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Original article

A double-blind, randomized clinical trial assessing the effects of a single dose of preemptive anti-inflammatory treatment in orthodontic pain

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ABSTRACT

Objective: Strategies about how to mitigate or prevent the appearance of pain associated with orthodontic treatment are poorly defined. Herein we conduct a prospective, double-blind, randomized controlled clinical trial assessing the effects of a single dose of anti-inflammatory medication to preemptively treat pain following the placement of orthodontic separating elastics.

Materials and methods: Fifty one participants were randomly selected and divided into three groups: (a) 17 patients took placebo one hour prior to the elastic separator placement; (b) 17 patients took 400 mg lumiracoxib one hour prior to the elastic separator placement; and (c) 17 patients didn't take anything prior to the procedure. Discomfort and pain intensity levels were measured by an analog 10-points visual scale at 2 hours, 6 hours, 24 hours, 2 days and 4 days after the procedure.

Results: When comparing the three groups (no treatment, placebo and active) no significant differences were found. Nonetheless, pain severity was always lower in individuals receiving the drug. Similar pattern was seen for the other time points.

Conclusions: Our study does not support the use of a single dose of medication with anti-inflammatory properties in the preemptive treatment of pain following an orthodontic procedure. Further investigation is required in order to ascertain whether recurrent doses (vs a single dose) can impact outcomes.

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1. Introduction

Pain represents a fundamental sensory experience in defensively alerting the body about imminent or actual damage.

Nonetheless, pain induced by certain medical or dental procedures (e.g. orthodontic treatment) may compromise patients' adherence and/or acceptance of the therapy.

The movement of the teeth induced by orthodontic mechanics damage several of the surrounding structures,

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including the periodontal ligaments. Cell membrane damage triggers the release of phospholipids, activation of the A2 phospholipase enzymes, and release of arachidonic acid which in turn stimulates, through the action of the cyclooxygenase enzyme, the production of prostaglandins, one of the key chemical mediators of pain¹. Clinical consequences include discomfort, with reduced motivation by the patients,² masticatory difficulties,³⁻⁵ sleeping problems and potential overuse of symptomatic medications.^{4,6-9}

This problem is not trivial since the prevalence, intensity, frequency and duration of pain (as well as amount of use of analgesics) seem to be considerably greater after the insertion of orthodontic arch wires than after tooth extractions.¹⁰ The pain occurs in the first 3 to 5 days following the procedures and it seems to be greater in adolescents (14 to 17 years old) relative to older ages¹¹ and within 24 hours of the procedure.^{9,12}

Accordingly, studies have focused on methods to mitigate pain during the course of orthodontic treatment.¹³⁻¹⁹ Results support the use of less aggressive orthodontic techniques, the use of bubble-gums or the use of plastic bite sticks within 8 hours of the procedures. The latter may increase vascular circulation on the periodontal ligament, with faster symptomatic release.¹³ Low level laser (gallium-arsenide-aluminium) targeting the gums and focusing on the medial third of the teeth root has also been investigated.^{14,15} Other studies focused on CO₂ laser applied to the gingival tissue in buccal and palatine regions of the teeth submitted to orthodontic forces.¹⁶ Transcutaneous electric neural stimulation (TENS) has also been used in order to decrease periodontal pain, either applied intra-orally (simultaneous use of electrode probes on the crown and palatine mucosa adjacent to the tooth) or extra-orally, bilaterally on the zygomatic arches¹⁷ as well as on the cheek in the lower bicuspid area.¹⁸ Finally, vibratory stimulation produced by patient controlled appliance has also been assessed to control pain after orthodontic appliance adjustments.¹⁹

Research has also focused on the use of anti-inflammatory and analgesic agents such as ibuprofen,²⁰⁻²⁶ aspirin,²⁰ naproxen sodium,^{23,24} acetaminophen^{25,26} and valdecoxib.²⁷ However, few studies focused on the preemptive treatment using anti-inflammatory medications (before the orthodontic procedure),^{21,27} and evidence to support this approach is required, either to justify it, or to avoid unnecessary treatments.

