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Influence of anxiety and catastrophizing on pain perception in orthodontic treatment and its association with inflammatory cytokines

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Abstract: Pain is common in orthodontic treatment, is subject to individual variation, and is associated with anxiety and stress, which can potentially become catastrophizing. The aim of the present study was to determine the variability of pain response after the insertion of orthodontic separators and to assess the association of pain levels with dental anxiety, catastrophizing, tooth sensitivity, and genetic expression of cytokines. To this end, 70 patients of both genders were divided into two equal groups according to the elastomeric separator used: G1 (Dentaurum) and G2 (Orthometric). Two separators were inserted in the mesial and distal sides of the lower right first molar. Participants were instructed to rate the level of pain at T0 (before insertion), T1 (just after insertion), and T2 (24 hours after insertion) on a visual analog scale. The gingival crevicular fluid was collected at T0 and T2. The levels of anxiety, catastrophizing, tooth sensitivity, and cytokine expression were also assessed. Statistical analysis was performed with the Fisher-Freeman-Halton, chi-squared, Spearman's correlation, and dependent and independent t tests (α=5%). Pain intensity was higher at T2 than at T1, in both groups (P<.05). An association was established (P<.05) between pain intensity at T1 and catastrophizing, and at T2 with anxiety and catastrophizing. Within-group differences in cytokine expression were found between T0 and T2. There was no correlation between cytokine expression and pain levels, anxiety, catastrophizing, and sensitivity at T2. Tooth separation produced variable pain levels, which were influenced by anxiety and catastrophizing, however, pain level was not correlated with increased cytokine expression.

Keywords: Orthodontics; Anxiety; Catastrophizing; Pain; Cytokines.

Introduction

Pain is one of the most important reasons that discourage patients from seeking orthodontic treatment.[1,2] It seems that orthodontic pain affects 70% to 95% of children undergoing orthodontic treatment, either with fixed or removable appliances, and it may begin 2 to 3 hours after appliance insertion and last up to 7 days.[3] During orthodontic therapy, pressure, ischemia, inflammation, and periodontal edema cause

pain. Being highly subjective, pain varies greatly depending on the individual and on several factors such as age, gender, emotional state, culture, and previous painful experiences.[4,5]

Inflammation is a biological process with the following signs and symptoms: flushing, heat and pain. During orthodontic treatment, a mechanical stimulus causes an inflammatory reaction in the periodontal ligament and, in response to this stimulus, active substances such as cytokines and enzymes are expressed by cells within the periodontal ligament.[6]

Psychological factors exert a great influence on pain perception. This relationship was explained by the Gate Control Theory,[7] which links sensory aspects of pain to psychological, cognitive, and behavioral factors. According to this theory, both anxiety and stress are highly correlated with pain perception. Other factors such as dental anxiety (psychological state) and catastrophizing have also been associated with orofacial and dental pain.[4,8]

Pain catastrophizing is a term used to describe individuals who exaggerate their pain experience more than the average person, or those who have a negative cognitive-affective response to predicted or actual pain.[9] Catastrophizing has a considerable influence on pain experience during dental treatment,[10] but with regard to pain caused by orthodontic treatment, few studies[4,8] have investigated the relationship with dental anxiety and catastrophizing.

Thus, this study aimed to determine the variability of responses to pain after the insertion of two types of orthodontic elastomeric separators and assess the association of participants' pain levels with anxiety, catastrophizing, tooth sensitivity and inflammatory cytokines present in the crevicular gingival fluid. The null hypothesis was that there is no correlation between the participants' pain level and anxiety and catastrophizing.

Methodology

The Research Ethics Committee at UNOPAR (University of North Parana) approved the protocol for this study.

The sample comprised of 70 patients divided into two groups: G1 (n=35), mean age of 25.7 ± 7.9 years, 24 female and 11 male participants, who used the ring-shaped elastomeric separator with a diameter of 2.1 mm and thickness of 1.27 mm (blue color, Dentaurum™, Germany); and G2 (n = 35), mean age of 24.8 ± 7.2 years, 29 female and 6 male participants, who used the ring-shaped elastomeric separator with a diameter of 3.9 mm and thickness of 1.06 mm (blue color, Orthometric, USA). The subjects presented with malocclusion and a referral for orthodontic treatment.

