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ORIGINAL ARTICLE

Effects of ibuprofen and low-level laser therapy on orthodontic pain by means of the analysis of interleukin 1-beta and substance P levels in the gingival crevicular fluid

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Abstract

Objective The goal of this study was to compare the effects of ibuprofen and low-level laser therapy in alleviating orthodontic pain observed after elastomeric separator placement (ESP) by means of the analysis of interleukin 1-beta (IL-1β) and substance P (SP) levels in gingival crevicular fluid (GCF) and visual analog scale (VAS).

Materials and methods A total of 60 subjects requiring ESP for the banding of maxillary first molars were randomly assigned to the ibuprofen, laser, and control groups. The ibuprofen and control groups received, respectively, 400 mg ibuprofen and placebo lactose tablets orally 1 h before ESP; the laser group received a single low-level laser irradiation session immediately after ESP. GCF samples were collected immediately after ESP (day 0) and on days 1, 3, and 7. Pain intensity was evaluated using the VAS immediately after ESP (baseline) and at hours 2 and 6, as well as on days 1, 3, and 7.

Results Although IL-1β levels increased significantly on days 1, 3, and 7 compared to day 0, intergroup comparison results revealed insignificant differences. SP levels indicated insignificant within-group differences. Only the SP levels of the ibuprofen group showed a significant decrease on days 0 and 1 compared to the laser and control groups. In all groups, VAS scores increased from baseline to a peak level on day 1, followed by a significant decrease on days 3 and 7. Intergroup comparison results of VAS scores indicated less pain intensity in the ibuprofen group compared to the control group at baseline.

Conclusions Only the ibuprofen group exhibited significant decreases in SP levels on days 0 and 1, as well as in VAS scores at baseline.

Keywords Orthodontics, corrective · Elastomeric separator · Periodontal ligament · Nonsteroidal anti-inflammatory agents · Visual analog scale

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Effekte von Ibuprofen und Low-level-Lasertherapie auf kieferorthopädische Schmerzen anhand der Analyse der Interleukin-1-β- und Substanz-P-Spiegel in der gingivalen Krevikularflüssigkeit

Zusammenfassung

Ziel Ziel dieser Studie war der Vergleich der Effekte von Ibuprofen und Low-level-Lasertherapie bei der Linderung kieferorthopädischer Schmerzen nach Anbringung des Elastomer-Separators (ESP). Dies wurde gemessen anhand der Analyse der Interleukin-1-β- (IL-1β) und Substanz-P (SP)-Spiegel in der gingivalen Krevikularflüssigkeit (GCF) und mittels der visuellen Analogskala (VAS).

Material und Methoden Insgesamt 60 Probanden, die für die Bänderung der ersten Molaren im Oberkiefer eine ESP benötigten, wurden randomisiert den Ibuprofen-, Laser- und Kontrollgruppen zugeordnet. Die Probanden in der Ibuprofen- und der Kontrollgruppe erhielten jeweils 400 mg Ibuprofen und Placebo-Laktosetabletten oral 1 h vor der ESP, die Probanden der Lasergruppe eine einzige Laserbestrahlungssitzung auf niedriger Stufe unmittelbar nach der ESP. GCF-Proben wurden unmittelbar nach der ESP (Tag 0) und an den Tagen 1, 3 und 7 gesammelt. Die Schmerzintensität wurde unter Verwendung der VAS unmittelbar nach der ESP (Ausgangswert) und zu den Stunden 2 und 6 sowie an den Tagen 1, 3 und 7 ausgewertet.

Ergebnisse Obwohl die IL-1β-Konzentrationen an den Tagen 1, 3 und 7 im Vergleich zu Tag 0 signifikant anstiegen, zeigten die Ergebnisse des gruppenübergreifenden Vergleichs unbedeutende Unterschiede. Die SP-Werte deuteten auf unerhebliche Unterschiede innerhalb der Gruppe hin. Nur die SP-Spiegel der Ibuprofen-Gruppe zeigten an den Tagen 0 und 1 im Vergleich zu den Laser- und Kontrollgruppen einen signifikanten Rückgang. In allen Gruppen stiegen die VAS-Werte an und erreichten am Tag 1 einen Spitzenwert, gefolgt von einem signifikanten Rückgang an den Tagen 3 und 7. Die Ergebnisse des Intergruppenvergleichs der VAS-Scores zeigten bei der Ibuprofen-Gruppe eine geringere Schmerzintensität im Vergleich zur Kontrollgruppe zu Studienbeginn.

Schlussfolgerungen Nur in der Ibuprofen-Gruppe zeigten sich signifikante Verringerungen der SP-Spiegel an den Tagen 0 und 1 sowie der VAS-Werte zu Studienbeginn.