Most studies evaluating medications did it so using non-steroidal anti-inflammatories (NSAIDs),²⁰⁻²⁵ which inhibit the cyclooxygenase (COX) enzyme, reducing the production of prostaglandins. There are two identified isomers of COX: Cyclooxygenase 1 (COX-1) important for platelet aggregation, glomerular filtration and gastric protection, and Cyclooxygenase 2 (COX-2) mainly involved in inflammation and considered to be an essential component of the inflammatory cascade that results in edema and pain.²⁸ Traditional NSAIDs indiscriminately block both cyclooxygenase (COX) types, and may cause gastric problems,²⁹ as well as interference in renal function, with decreased perfusion, glomerular filtration and interstitial nephritis.³⁰⁻³² Medications that selectively block COX-2 were developed with the aim of avoiding interference with physiological functions.³³

Accordingly, herein we conduct a randomized clinical trial using a COX-2 selective inhibitors medication (lumiracoxib) to preemptively treat pain following the placement of orthodontic separating elastics. We emphasize that although the drug is no longer available in many countries, the principle (preemptive treatment) remains of interest and results are certainly not specific to the drug.

2. Materials and methods

The sample consisted of 87 graduate or postgraduate students from the Dentistry School of Universidade Federal Fluminense, (Niterói, RJ, Brazil). Of them, 51 completed the study (Table 1). Reasons for dropping the study included missing or incomplete information (n=18); discomfort due to the elastic bands (n=10); use of analgesic medication during study (n=6). Two lost their diaries and were unwilling to be resubmitted to the intervention. Participation was voluntary and all subjects signed an informed consent form. The form and protocol were approved by the University's Ethics Committee.

Inclusion criteria were:

- 1) At least 18 years of age;
- 2) Presence of second molars and second bicuspids, since separating elastics had to be fixed on the first molars.
- 3) No clinical signs of gingival inflammation.

Exclusion criteria were:

- 1) Use of any medication that could interfere with results over two weeks before the procedure;
- 2) Any of the following conditions, screened through a questionnaire: cardiopathies, nephropathies, hepatopathies and/or gastrointestinal disorders, diabetes, high cholesterol levels, blood vessel obstructions, allergy to anti-inflammatory drugs, intolerance to lactose, pregnancy.

Ten-point Visual Analog Scales (VAS) were used for evaluation of pain intensity on five different occasions. Patients were instructed to consider "0" as absence of pain, and "10" as unbearable pain. Based on results, pain levels were stratified as absent (0), mild (1-3), moderate (4-7) and severe (8-10).

Two separating elastics (Dentaurum GmbH, Ispringen, Germany) with a diameter of 2.1 mm were placed one on the mesial and the other on the distal region of the first molars of all participants. The elastics were inserted in the proximal areas of the lower left first molars of nearly all subjects, with the exception of 6 patients, where the lower right first molars were used since they were better positioned relative to the adjacent teeth.

Patients were randomly assigned into one of three groups by drawing lots. To ensure similarity in size of the groups, randomization was stratified in blocks of ten (permuted-block randomization). Those in the placebo group took a capsule

Table 1 – Demographics of the sample.

Groups	Mean age	Male	Female
A-Placebo (n = 17)	22.64	4	13
B-Lumiracoxib (n = 17)	24.64	4	13
C-Control (n = 17)	22.47	5	12

of placebo one hour prior to the procedure; those enrolled in the Lumiracoxib group took a capsule of 400 mg of lumiracoxib one hour prior to elastic placement; those enrolled in the control group did not take any capsule (no treatment). The placebo and lumiracoxib capsules were perfectly identical and neither the researchers nor the subjects knew the groups of each subject, as well as the patients of the non medication group knew about the use of capsules by the other two groups.

After the placement of separating elastics, participants were instructed to rate their VAS at the following time intervals: 2 hours, 6 hours, 24 hours, 2 days and 4 days following the placement of separating elastics. Patients were asked not to use any medication during the study, as well as to keep proper oral hygiene, in order to prevent gingival inflammation that could interfere with results.

2.1. Statistical Analysis

The VAS was given to a statistician blinded to study group. Summary tables and descriptive statistics were used to summarize the data (central trend, median, variance and standard deviation).

The Kruskal-Wallis test ($\alpha=0.05$) was carried out to estimate differences in the severity of pain across groups, for each time point. The Friedman test ($\alpha=0.05$) was performed to estimate differences within the same group on different time points and for pairwise comparisons across the time points. A Bonferroni's *post-hoc* test was applied for multiple comparisons.

