initiate and reactivate clinical manifestations in BD. The relationship between the oral environment and the disease pathogenesis can be summarized as follows: first, oral ulcers are the most common and usually the first clinical manifestation of BD. Second, an augmented immune response to oral streptococci is observed in BD patients, and finally an increased incidence of tonsillitis and dental caries, and aggravation of the disease by dental treatments are important observational clues in clinical practice (6–14).

Poor oral health regarding dental and periodontal health is observed in patients with BD (5, 15–18) and is associated with a more severe disease spectrum (5, 18). Yet, no prospective clinical study was carried out to confirm the effects of dental and periodontal treatments both in the short and long terms in patients with BD. The aim of this study was to evaluate the influence of dental and periodontal treatments to the course of oral ulcers and other disease manifestations in patients with Behcet's disease during a 6-month follow-up period.

Materials and methods

Patients

A total of 58 patients with BD having a history of recurrent oral ulcers were followed in two different centres included in this study. All patients fulfilled the International Study Group criteria for BD (19). Thirty-five of the patients that were referred consecutively from the BD outpatient clinic of the Rheumatology Department in Gulhane School of Medicine, Ankara allocated in the intervention arm of the study. Yet, six BD patients were excluded in the pre-treatment and/or treatment period due to lack of cooperation. Finally, 29 BD patients (F/M: 15/14, mean age: 39.6 ± 6.9 years) were included in the intervention group. In addition, 29 age- and gender-matched consecutive patients with similar treatment protocol (F/M: 15/14, mean age: 39.4 ± 10.6 years) from the BD outpatient clinic of the Rheumatology Department of Marmara University Medical School were served as controls. The clinical features of the groups are given in Table 1. Nearly one-third of the patients ($n = 10$) had been under the treatment of immunosuppressive (azathioprine or corticosteroids), and remaining patients ($n = 19$) had been on colchicine (1–2 mg/day) in either patient groups. Disease severity score reflecting organ involvement was also calculated in both groups (20).

Assessments

Two dentists (UK in the intervention group and GM in the control group) carried out all oral examinations of their local patients having BD. Clinical examination of all patients were carried out at each visit by rheumatologists and a dermatologist at corresponding units.

Interventions

Patients were evaluated at baseline visit, pre-trial observation period (1 month), treatment period (1 month) and 6 months after treatments or oral hygiene education.

Baseline visit

Patients were selected in both arms of this study and matched according to age, gender and treatment protocol. Patients were instructed to collect data on a chart about the number and duration of oral ulcers, frequency of tooth brushing and other relevant clinical manifestations on a monthly basis, during the whole study period at baseline visit.

Table 1 Organ involvement according to patient groups

	Intervention group, n (%)	*Control group, n (%)*	*P-value*[a]
Oral ulcer	29 (100)	29 (100)	–
Genital ulcer	29 (100)	29 (100)	–
Erythema nodosum	29 (100)	29 (100)	–
Arthritis	17 (58.6)	12 (41.4)	0.189
Vascular involvement	9 (31)	6 (20.7)	0.368
Uveitis	5 (17.2)	11 (37.9)	0.078

[a]Chi-square test was used in the analysis.

Pre-treatment period

Pre-treatment period took place at 1 month following the baseline visit. Data about oral ulcer and disease pattern as well as oral hygiene as previously described were recorded by patients during 1 month.

Pre-treatment assessment of oral health

To determine baseline oral health status and the individual treatment plan, patients were evaluated before any treatment intervention by both dentists at the end of pre-treatment period. Dental indices including the number of extracted teeth, carious teeth and filled teeth, and periodontal indices regarding plaque index (PL I), gingival index (GI), sulcus bleeding index (SBI), periodontal probing depth (PPD), clinical attachment level (CAL), were used in the evaluation of the patients' oral health status (21). Periodontal treatment was planned according to standard basic protocol (22).