Schlüsselwörter Kieferorthopädie, korrigierende · Elastomer-Separator · Parodontales Ligament · Nichtsteroidale antiinflammatorische Wirkstoffe · Visuelle Analogskala

Introduction

Pain is a sophisticated experience that includes sensations evoked by and in reaction to noxious stimuli [17]. During the various phases of orthodontic treatment, pain develops in response to the tension and pressure zones generated in the periodontal ligament following the application of force [2, 17]. This leads to the secretion of inflammatory mediators such as histamine, serotonin, dopamine, glycine, cytokines, leukotrienes, prostaglandins, and substance P, which stimulate free nerve endings, resulting in the perception of pain [2, 4].

Early orthodontic pain is usually caused by the insertion of elastomeric separators into the mesial and distal interproximal spaces of the tooth to be banded to create adequate space for proper placement [1, 2]. Recent studies have demonstrated that the pain reaches its peak at 24 h, then gradually decreases over 7 days [16, 25]. Pain intensity is sometimes perceived as extremely high and can be sufficient to cause a significant number of patients to discontinue treatment [16, 23, 25].

Nonsteroidal anti-inflammatory drugs, which block prostaglandin synthesis by inhibiting cyclooxygenase activity, are among the most common orthodontic pain management methods [3, 17]. These drugs may decrease the orthodontic tooth movement rate and potentially cause many systemic side effects, such as gastric and duodenal ulceration, coagulation disorders, congestive heart problems, and allergic reactions [4, 31].

The application of low-level laser therapy (LLLT) has also been reported as an efficient means of alleviating orthodontic pain without apparent side effects [9]. LLLT is thought to reduce pain by increasing local blood flow, inhibiting inflammatory substance secretion, inducing neurotransmitter release, altering the conduction and excitation of peripheral nerves, and stimulating endorphin release [2, 4]. However, a literature review on the effectiveness of LLLT in alleviating orthodontic pain showed conflicting results after elastomeric separator placement (ESP). Although some studies found LLLT to be effective [2, 9, 10, 21, 23], others refuted its effectiveness [4, 11, 24].

The intensity of orthodontic pain can be evaluated subjectively using the visual analog scale (VAS) [16, 21, 25] or objectively using chemical analysis of the gingival crevicular fluid (GCF) [24, 26]. GCF analysis is a useful, noninvasive method for detecting the biochemical mediators released during tooth movement that has reasonable sensitivity [13, 24, 26]. In GCF, proinflammatory mediators such as interleukin 1-beta (IL-1β) and prostaglandin E_2 (PGE_2), and neuropeptides such as substance P (SP) were associated

with pain [13, 26]. After a review of studies on alleviating orthodontic pain observed after ESP, it was determined that the effects of many drugs and LLLT were evaluated subjectively by VAS [1–4, 9–11, 21, 23, 25, 31]. Furthermore, the effects of ibuprofen and LLLT were compared using PGE_2 levels in GCF and VAS in only one study [24]. Therefore, this study aimed to compare the effects of ibuprofen and LLLT in alleviating orthodontic pain observed after ESP by analyzing IL-1β and SP levels in GCF and VAS. The null hypothesis was that there would be no difference between the effects of ibuprofen and LLLT in terms of orthodontic pain relief.

Materials and methods

Subjects

A total of 60 subjects who were referred to the Department of Orthodontics, Faculty of Dentistry, at Van Yüzüncü Yıl University between October 2017 and January 2019 were included in this randomized controlled clinical trial. Ethical approval was obtained from the research ethics committee of Van Yüzüncü Yıl University's Faculty of Medicine (26.07.2017/04). Written informed consent was obtained from all participants after they were provided a detailed description of the study. The inclusion criteria were as follows: being older than 18 years, requiring ESP at the beginning of orthodontic treatment for the banding of maxillary first molars, intact maxillary dentition (except third molars), fully erupted maxillary first molars without any treated or untreated apical lesions, tight contacts between the posterior teeth, not currently pregnant and lactating, the absence of systemic and periodontal diseases and chronic or neural pain, no current use of analgesics or antibiotics that interfere with pain perception, no contradiction to the use of ibuprofen, and the absence of gingival pigmentation where the laser would be applied. The exclusion criteria were previous orthodontic treatment and failure to complete the questionnaire or to continue with the follow-up appointments.

Sample size calculation

In a previous study, the standard deviation (σ) for IL-1β levels before bracket placement was 11.6 pg/mL [12], in the present study, it was considered as 11 pg/L. Furthermore, for a 0.05 type I error rate, the effect size and Z values were assumed to be 5 and 1.96, respectively. Based on this information, the sample size was calculated to be a minimum of 18.6 (≅19) according to the equation of sample size calculation ($n = Z^2\sigma^2/d^2$).

Randomization

The subjects were randomly assigned to the ibuprofen, laser, and control groups using a simple randomization technique. We asked each subject to choose one of 60 closed envelopes that were divided equally among the three groups. The male to female ratio was also equal for each group. An operator outside the study performed the random allocation. Elastomeric separators (3M Unitek, Monrovia, CA, USA) were inserted by a single investigator (YK) at the mesial and distal interproximal spaces of the maxillary first molars.