3. Results

The three groups showed similar ages and gender distribution (Table 1). The three groups had in common the fact that

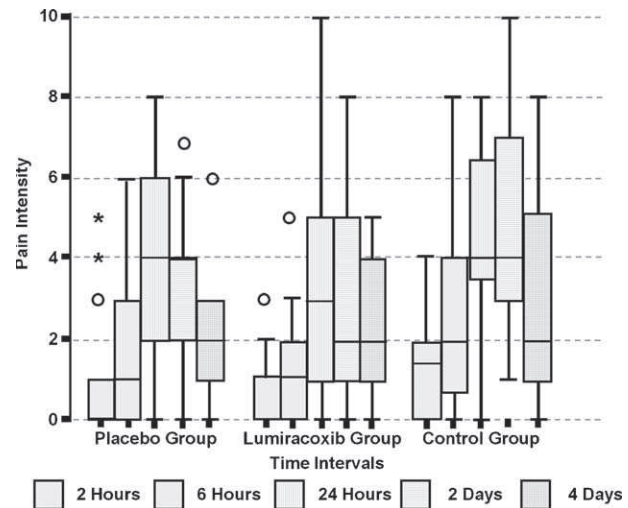


Fig. 1 – Box plot of pain intensity at different time points in three examined groups.

a feeling of discomfort was observed within the first 2 hours, which became more intense 6 hours later, reaching its peak 24 hours after the separating elastics were inserted and lingering into the second day (Fig. 1 and Table 2). In individuals not receiving any treatment (control group), pain reached moderate severity at the 24-hour assessment (median value of 4.0); it remained moderate at 48 hours (median value of 4.0), and was rated as mild at 4 days (median value of 2.0). Statistical differences ($p \leq 0.001$) were seen when the 2-hour period was compared with 24-hour period and 2-day period, and when the 6-hour period was compared with the 24-hour period ($p \leq 0.05$).

For the placebo group, the peak of pain was also observed after 24 hours (median value of 4.0), as well as in the control

Table 2 – Descriptive statistics and statistical comparisons of pain severity at different time points as a function of treatment group.

Time		Groups			p (Intergroup)
		Placebo	Lumiracoxib	Control	
2 hours	25 th percentile	0.0	0.0	0.0	0.373 ns
	Median	0.0	0.0	2.0	
	75 th percentile	1.0	1.0	2.0	
6 hours	25 th percentile	0.0	0.0	0.0	0.345 ns
	Median	1.0	1.0	2.0	
	75 th percentile	3.0	2.0	3.0	
24 hours	25 th percentile	2.0	0.0	3.0	0.059 ns
	Median	4.0	3.0	4.0	
	75 th percentile	6.0	4.0	7.0	
2 days	25 th percentile	2.0	1.0	3.0	0.076 ns
	Median	4.0	2.0	4.0	
	75 th percentile	4.0	4.0	5.0	
4 days	25 th percentile	1.0	1.0	1.0	0.258 ns
	Median	2.0	2.0	2.0	
	75 th percentile	3.0	4.0	5.0	
p (Intragroup)	0.000*	0.001*	0.000*		

ns: not significant.

* $p \leq 0.001$.

group. Significant differences ($p \leq 0.005$) were seen between the 2 hours and 24 hours, between 2 hours and 2 days and between 6 hours and 24 hours. Significant differences were also present between 24 hours and 4 days ($p \leq 0.05$).

For the active group (lumiracoxib), the peak of pain (median value of 3.0) was also recorded after 24 hours. Significant differences ($p \leq 0.005$) were seen between 2 hours and 24 hours and between 2 hours and 2 days. Significant differences ($p \leq 0.05$) were also assessed between 6 hours and 24 hours and between 6 hours and 2 days.

When comparing the three groups (Fig. 1 and Table 2) no statistically significant differences were found comparing the pain intensity in the five stages under analysis. Nonetheless, the VAS values were always and consistently lower in individuals receiving drug. Taking the 24 hours as an example, median pain was 4.0 in the no treatment group, 4.0 in the placebo group and 3.0 in the active treatment group. Similar pattern was seen for the other time points.