The sample size was calculated using G Power 3.1 software (Kiev Universität, Germany) based on a pilot study with 25 patients. For this analysis, dental sensitivity was used as the primary outcome variable and the following variation was observed: G1 = -0.34 ±1.46 *versus* G2= 0.48 ±0.94, α level of 0.05 and effect size of 0.68 according to the Cohen statistical power analysis. Thus, a minimum sample size of 70 subjects was obtained (35 per group).

The recruited patients were treated at the UNOPAR post-graduate clinic, where they were given instructions concerning the study and signed an informed consent form (ICF). The following characteristics were established as the inclusion criteria for the study: good general and oral health, presence of lower first molar with healthy mesial and distal surfaces in contact with adjacent teeth (tested by dental floss resistance), and healthy upper incisors. The following exclusion criteria were applied: subjects with any depressive disorder or chronic pain syndrome; currently using medication that could affect pain sensitivity, active caries or periodontal disease; presence of extensive restorations or previous trauma; and endodontic treatment of upper incisors.

A single examiner inserted the orthodontic separators, one in each side of the lower right permanent molar (mesial an distal), with the aim of separating them (Figure 1). The elastic was inserted without stretching by first passing the tooth contact point and then moving it upward toward the occlusal surface. This professional explained the study to all of the patients.

Next, the participants were invited to complete a questionnaire that included the Visual Analogue

Figure 1. Intraoral photograph showing the elastomeric separators.

Scale (VAS). On this scale, the participants made a small vertical mark to indicate the amount of discomfort felt at each moment assessed, which were represented by a separate line each. The participants completed this scale at three different points in time: T0) immediately before inserting the separators; T1) just after insertion; and T2) 24 hours after insertion.[8] The VAS marks represented the severity of pain (pain score). All patients were reminded via text message to draw their markings.

The subjects were assessed with regard to the levels of anxiety (Dental Anxiety Scale, Revised - DAS-R and the state-trait anxiety inventory - STAI) and catastrophizing (pain catastrophizing scale - PCS). After 24 hours, the tooth sensitivity test was performed and pain levels were rated on the VAS. The score of each participant was obtained based on the normative values for each scale. The tooth sensitivity test[11] was performed with a cold thermal test, using -50°C Endo-Frost cold spray (Roeko, Langenau, Germany). This test was performed on the upper right incisor, after a relative isolation with a cotton roll on each side and drying with an air jet. The cold spray was applied to a cotton ball at a distance of three centimeters for three seconds. After the crystallization of the thermal agent, the cotton ball was placed in the middle third of the buccal aspect for a maximum of five seconds, with the participant then rating the painful sensation on the VAS. This test was repeated twice with a 5-minute interval.[12]

The gingival crevicular fluid was collected from the mesial and distal surfaces of the lower left first molar of each patient. The collection was performed before the placement of the elastic ring (T0) and 24 hours (T2) after. Before collection, the tooth was washed and any residue of plaque around the tooth was removed with a cotton ball. Isolation of the area was performed with cotton rolls, and the tooth was gently dried. The gingival crevicular fluid was collected with the aid of first-series 25 mm paper cones (Maillefer-Dentsply Profile). Two collections were made on the mesial surface and two on the distal surface. The paper cone was inserted into the gingival groove to a depth of 1 mm for 30 seconds without excessive pressure then removed; after waiting 90 seconds, the procedure was repeated. Paper cones with blood residue and/or saliva were discarded. After removal, the paper cones were stored in sterile Eppendorf tubes identified by surface and by time T, and frozen at a temperature of -80°C until analysis.[13]

The statistical treatment of data was performed with the Statistical Package for Social Sciences (SPSS)

18.0 software (IBM, England, United Kingdom) (α = 5% and 95%CI).