Analysis of the orthodontic records collected at the beginning of treatment revealed that the ibuprofen group included 20 normodivergent subjects (SN/GoGn (°): 30.66 ± 3.72) with skeletal class I malocclusions (ANB (°): 2.68 ± 1.39), whereas the laser group included normodivergent subjects (SN/GoGn (°): 31.14 ± 3.57) with 17 skeletal class I (ANB (°): 2.74 ± 1.20) and three mild skeletal class II malocclusions (ANB (°): 5.33 ± 0.25). In addition, in the control group, there were three hyperdivergent subjects (SN/GoGn (°): 37.63 ± 0.85) with skeletal class I malocclusions (ANB (°): 2.06 ± 0.81) and 17 normodivergent subjects (SN/GoGn (°): 31.03 ± 2.75) with 14 skeletal class I (ANB (°): 2.27 ± 0.95) and 3 mild skeletal class II (ANB (°): 5.2 ± 0.4) malocclusions. All subjects had moderate (4–6 mm) to severe (>6 mm) crowding in the maxillary and mandibular dental arches, and all treatments were performed with extraction or nonextraction [28].

Study groups

The ibuprofen group received 400 mg ibuprofen orally 1 h before ESP, and the laser group underwent a single LLLT irradiation session immediately after ESP. The control group received placebo lactose tablets 1 h before ESP. The ibuprofen and placebo lactose tablets were placed in identical capsules to blind the subjects and investigator to the treatment group. Subjects were told not to take any other analgesics during the observation period.

Laser parameters and procedure

An 810 nm semiconductor gallium aluminum arsenide (Ga-Al-As) diode laser device (Cheese Diode Laser, Wuhan Gigaa Optronics Technology Co. Ltd., Wuhan, China) with continuous emission mode was used for this study (Fig. 1a). For each quadrant, a total of 8 doses of laser irradiation (2 J/cm², 100 mW, 10 s) were applied to the cervical third of the roots. The mesial and distal aspects of the first molars, the mesial aspect of the second premolars and the distal one of the second molars were irradiated from both the buccal



Fig. 1 Diode laser device (**a**, Cheese Diode Laser, Wuhan Gigaa Optronics Technology, Wuhan, China) and laser application in the molar region (**b**)
Abb. 1 Diodenlasergerät (**a**, Cheese Diode Laser, Wuhan Gigaa Optronics Technology Co. Ltd, Wuhan, China) und Laseranwendung im Backenzahnbereich (**b**)



Fig. 2 Gingival crevicular fluid (GCF) sample collection using standardized sterile paper strips
Abb. 2 Entnahme von GCF („gingival crevicular fluid") unter Verwendung standardisierter steriler Papierstreifen

and the palatal sides. During the exposure, the tip was held perpendicular and in contact with the mucosa (Fig. 1b).

Pain assessment

Subjects' pain intensity was evaluated use a questionnaire containing the VAS (10 cm horizontal line with the number 0 representing no pain and the number 10 representing the worst pain possible). The pain assessment was conducted at baseline, in hours 2 and 6, and on days 1, 3, and 7. On the questionnaire containing the given evaluation time points, each subject was asked to mark a vertical line crossing the horizontal line at the point that best represented their perceived level of pain.

GCF sampling

GCF samples were collected from the mesiobuccal and distobuccal gingival crevices of the maxillary first molars on day 0 (immediately after ESP in the ibuprofen and control groups and after laser application in the laser group), as well as on days 1, 3, and 7. Prior to GCF sampling, the teeth were washed, gently air dried, and isolated with cotton rolls. Standardized sterile paper strips (Periopaper, Proflow, Inc., Amityville, NY, USA) were gently inserted into the gingival crevices until mild resistance was felt and were left in place for 30 s (Fig. 2). After removing the first strip and waiting for one minute, a second strip was placed on the same side for another 30 s. Strips contaminated with blood or exudate were discarded. Samples were then placed separately into coded, sealed plastic microcentrifuge tubes, covered with paraffin and stored at –70 °C until the day of analysis.

Enzyme-linked immunosorbent assay

On the day of analysis, microcentrifuge tubes containing periopaper strips were left at room temperature for 30 min. The tubes were then centrifuged at 2000 rpm for 5 min, and the strips were removed.

The GCF levels of IL-1β (range 20–6000 pg/L) and SP (range 5–200 ng/L) were analyzed using commercial enzyme-linked immunosorbent assay (ELISA) kits (IL-1β ELISA Kit [catalog no: YLA1539HU], SP ELISA Kit [YLA1813HU]; Biosource, Invitrogen Corporation, Carlsbad, CA, USA). All assay procedures were carried out according to the manufacturer's instructions. The intra- and interassay coefficients of variation for IL-1β were lower

Table 1 Descriptive statistics of study groups
Tab. 1 Deskriptive Statistik der Studiengruppen