4. Discussion

NSAIDs are peripherally-acting non-opioid analgesics. As mentioned, they inhibit the COX enzymes which modulate prostaglandin formation from arachidonic acid originated from the rupture of cells membranes. Prostaglandins are not only essential for the inflammatory cascade, but also for stimulating bone resorption, by increasing the number and function of osteoclasts.³⁵⁻³⁷ NSAIDs do not totally block prostaglandins, but significantly reduce their formation. These drugs would be useful in controlling pain secondary to orthodontic tooth movement, which is in turn triggered by local tissue inflammation. On the other hand, the blockage of the inflammatory response may interfere with the alveolar bone resorption necessary for the tooth movement.^{34,35} Nonetheless, since they are used for short periods of time, they seem not to cause any significant changes in dental movement, while providing welcoming post-procedure analgesia.³⁶⁻³⁸

Although pain is an important problem in the field of orthodontics, this topic has, paradoxically, yielded very few publications. The inflammatory component generated by orthodontic treatment is well documented, and translates in intense discomfort to patients. Strategies to treat established pain or to preempt the development of pain in the first place will likely translate into increased adherence to treatment and improved satisfaction.

Randomized clinical trials (RCTs) are the best source for providing reliable, evidence-based information about therapeutics. Herein we used a prospective, double-blind RCT to estimate the value of using an anti-inflammatory medication to preempt pain secondary to orthodontic procedures.

This study presents a few limitations. First, as compared to align and levelling, simulation of orthodontic treatment using separator placement may cause less pain. Nonetheless, since pain is an individual experience, some participants had important pain even after these less important forces; accordingly, the potential for improvement was narrower than we expected, and consequently we may be underpowered to see differences, even though it is clear that individuals

receiving the active treatment had lower scores of pain for all assessments. Second, the medication used in our study is no longer available. Nonetheless, the principle applies, and it is unlikely that the particular choice of medication significantly alter the results. Other Cox-2 medications remain available, and the efficacy of them is similar to non-selective anti-inflammatory medications anyway. Strengths of our study include the double-blind design and the rigorous assessments and the homogeneity of the sample.

In the present study, we observed that the three groups had some discomfort 2 hours following elastic placement, which worsened within 6 hours and peaked within 24 hours. After this period, although the discomfort lasted for 2 days, it gradually improved. Pain peaked 24 hours after the orthodontic procedure, a finding that has been reported by other studies.^{22,23}

As exposed above, although patients receiving active treatment reported less pain, the observed between-group differences were not statistically significant at any of the trial's five stages. Young et al²³ also demonstrated the effects of another nonsteroidal selective COX-2 inhibitor (valdecoxib), which revealed a tendency towards reducing pain, although significance was also not achieved. Studies with other anti-inflammatory medications yielded positive results.^{20-25,28} However, studies comparing drugs (which would allow recommendations about ideal treatment), are missing.

Pain is a subjective feeling characterized by subconscious arousal and motor inhibition. Being subjective, interindividual variability is high. That is why, in addition to the control group, we had a no treatment group. The goal was to assess pain behavior without the interference of any expedient that might affect the results.

Nonetheless, our study does not support the use of a single dose of medication with anti-inflammatory properties in the preemptive treatment of pain following an orthodontic procedure. Further investigation is required in order to ascertain (i) the real usefulness of preemptively using nonsteroidal anti-inflammatory drugs; (ii) the most effective dosage; (iii) the most tolerable dosage; and (iv) the dosage with fewest side effects. Also if recurrent doses (vs a single dose) impact outcomes.

5. Conclusions

The present RCT failed to demonstrate the benefit of the preemptive treatment of pain following an orthodontic procedure, although the group that received a nonsteroidal anti-inflammatory drug reported less pain at all examined time points.

Conflict of interest

The authors have reported no conflicts of interest.

Riassunto

Obiettivo: *Le strategie finora adottate al fine di attenuare o di prevenire l'insorgenza del dolore associato al trattamento ortodontico non sono ancora chiaramente e perfettamente definite. Si è deciso di*

portare avanti un trial clinico controllato, randomizzato, a doppio-cieco e prospettico per valutare gli effetti di una singola dose di antinfiammatorio per trattare preventivamente il dolore a seguito dell'inserimento di elastici separatori ortodontici.

Materiali e metodi: Sono stati scelti in modo randomizzato cinquantuno pazienti che sono poi stati divisi in tre gruppi: (a) a 17 pazienti è stato somministrato placebo un'ora prima dell'inserimento del separatore elastico; (b) a 17 pazienti sono stati somministrati 400 mg di lumiracoxib un'ora prima dell'inserimento del separatore elastico; a 17 pazienti non è stato somministrato nulla. I livelli di discomfort e di intensità del dolore sono stati misurati avvalendosi di una scala analogica visiva (VAS) a 10 punti, dopo 2 ore, 6 ore, 24 ore, 2 giorni e 4 giorni dal procedimento.