For testing the pairing of samples, the independent t-test (age) and the chi-squared test (gender) were used. Comparisons of pain intensity and sensitivity at both moments between groups, the Fisher-Freeman-Halton and Wilcoxon tests were performed. Moreover, to assess the association between pattern of anxiety and pain intensity or sensitivity, the Spearman's correlation was used. The dependent t-test was used for intragroup comparisons of cytokine expression at both points in time (T0 and T2) and an independent t-test was used for between-group assessment. The Spearman correlation test was used to investigate the correlation between cytokine expression and pain levels, anxiety, catastrophizing, and tooth sensitivity.

Results

The results showed that the groups were paired according to age (p = 0.55) and gender (p = 0.18).

After inserting the separator (T1), there was a higher prevalence of pain in G2 compared to G1, although this pain was mild (p = 0.04, Table 1). However, after 24 hours (T2) there was no difference between the groups regarding the sensation of pain (p = 0.99, Table 1).

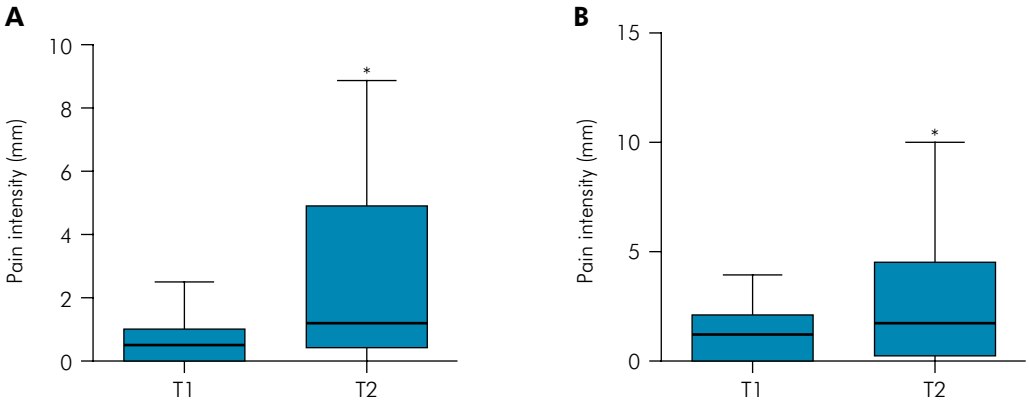
Pain intensity was greater at T2 than at T1 for both G1 (p = 0.0005) and G2 (p = 0.003), according to the Wilcoxon Test (Figure 2, A and B).

There was no difference in sensitivity between the groups at either T1 or T2 (Table 2).

Table 1. Prevalence of pain immediatelt after separator insertion (T1) and at T2 according to the VAS: Fisher-Freeman-Halton Test (P).

Variable	Pain - n (%)				Total - n (%)	p-value
	No pain	Mild	Moderate	Intense		
T1						
G1	16 (45.7)	16 (45.7)	3 (8.6)		35 (100)	
G2	10 (28.6)	25 (71.4)	0 (0)		35 (100)	0.04*
Total	26 (37.1)	41 (58.5)	3 (4.4)		70 (100)	
T2						
G1	11 (31.4)	15 (42.9)	5 (14.3)	4 (11.4)	35 (100)	
G2	11 (31.4)	15 (42.9)	5 (14.3)	4 (11.4)	35 (100)	> 0.05
Total	22 (31.4)	30 (42.9)	10 (14.3)	8 (11.4)	70 (100)	

Statistically significant (p < 0.05).



*Statistically significant, Wilcoxon Test (medians and quartiles), p < 0.05.

Figure 2. Pain intensity just after separator insertion (T1) and at T2 for both groups: Group 1 (A) and Group 2 (B).

There was no statistically significant difference in dental anxiety between G1 and G2 groups ($p > 0.05$) (Table 3).