Groups	Sex (Female/male)	Age (years)			p^a
		Female	Male	Total	
		Mean ± SD	Mean ± SD	Mean ± SD	
Ibuprofen	10/10	20.68 ± 3.33	21.30 ± 2.66	20.99 ± 2.95	0.653
Laser	10/10	22.08 ± 1.73	22.53 ± 2.15	22.30 ± 1.91	0.613
Control	10/10	21.07 ± 3.28	22.99 ± 2.69	22.03 ± 3.08	0.171
p^b	–	0.542	0.315	0.276	–

SD standard deviation
[a]Indicates differences between the female and male
[b]Indicates differences between the groups

Table 2 Group and time interval comparison results of interleukin 1-beta (pg/L) levels
Tab. 2 Gruppen- und Zeitintervallvergleichsergebnisse der Interleukin-1-β-Werte (pg/l)

	Groups	Day 0	Day 1	Day 3	Day 7	*p*
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Interleukin 1-beta	Ibuprofen	1010.79 ± 176.75b	1234.13 ± 54.10a	1256.23 ± 45.57a	1239.49 ± 91.41a	0.001
	Laser	1026.25 ± 171.50b	1276.51 ± 67.05a	1346.29 ± 129.93a	1274.92 ± 63.79a	0.001
	Control	1058.20 ± 184.25b	1274.47 ± 23.82a	1280.01 ± 61.96a	1269.93 ± 55.32a	0.002
	p	0.883	0.244	0.175	0.596	–

SD standard deviation, *Day 0* Immediately after elastomeric separator placement
Repeated measures ANOVA (analysis of variance) were performed
a, b: → Different lower cases in the same row represent statistically significant differences between the time-intervals

Table 3 Group and time-interval comparison results of substance P (ng/L) levels
Tab. 3 Gruppen- und Zeitintervallvergleichsergebnisse der Substanz-P-Werte (ng/l)

	Groups	Day 0	Day 1	Day 3	Day 7	*p*
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Substance P	Ibuprofen	317.70 ± 21.77B	327.96 ± 26.41B	326.84 ± 13.61	327.42 ± 36.97	0.840
	Laser	357.66 ± 21.73A	369.99 ± 27.31A	351.71 ± 60.84	364.11 ± 30.40	0.794
	Control	354.71 ± 24.31A	360.16 ± 20.22A	365.77 ± 24.61	338.01 ± 31.78	0.296
	p	0.004	0.010	0.202	0.105	–

SD standard deviation, *Day 0* Immediately after elastomeric separator placement
Repeated measures ANOVA (analysis of variance) were performed
A, B: ↓ Different upper cases in the same column represent statistically significant differences between the groups

than 8% and 10%, respectively. For SP, they were 8% and 10%, respectively. The sensitivity was 10.7 pg/L for IL-1β and 2.39 ng/L for SP. The results were expressed as pg/L and ng/L for IL-1β and SP, respectively. To calculate the concentrations of IL-1β and SP, the standard graph was created using the curve expert 1.4 program. Then, it was calculated using this standard plot of IL-1β and SP absorbents in the sample.

Statistical analysis

Descriptive statistics for the studied variables were presented as means and standard deviations. The normality assumption of the variables was tested using the Kolmogov–Simirnov test. The Kruskal–Wallis and Friedman tests were used for nonnormally distributed variables, and two-way repeated measurement analysis of variance (ANOVA) was performed to compare groups (independent factor) and time intervals (dependent factor) for normally distributed variables. The Duncan multiple comparison test was also used to identify various groups. All statistical analyses were conducted using SPSS software for Windows (version 22.0; IBM, Armonk, NY, USA), and the level of statistical significance was set at 5%.

Results

Descriptive statistics for the study groups are presented in Table 1. After intra- and intergroup comparisons, insignificant differences in age distribution were identified using an equal female-to-male ratio.