Treatment period and assessments

After a 4-week pre-trial observation period, BD patients, recruited at Marmara University Medical School served as controls, were given only basic oral hygiene education and followed without any dental or periodontal treatments.

After the same observational period, BD patients followed at Gulhane School of Medicine undertook dental or periodontal treatments in addition to the oral of hygiene education. Treatment protocol consists of filling of carious teeth with suitable filling material, as well as periodontal therapy including intensive removal of calculus and biofilm in the supragingival and subgingival area, with the use of scaling, root planning and polishing. Root fragments and teeth that could not be saved were extracted. All dental and periodontal treatments were started at the time when the patient was free of oral ulcers for at least 5 days and completed within the first 2 weeks of a month. Patients in the intervention group were examined at days 2, 4, 8, 15 and 30 for oral ulcer pattern during the one-month treatment period. The number of newly occurring oral ulcers at these days was recorded, and the sum of the number of oral ulcers occurred during this period was calculated.

6-month post-treatment visits

These visits took place 6 months following the termination of dental or periodontal treatments or oral hygiene education. Assessments in these visits include oral health status and collection of the patient recorded data about the oral ulcers and tooth brushing. The study was approved by the Human Research Ethical Committees of Gulhane and Marmara University Medical Schools, and the informed consent was given by the patients at the time of study entry.

Statistical analysis

Data were analysed by using SPSS 11.0 statistic programme (SPSS Inc., Chicago, IL, USA). Chi-square test, unpaired *t*-test and paired *t*-test were used in the analysis. A $P \leq 0.05$ is accepted to be significant.

Results

The organ manifestations of BD patients were given in Table 1. No significant difference was observed in major organ involvement ($P > 0.05$) and disease severity scores (intervention group: 4.8 ± 1.8 vs. control group: 5.1 ± 1.7) in both patient groups ($P = 0.55$). Although 35 patients were included in the intervention group in the beginning, six patients dropped-out due to non-attendance to the dental clinic and control visits.

Pre-treatment period

The number of oral ulcers and the frequency of tooth brushing were also similar in both groups ($P = 0.134$ and $P = 0.112$, respectively). However, the duration of healing time was higher in the intervention group than the control group (9.7 ± 3.8 vs. 7.2 ± 2.5) ($P = 0.008$) (Table 2).

Pre-treatment assessment of oral health

The number of filled teeth was also found to be higher in the intervention group (3.1 ± 3.2) compared with controls (0.5 ± 1.01) ($P = 0.000$). No significant difference was found in scores of other dental and periodontal indices between the groups ($P > 0.05$) (Table 2).

Treatment period

In the intervention group, the mean scores of the PL I, GI and SBI (2.04 ± 0.8, 1.8 ± 0.7 and 1.7 ± 0.4, respectively) and periodontal pocket depth (2.8 ± 1.1) in the pre-treatment period were significantly higher than those after periodontal treatments, as had been predicted (0 ± 0 for indices) ($P < 0.005$). All carious teeth were filled by suitable filling materials during the treatment procedure. An increase in the frequency of tooth brushing was seen after treatments (1.5 ± 0.7) compared with pre-treatment (0.7 ± 0.5) ($P = 0.000$) (Table 2).

In the intervention group, the number of oral ulcers significantly increased in the treatment period (6.4 ± 2.3) compared to that in the pre-treatment period (4.8 ± 2.3) ($P = 0.000$). The increase in the number of newly occurring oral ulcers (4.1 ± 3.5) was especially prominent within 2 days during the treatment period (3–30 days: 2.3 ± 1.2) ($P = 0.002$). However, no systemic activation was seen during this period. In contrast, no significant difference was observed in the dental and periodontal health and oral ulcer course in the control group when compared with the results of one month previously ($P > 0.05$).