When the patterns of anxiety and catastrophizing were evaluated, no differences were observed between groups ($p > 0.05$). However, a correlation was observed between catastrophizing (PCS) and pain intensity as well as between anxiety (STAI-S) and tooth sensitivity just after inserting the separator (T1). At T2, a correlation was observed between variables related to anxiety (STAI-S and STAI-T) and catastrophizing (PCS) and pain intensity. On the other hand, in relation to tooth sensitivity, the only correlation found was with anxiety (STAI-S) (Table 4).

Table 2. Prevalence of tooth sensitivity according to the VAS for both groups at T1 and T2: Fisher-Freeman-Halton Test (P)

Group	Pain - n(%)				Total	p-value
	No pain	Mild	Moderate	Intense	n (%)	
T1						
G1	6 (17.1)	17 (48.6)	10 (28.6)	2 (5.7)	35 (100)	
G2	2 (5.7)	20 (57.1)	10 (28.6)	3 (8.6)	35 (100)	> 0.05
Total	8 (11.4)	37 (52.9)	20 (28.6)	5 (7.1)	70 (100)	
T2						
G1	5 (14.3)	18 (51.4)	9 (25.7)	3 (8.6)	35 (100)	
G2	1 (2.9)	17 (48.6)	14 (40)	3 (8.6)	35 (100)	> 0.05
Total	6 (8.6)	35 (50)	23 (32.8)	6 (8.6)	70 (100)	

Table 3. Prevalence of anxiety in the DAS-R for both groups: Fisher-Freeman-Halton Test (P).

Groups	DAS-R - n(%)					p-value
	Little anxious	Slightly anxious	Moderately anxious	Extremely anxious	Total	
G1	20 (57.2)	13 (37.1)	2 (5.7)	0 (0)	35 (100)	
G2	12 (34.3)	19 (54.3)	4 (11.4)	0 (0)	35 (100)	> 0.05
Total	32 (45.7)	32 (45.7)	6 (8.6)	0 (0)	70 (100)	

Table 4. Correlation between variables related to anxiety and tooth sensitivity and the pattern of pain in the studied population.

Variables	Median (1st Q–3rd Q)	Pain intensity		Tooth sensitivity	
		Spearman's correlation (rS)	p-value	Spearman's correlation (rS)	p-value
1					
PCS	5 (1–10)	0.52	0.0001*	0.06	0.60
DAS-R	6 (4–8)	0.24	0.05	0.23	0.06
STAI-S	36 (30–42)	0.17	0.15	0.29	0.02*
STAI-T	40 (35–46)	0.18	0.14	0.15	0.22
T2					
PCS	5 (1–10)	0.34	0.004*	0.14	0.25
DAS-R	6 (4–8)	0.15	0.23	0.19	0.11
STAI-S	36 (30–42)	0.27	0.02*	0.33	0.006*
STAI-T	40 (35–46)	0.26	0.03*	0.21	0.08

*Statistically significant ($p < 0.05$).

There was an within-group difference in the expression of cytokines, when comparing T0 and T2, the only exception being for IL-8 in G2 (Table 5).

There was no significant difference in cytokine expression in the between group comparison ($p > 0.05$). At T2, there was no correlation between the expression of cytokines with the analyzed variables (Table 6).

Discussion

Pain is often present during dental treatment, including orthodontics. In corrective orthodontic treatment, tooth separation is required before the installation of bands and, in some cases, for desirable interproximal stripping.[14]

The instrument selected for pain quantification, the VAS, is a sensible, reliable, and easy-to-use method.[15] The present study found more pain only in G2 just after separator insertion (T1). Even though a lower level of pain might be expected with the thinner separator, this was not the case. An explanation for this may lie in the subjective nature of pain and the relationship between pain and anxiety. This result is in agreement with a study by Bergius et al. (2008)[4] in which they concluded that there is a close relationship between anxiety and the perception of pain felt by the patients.