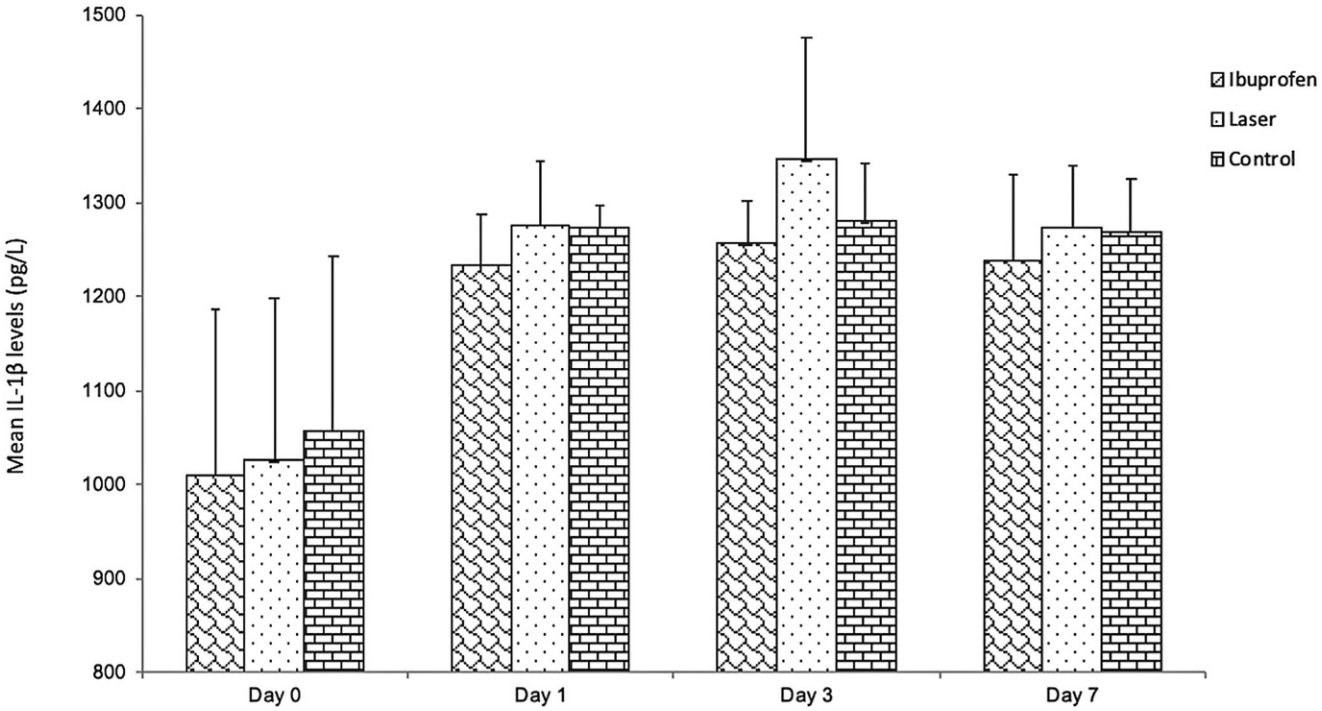


Fig. 3 Mean interleukin 1-beta (IL-1β) levels for ibuprofen, laser and control groups at different time intervals
Abb. 3 Mittlere IL(Interleukin)-1β-Werte für die Ibuprofen-, die Laser- und die Kontrollgruppe in verschiedenen Zeitintervallen

Intragroup comparison results

In all three groups, while a significant increase in IL-1β levels was observed on days 1, 3, and 7 compared to day 0, SP levels exhibited insignificant differences between all time intervals (Tables 2 and 3; Figs. 3 and 4). Furthermore, in all groups, VAS scores indicated a significant increase in pain intensity from baseline to a peak level on day 1, as well as a significant decrease on days 3 and 7 (Table 4; Fig. 5).

Intergroup comparison results

No significant differences in IL-1β levels were identified between the groups across all time intervals (Table 2; Fig. 3). The SP levels in the ibuprofen group decreased significantly on days 0 and 1 when compared to that of the laser and control groups (Table 3; Fig. 4). Although group comparison results of VAS scores indicated reduced pain intensity in the ibuprofen and laser groups compared to the control group, only the difference between the ibuprofen and control groups at baseline was significant (Table 4). The differences between the ibuprofen, laser, and control groups at hours 2 and 6 and on days 1, 3, and 7 were insignificant (Table 4; Fig. 5).

Discussion

Orthodontic pain is an inflammatory process that begins with vascular obstruction and continues with a cascade of inflammatory responses, including vascular changes, inflammatory and immune cells accumulation, and the release of proinflammatory mediators and neuropeptides [17, 19]. The association of some proinflammatory mediators, such as PGE_2 and IL-1β, and neuropeptides, such as SP, with pain intensity during various phases of orthodontic treatment was investigated previously [12–14, 18, 24, 26, 30]. In three of these studies, the evaluations were performed after ESP. Giannopoulou et al. [13] reported that pain intensity at 1 h was associated with increased PGE_2 levels, whereas pain intensity at 24 h was associated with increased IL-1β levels. Sampaoi et al. [26] reported an insignificant increase in IL-1β levels at 24 h compared to baseline. Oshagh et al. [24] compared the effects of ibuprofen and LLLT in alleviating orthodontic pain but found no correlation between PGE_2 levels in GCF and pain perception. A review of the remaining studies in the literature indicated that the analgesic effects of many drugs and LLLT were evaluated only subjectively using the VAS [1–4, 9–11, 21, 23, 25, 31]. This is the first study to compare the effects of ibuprofen and LLLT objectively using IL-1β and SP levels in GCF, as well as subjectively using the VAS.