Scores of PL I, GI and SBI, periodontal pocket depth and the number of carious teeth were significantly decreased in the intervention group compared with those in the controls ($P < 0.05$). As all carious teeth were filled with suitable material, the number of filled teeth in the intervention group was significantly higher than the controls ($P = 0.000$). No significant difference was observed in CAL between the groups ($P = 0.471$).

Although an increase in the number of oral ulcers was observed in the intervention group compared to control group (6.4 ± 2.3 vs. 4.8 ± 4.3), no significant difference was observed ($P = 0.153$). However, healing time of oral ulcer was significantly increased in the intervention group (12.2 ± 3.9) compared with controls (7.6 ± 2.8) ($P = 0.000$). The frequency of tooth brushing also increased in the intervention group (1.5 ± 0.7 vs. 0.9 ± 0.2) ($P = 0.000$).

6-month post-treatment visits

Scores of PL I, GI and SBI decreased in the treatment period compared with pre-treatment ($P = 0.000$, $P = 0.000$ and $P = 0.000$, respectively) and 6 months after treatment ($P = 0.000$, $P = 0.003$ and $P = 0.000$, respectively). PPD was also higher in the pre-treatment observation period compared with those in the treatment period ($P = 0.001$) and in the 6th month after treatment ($P = 0.025$). In addition, these parameters in

Table 2 Oral health status and the number of oral ulcers in the study groups

	Pre-treatment period			*Treatment period*			*Sixth month after treatment*		
	Intervention group	*Control group*	*P-value*[a]	*Intervention group*	*Control group*	*P-value*[a]	*Intervention group*	*Control group*	*P-value*[a]
Plaque index	2.04 ± 0.8	1.7 ± 1.01	0.266	0.0	1.8 ± 1.02	**0.000**	1.1 ± 0.7	2.2 ± 1.9	**0.005**
Gingival index	1.8 ± 0.7	2.1 ± 1.1	0.206	0.0	2.2 ± 1.04	**0.000**	1.3 ± 0.6	1.7 ± 0.9	0.07
Sulcus bleeding index	1.7 ± 0.4	2.02 ± 1.03	0.109	0.0	2.1 ± 1.1	**0.000**	1.1 ± 0.3	1.9 ± 0.8	**0.000**
Periodontal pocket depth (mm)	2.8 ± 1.1	2.7 ± 0.6	0.847	2.2 ± 0.7	2.8 ± 0.6	**0.002**	2.4 ± 0.7	2.5 ± 0.9	0.695
Clinical attachment level (mm)	4.2 ± 1.6	4.3 ± 1.3	0.991	4.03 ± 1.1	4.3 ± 1.5	0.471	3.9 ± 1.3	4.6 ± 0.9	**0.017**
Carious teeth	0.9 ± 1.01	1.1 ± 1.8	0.993	0.0	1.1 ± 1.8	**0.000**	0.3 ± 0.7	1.6 ± 1.4	**0.000**
Extracted teeth	4.8 ± 5.2	4.9 ± 5.4	0.882	5.9 ± 7.1	4.9 ± 5.4	0.621	5.9 ± 7.1	5.04 ± 4.9	0.633
Filling teeth	3.1 ± 3.2	0.5 ± 1.01	**0.000**	4.1 ± 3.4	0.9 ± 1.4	**0.000**	4.1 ± 3.4	1.0 ± 2.02	**0.000**
Number of oral ulcer	4.8 ± 3.2	3.7 ± 2.3	0.134	6.4 ± 2.3	4.8 ± 4.3	0.153	1.9 ± 1.5	2.8 ± 2.4	0.120
Healing time of oral ulcers (days)	9.7 ± 3.8	7.2 ± 2.5	**0.008**	12.2 ± 3.9	7.6 ± 2.8	**0.000**	8.5 ± 2.4	7.3 ± 3.01	0.118
Tooth brushing/day	0.7 ± 0.5	0.8 ± 0.3	0.112	1.5 ± 0.7	0.9 ± 0.2	**0.000**	0.7 ± 0.4	0.8 ± 0.2	0.141

[a]Unpaired *t*-test was used in the analysis.
Bold values, statistically significant.