Risultati: Quando raffrontiamo i tre gruppi (nessun trattamento, placebo e trattamento attivo) non riscontriamo differenze significative. Nondimeno, l'intensità del dolore è sempre meno accentuata nei soggetti che assumono il farmaco. Un comportamento simile è stato riscontrato per le diverse scansioni temporali.

Conclusioni: Il nostro studio non è quindi a favore dell'uso di una singola dose di farmaco anti-infiammatorio nel trattamento preventivo del dolore a seguito di un intervento ortodontico. Sono però necessarie altre ricerche per valutare se dosi ricorrenti (rispetto alla singola dose) possano avere un'influenza sul risultato finale.

Résumé

Objectif: Les stratégies pour atténuer ou pour prévenir l'apparition de la douleur associée à un traitement orthodontique ne sont pas pour l'instant bien cernées. On a mené un essai clinique contrôlé, aléatoire, en double-aveugle, prospective pour évaluer les effets d'une simple dose d'anti-inflammatoire pour traiter au préalable la douleur se dégageant du placement d'élastiques de séparation orthodontiques. **Matériels et méthode:** Cinquante et un participants ont été choisis de manière aléatoire et ensuite divisés en trois groupes: (a) on a administré du placebo à 17 patients, une heure avant le placement du séparateur élastique; (b) on a administré 400 mg de lumiracoxib à 17 patients, une heure avant la procédure et (c) on n'a rien administré à 17 patients avant la procédure. On a mesuré le malaise et l'intensité de la douleur à l'aide d'une échelle visuelle analogique (EVA) à 10 points au bout de 2 heures, 6 heures, 24 heures, 2 jours et 4 jours après la procédure.

Résultats: Lorsqu'on compare les trois groupes (aucun traitement, placebo et traitement actif) on n'enregistre aucune différence significative. Toutefois, l'intensité de la douleur a été toujours plus faible chez les sujets qui avaient reçu le médicament. Un modèle semblable s'impose aussi pour les autres délais de temps.

Conclusions: Notre étude ne soutient pas l'utilisation d'une simple dose de médicament anti-inflammatoire pour traiter de façon préventive la douleur suite à un traitement orthodontique. D'autres recherches sont donc nécessaires pour vérifier si des doses répétées (par rapport à une simple dose) peuvent influencer les résultats.

Resumen

Objetivo: Las estrategias sobre cómo aliviar o prevenir la aparición de dolor relacionado con el tratamiento ortodóncico están definidas de manera insatisfactoria. En el caso que nos ocupa, hemos llevado a cabo un ensayo clínico controlado, aleatorio, de doble ciego prospectivo que valora los efectos de una simple dosis de fármaco antiinflamatorio para tratar previamente el dolor, a raíz de la colocación de elásticos de separación ortodóncicos.

Materiales y métodos: 51 participantes fueron seleccionados de manera aleatoria y divididos en tres grupos: (a) a 17 pacientes se les administró placebo una hora antes de la colocación del separador elástico; (b) a 17 pacientes se les administró 400 mg de lumiracoxib una hora antes de la colocación del separador elástico; y (c) a 17 pacientes no se les administró nada antes del procedimiento. Los niveles de molestia y dolor fueron medidos mediante una escala visual analógica (VAS) de diez puntos al cabo de 2 horas, 6 horas, 24 horas, 2 días y 4 días después del procedimiento.

Resultados: Al comparar a los tres grupos (sin tratamiento, con placebo y con tratamiento activo) no se experimentan diferencias significativas. Sin embargo, la severidad del dolor siempre fue más baja en los sujetos a los que se les administró el fármaco. Un patrón parecido fue identificado para las otras temporizaciones.

Conclusiones: Nuestro estudio no respalda la utilización de una simple dosis de fármaco con propiedades antiinflamatorias en el tratamiento previo del dolor a consecuencia de un tratamiento ortodóncico. Sin embargo, más investigaciones son necesarias para comprobar si dosis repetidas (con respecto a la dosis sencilla) pueden influir en los resultados.

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