Individual factors thought to influence pain intensity include previous pain experiences, emotional state, stress, cul-

Table 4 Intragroup and intergroup comparison of visual analog scale (VAS) scores recorded at different time intervals
Tab. 4 Intra- und Intergruppenvergleich von in verschiedenen Zeitintervallen aufgezeichneten VAS(visuelle Analogskala)-Werten

Groups	Baseline Mean±SD	Second Hour Mean±SD	Sixth Hour Mean±SD	First Day Mean±SD	Third Day Mean±SD	Seventh Day Mean±SD	[b]*p*
Ibuprofen	0.95 ± 0.94bB	1.30 ± 1.38ab	1.50 ± 1.53ab	2.00 ± 1.02a	0.70 ± 1.17b	0.50 ± 1.23b	0.001
Laser	1.40 ± 1.39abAB	1.75 ± 1.68ab	2.10 ± 2.02a	2.50 ± 1.52a	0.60 ± 1.04b	0.15 ± 0.48b	0.001
Control	2.10 ± 1.48abA	2.30 ± 1.34a	2.50 ± 1.35a	3.25 ± 1.88a	0.30 ± 0.65b	0.40 ± 1.04b	0.001
[a]*p*	0.038	0.091	0.105	0.094	0.529	0.645	–

SD standard deviation, *Baseline* Immediately after elastomeric separator placement
[a]Kruskall–Wallis test was performed
[b]Friedman test was performed
A, B, C: ↓ Different upper cases at the same column represent statistically significant differences between the groups
a, b, c: → Different lower cases at the same row represent statistically significant differences between the time-intervals

tural background, individual pain threshold, age, and gender [3, 4, 17]. Blinding of subjects is considered a critical method for eliminating these factors on the accuracy of pain assessment [4]. Furthermore, recent studies found no effect of gender on pain intensity [6, 9], whereas Brown and Moerenhout [8] found a higher level of pain in adolescents than in preadolescents and adults in all phases of orthodontic treatment. Nevertheless, in this study, to prevent possible gender-related changes, the male-to-female ratio was kept equal, and only adults were included to prevent age-related differences. Other factors were ignored.

Although the measurement intervals and peak period vary among studies, orthodontic pain generally begins within a few hours, increases over the next 24–48 h, starts to decrease on day 3, and disappears within 7 days [16, 17, 20]. Therefore, in the present study, GCF evaluations were performed after elastomeric separator placement and on days 1, 3, and 7. In addition to these measurement intervals, hours 2 and 6, which are frequently assessed in the literature, were added to the VAS measurements for a comprehensive evaluation [23, 27, 31].

Although there is no universal recommendation regarding the use of analgesics to alleviate orthodontic pain observed after ESP, paracetamol (acetaminophen) and ibuprofen are commonly used [1, 6, 7, 31]. In some studies comparing the pre-emptive and postoperative administration of these two drugs at various doses, ibuprofen was more effective than paracetamol [1, 7, 25], whereas insignificant differences were determined in other studies [15, 29]. Furthermore, in two studies in which only the pre-emptive administration of ibuprofen and paracetamol were compared, insignificant differences were also found [6, 31]. In the present study, ibuprofen was preferred due to its anti-inflammatory properties since it is thought that pain perceived from orthodontic treatment is secondary to anti-inflammatory reaction, as well as analgesic and antipyretic properties as seen in paracetamol [6, 20, 22, 25, 31].

Inflammation and associated pain decrease in pre-emptive analgesia because the body distributes the medication before tissue injury occurs and the release of prostaglandins is reduced [5, 6, 22, 27]. In the literature, a few studies compared the effects of pre-emptive ibuprofen, postoperative ibuprofen, and placebo therapy in alleviating orthodontic pain observed after ESP. Among these Bernhardt et al. (2001) and Sateen Law et al. (2000) stated that pre-emptive ibuprofen administration significantly decreased perceived pain at 2 h, whereas the differences among the groups at subsequent postoperative time periods were insignificant [5, 27]. In contrast, Minor et al. (2009) reported a significant decrease in perceived pain at 6 h, at bedtime, and in the morning, as well as an insignificant decrease at 2 h in subjects who were administered ibuprofen pre-emptively. In addition, the differences between the postoperative ibuprofen and placebo groups were insignificant [22]. In light of this information, we chose to use 400 mg dose of ibuprofen 1 h before ESP. Unlike in those studies in which pain intensity was first evaluated 2 h after ESP using the VAS, we identified a significant decrease in the ibuprofen group compared to the control group at baseline. The insignificant decrease at 2 h might have resulted from the decrease after peak plasma concentration of ibuprofen, which is 1–2 h after administration.

A review of the literature suggested that the wavelength 810 nm provides deeper laser penetration into tissue, with the possibility of reaching the cortical and alveolar bones [2, 4, 23]. Moreover, this wavelength had an advanced analgesic effect [9, 10]. Because doses above 20 J/cm^2 have an inhibitory action, the use of lower doses is recommended to make the treatment more effective [2, 9, 23]. Therefore, in this study, an 810 nm Ga-Al-As semiconductor diode laser device was used, and eight points of irradiation per tooth at dosages of 2 J/cm^2 per point and a total of 16 J/cm^2 per tooth were selected.