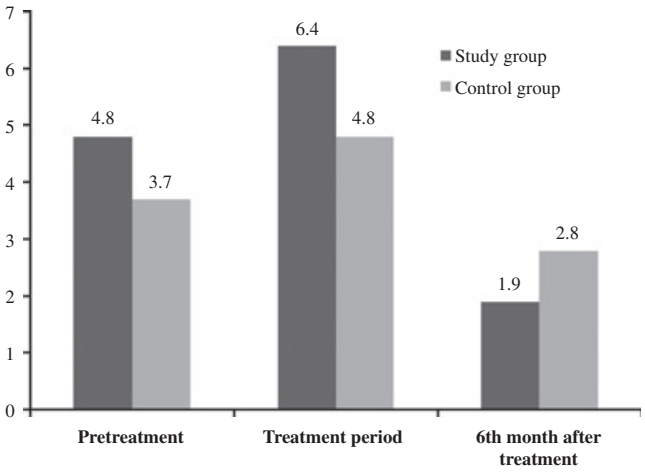

Figure 1 The number of oral ulcers in the study groups according to three different time periods.

the 6th month were also higher than treatment period ($P = 0.000$). The number of carious teeth was also significantly lower during the treatment period compared to the pre-treatment ($P = 0.000$) and 6th month ($P = 0.026$).

Six months after the treatment, the number of oral ulcers (1.9 ± 1.5) was significantly lower compared to pre-treatment observation period (4.8 ± 3.2) and treatment period (6.4 ± 2.3) ($P = 0.000$ and $P = 0.000$, respectively) (Fig. 1). Healing time of the oral ulcers increased in the treatment period (12.2 ± 3.9) compared with the pre-treatment period (9.7 ± 3.8) ($P = 0.000$) and decreased in the 6th month (8.5 ± 2.4) ($P = 0.000$). The frequency of tooth brushing increased in the treatment period (1.5 ± 0.7) compared with pre-treatment (0.7 ± 0.5) ($P = 0.000$), whereas it decreased in the 6th month (0.7 ± 0.4) compared with the treatment period ($P = 0.209$).

The patients' PL I and sulcus bleeding clinical attachment level were found to be significantly lower in the intervention group compared to those in the controls ($P < 0.05$). Although scores of GI were decreased, a significant difference was not reached ($P = 0.07$). Frequency of tooth brushing was similar in both groups. Although the number of oral ulcers was observed to be lower in the intervention group (1.9 ± 1.5) compared with that in the controls (2.8 ± 2.4), no significant difference was observed ($P = 0.12$) (Table 2). CALs were higher in the control group compared with the intervention group ($P = 0.017$).

In the control group, CALs were significantly increased in the 6th month examination compared with pre-treatment observation period and the first month of follow-up ($P = 0.000$). Interestingly, the number of oral ulcers also decreased in this group in the 6th month compared with the observation period of the study, with a borderline significance ($P = 0.053$). No significant difference was observed in dental and periodontal indices during the duration of the study, although some changes were seen in them ($P > 0.05$).

Discussion

Periodontal infections are reported to be associated with the onset and progression of serious disorders (23–25), such as atherosclerosis and coronary heart disease (23, 26–28), diabetes mellitus, pre-term low birth-weight babies and chronic obstructive pulmonary disease (29). Similarly, poor oral health was observed in patients with BD (15, 18). Oral ulcers as a common clinical condition occur in the oral mucosa, and the oral environment could have a role in the initiation of the disease (3, 5). The pathogenic leakage is microbial plaque accumulations that is a complex ecosystem around the gingiva and also carries an increased risk of increased disease severity (15). Increased oral manifestations are seen after dental treatment as a clinical observation in BD patients (10), yet there is no prospective controlled study evaluating the effects of dental and periodontal treatments on disease courses in both the short and long term follow-up.