Although there were no differences between groups, there was a significant difference within each group over the course of the experimental period, considering separator insertion (T1) and its removal after 24 hours (T2). This increase in painful sensation after 24 hours is well established in the literature.[16-18] It has been reported that immediate pain is a result of ligament compression, but the subsequent pain that occurs 24 hours after appliance insertion is recognized as inflammatory and neuropathic pain caused by the release of inflammatory mediators. In animal studies, expression of pain-related substances is observed 24 hours after tooth movement.[19]

Regarding the assessment of anxiety by the DAS-R, there was no significant correlation between pain level and dental anxiety. Some studies showed that patients with higher dental anxiety express higher pain levels in orthodontic procedures.[4] This behavior was not observed in the current study. Dental visits and other procedures where the patient is continuously informed about the treatment to be performed have been shown to have more positive effects on decreasing anxiety.[20]

This study found a significant correlation between catastrophizing (PCS) and pain intensity just after separator insertion (T1) and at T2. It is worth noting that PCS was the most effective instrument for

Table 5. Intragroup comparison (T0-T2): dependent t test (P).

Cytokines	T0 (Mean / SD)	T2 (Mean / SD)	p-value
G1			
IL 1B	24.59 / 6.78	33.28 / 4.09	< 0.0001*
IL 6	5.21 / 1.49	9.08 / 2.32	< 0.0001*
IL 8	57.22 / 7.16	60.08 / 7.40	< 0.0001*
TNF	21.77 / 4.21	30.45 / 4.99	< 0.0001*
G2			
IL 1B	27.66 / 9.67	34.66 / 4.91	< 0.0001*
IL 6	4.28 / 1.08	9.96 / 2.97	< 0.0001*
IL 8	56.31 / 6.67	57.25 / 6.96	0.2514
TNF	21.54 / 3.80	30.47 / 5.20	< 0.0001*

*Statistically significant ($p < 0.05$).

Table 6. Non-parametric correlation between scales and inflammatory cytokines (T2): Spearman's Correlation (P).

Cytokines	VAS	PCS	STAI-E	STAI-T	DAS-R	Sensitivity
	p-value	p-value	p-value	p-value	p-value	p-value
IL1B	0.30	0.98	0.13	0.45	0.15	0.45
IL 6	0.21	0.91	0.89	0.15	0.25	0.20
IL 8	0.82	0.48	0.81	0.71	0.86	0.74
TNF	0.31	0.52	0.65	0.35	0.58	0.19

identifying this. These results reinforce those reported by Lin et al.[21] where tooth pain during orthodontic treatment with fixed appliances is greater in patients scoring high for catastrophizing.

Additionally, the present study observed a significant correlation between the pattern of anxiety verified by the STAI and the prevalence of pain and tooth sensitivity. Both groups showed a significant correlation between anxiety level and pain intensity for STAI-S and STAI-T at T2. These results also corroborate a study by Beck et al.,[8] which noted similar behavior in their sample.

Furthermore, the current study verified a significant correlation between state of anxiety (STAI-S) and tooth sensitivity. The verification of tooth sensitivity by the cold thermal test allows the investigation of the individual preoperative reaction of each subject to a painful stimulus.[8]

A significant increase in cytokine level was found in both groups at T2, with the exception of IL-8 in G2. A previous study, in which orthodontic separators were fitted , found that there was a significant increase in cytokine expression levels peaking after 1 day,[18] which confirms the findings in the current study. Also, there was no significant association between cytokine expression in crevicular gingival fluid and catastrophizing at T2, contradicting a study in which catastrophizing pain was not associated with cortisol but was strongly associated with the reactivity of IL-6.[22] This may have occurred due to the short period of time that the orthodontic separator was in place.

One limitation of this study must be considered. As pain is subjective in nature and varies among individuals, its measurement is difficult, even when using similar criteria. Thus, a study using the split-mouth technique could be a better method for comparing the groups.

Thus, the current results have shown that the variability of pain levels was influenced by psychological factors such as catastrophizing and anxiety, and the null hypothesis was rejected. The findings indicate that psychological factors have a great influence on pain perception.

Conclusion

It may be concluded that:

a. Tooth separation produced different pain levels regardless of the type and commercial brand of the elastomeric ring.
b. Pain levels were influenced by psychological factors such as catastrophizing and anxiety.
c. Catastrophizing and anxiety were not correlated with increased cytokine expression.

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