Studies related to use of the individual irradiation method to alleviate orthodontic pain observed after ESP reported conflicting results. Although single irradiation applied after ESP was effective compared to the control group in some studies [10, 23], others denied its effectiveness [11]. Like-

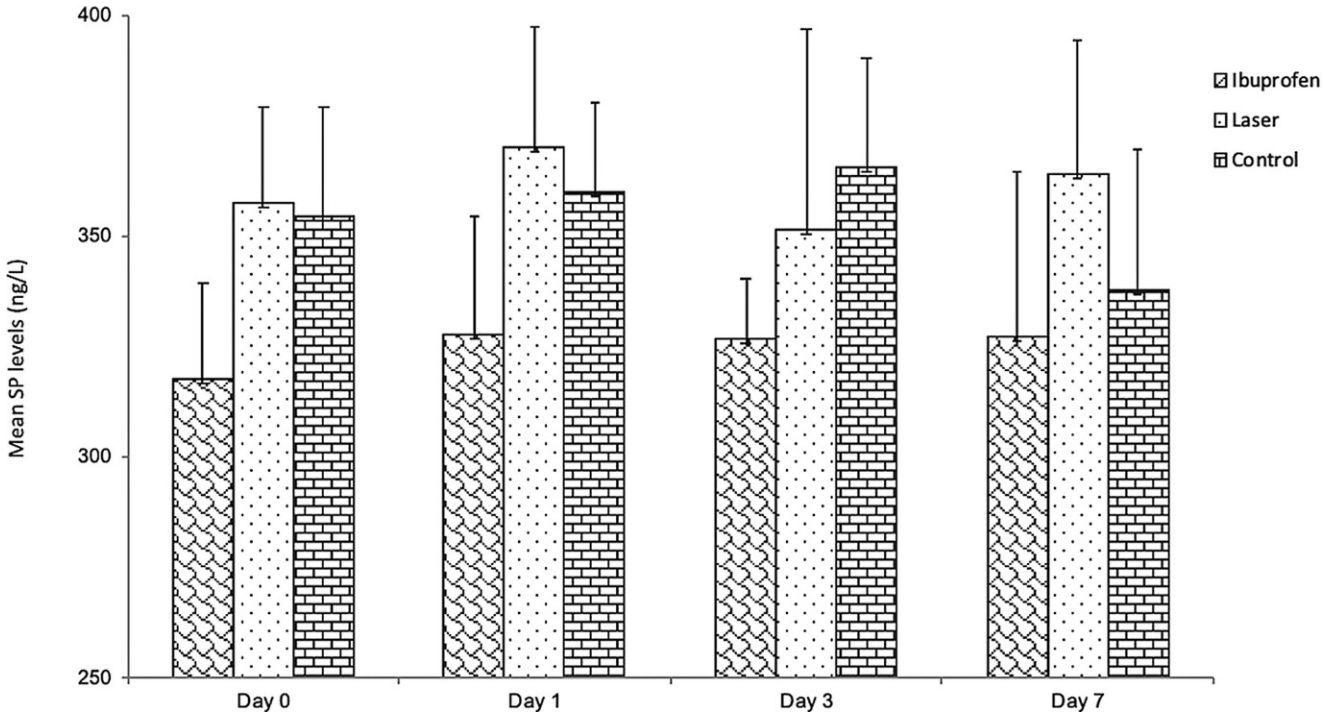


Fig. 4 Mean substance P (SP) levels for ibuprofen, laser, and control groups at different time intervals
Abb. 4 Mittlere Substanz-P-Werte für die Ibuprofen-, die Laser- und die Kontrollgruppe in verschiedenen Zeitintervallen