In this study, we observed that oral ulcer formation was triggered by dental and periodontal treatments within 2 days, whereas flare-up of systemic manifestations was not seen during the treatment and follow-up period. The activation of oral ulcers could be explained by local trauma and activation of systemic immune response to oral microbial pathogens and mediators in BD. Trauma related to the mouth mirror, the tip of saliva suction and other devices used during treatment could lead to an activation of oral ulcers. Periodontitis is a chronic infection in the gums leading to alveolar bone destruction. Subgingival biofilms constitute enormous and renewed bacterial load. The tissue concentrations of lipopolysacharides, soluble antigens, cytokines such as tumour necrosis factor (TNF)-a, interleukin (IL)-1b and interferon γ and prostaglandin E2 are fairly elevated in the disease course. Therefore, periodontium can serve as a reservoir of these mediators, which can then enter the circulation and trigger systemic effects continuously (29). Moreover, periodontal procedures are the pathways for the entrance of oral bacteria to the bloodstream (28, 29). An intense transient bacteraemia and the moderate acute systemic inflammatory response as well as local gingival soft tissue damage could be seen by periodontal treatment. Acute release of cytokines to the sera such as TNF-a and IL-1b within a 24-h period is documented, whereas both cytokines' concentration return to values similar to baseline 1 week and 1 month following therapy (23).

In the intervention group, the number of oral ulcers significantly decreased without a complete remission in the 6th month of follow-up. Elimination of inflammatory responses triggered by microorganisms might have a central role in explaining this result. The decrease in bacterial load and local tissue inflammation is associated with the improvement of the clinical parameters (probing pocket depths, bleeding on probing, etc) after periodontal therapy (30) and removal of carious material, including Streptococci after dental therapy (5). Adhesion of *Streptococcus sanguis* to buccal tissue in the duration of oral ulcer formation (7, 13), presence of

Streptococcus mitis and *Streptococcus salivarious* as dominant strains in the subgingival biofilm and saliva (31), molecular mimicry and possible cross-reactivity between microbial and human heat shock proteins (HSPs) (32) all support the close interaction between anti-microbial responses and innate and adaptive immunity in BD. Previously reported prolonged activation of innate immune response by oral pathogens and inflammatory mediators in BD might be decreased by dental and periodontal treatments. This later might lead to a diminished adaptive immune response (3). Similarly, local triggering factors such as trauma and oral streptococci are suggested in the pathogenesis of recurrent aphthous stomatitis (RAS). Cross-reactivity between a streptococcal 60–65 kDa HSP and the oral mucosa is also demonstrated in RAS (33).

Frequency of tooth brushing was increased during treatment in the intervention group. However, in the 6th month, this was decreased to the baseline level. Parallel to this, scores of dental and periodontal indices were slightly increased in the 6th month. A change in tooth brushing habits is a crucial part of disease management and a decrease in the time between the recall periods may be more effective.

There are two main limitations of this study. The number of individuals included in this analysis was relatively small. Thirty-five patients were included in the intervention group in the beginning, however, six patients dropped-out because of non-attendance to the dental clinic and control visits. We plan to extend our observations in a larger patient data set. The other point was the referral bias as patients were followed-up in two different Rheumatology clinics. The control group was selected and age and gender matched according to the treatment protocols during the same time span to overcome this problem. A high inter-observer concordance was also present between the two clinicians of the study.

Conclusion

This is the first prospective clinical study in BD patients to demonstrate that dental and periodontal therapies are associated with flare-up of oral ulcers in the short term but decrease their number in longer follow-up. We, therefore, suggest that maintenance of oral health by dental and periodontal treatments, oral hygiene habits and regular dental checkups could have a role in improving oral health and must be a main part of treatment protocols. Whether our results extend to longer follow-up and different patient subgroups require further studies.

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