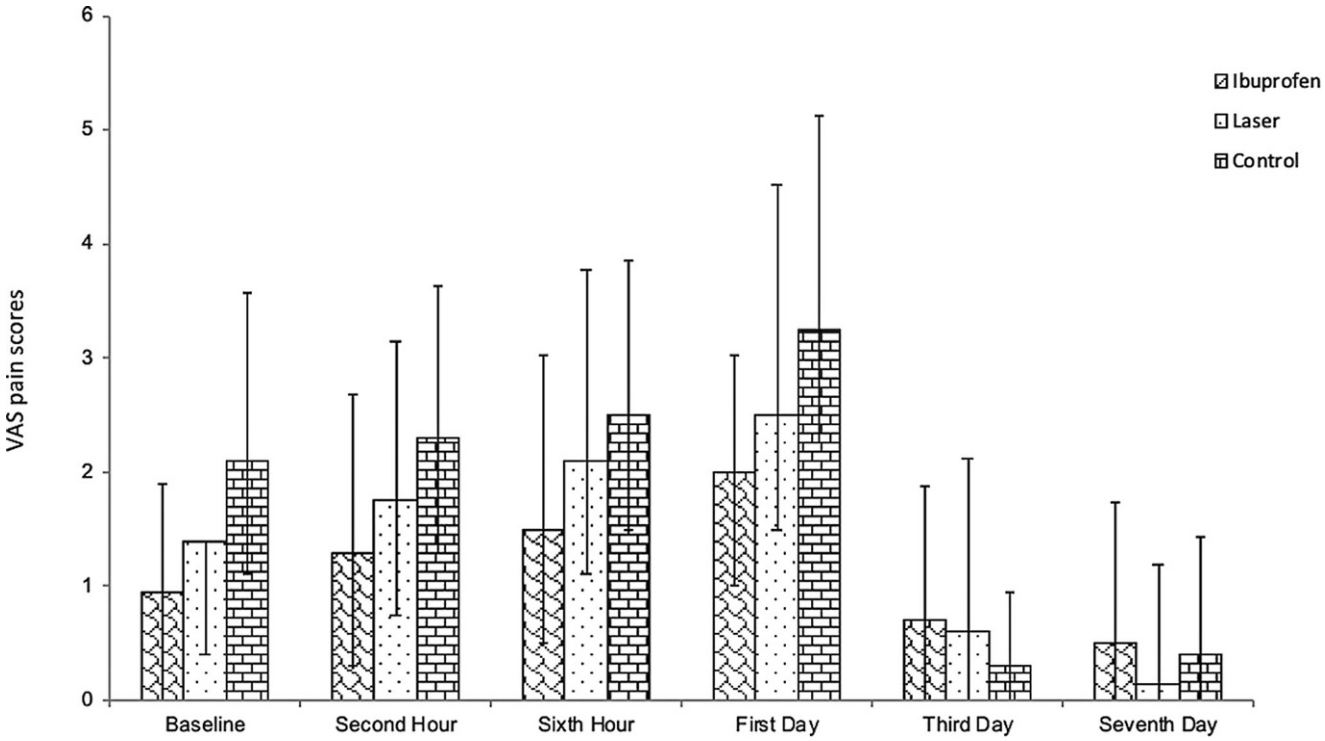


Fig. 5 Visual analog scale (VAS) pain scores for ibuprofen, laser and control groups at different time intervals
Abb. 5 VAS(visuelle Analogskala)-Werte für die Ibuprofen-, die Laser- und die Kontrollgruppe in verschiedenen Zeitintervallen

wise, the effectiveness of multiple irradiations was also supported [9, 11] in some studies and rejected in others [16]. Only one study compared a single irradiation session applied after ESP with two irradiation sessions applied immediately and 24 h after ESP; this study reported insignificant differences between the groups' pain-alleviating effects [2]. Therefore, in this study, we chose to administer a single irradiation session immediately after ESP, and we found insignificant effects compared to the control group, consistent with Furquim et al. [11]. The irradiation sessions were performed from the buccal and palatal sides because we thought that single-sided irradiation might fail to stimulate the entire periodontal ligament, leading to the occurrence of pain [4].

The intragroup comparison results of our study showed that the IL-1β levels of elastomeric separator treated teeth increased significantly on days 1, 3, and 7 compared to day 0 in the ibuprofen, laser, and control groups. This is in agreement with Giannopoulou et al., who observed a significant increase in IL-1β levels in elastomeric separator treated teeth after 1 h and on days 3 and 7 compared to teeth where elastomeric separators were not applied [13]. In contrast, Sampaio et al. found an increase in IL-1β levels only 24 h after ESP, but this increase was insignificant when compared to baseline values [26].

Only one study in the literature compared the SP levels of elastomeric separator treated teeth to those where elastomeric separators were not applied. Although the results of this study showed insignificant differences 1 h after ESP, on days 3 and 7, the SP levels of elastomeric separator treated teeth were significantly higher [13]. However, in this study, the SP levels of elastomeric separator treated teeth were only determined immediately after ESP and on days 1, 3, and 7. Insignificant differences were found among the groups at all time intervals.

To the best of our knowledge, no study in the literature has compared the effects of ibuprofen and LLLT in alleviating orthodontic pain observed after ESP using analysis of IL-1β and SP levels in GCF. Intergroup comparison results of the present study indicated no significant differences between the groups in terms of IL-1β levels, whereas a significant decrease in SP levels was found in the ibuprofen group on days 0 and 1 compared to the laser and control groups.

Although the VAS is a subjective method, due to the advantages such as providing subjects the ability to indicate the exact pain intensity and providing maximum opportunity for expressing the individual's response style, we used this pain measurement tool in this study [2, 10, 17]. Consistent with the results of previous studies, VAS scores in this study indicated a significant increase in pain intensity from baseline to a peak level on day 1, followed by a significant decrease on days 3 and 7, in all groups [2, 6, 7, 21, 23, 27].

In the literature, only Oshagh et al. compared the analgesic effects of ibuprofen and LLLT and reported insignificant differences in VAS pain scores between the groups. Unlike in our study, Oshagh et al. had no control group, and they evaluated pain intensity before ESP and at 1 and 24 h after ESP [24]. Intergroup comparison results of our study also showed insignificant differences in VAS pain scores between the ibuprofen and laser groups at all time intervals. However, when compared to the control group, although less pain intensity was observed in the ibuprofen and laser groups, only the difference between the ibuprofen and control groups at baseline was statistically significant.

Compared to the laser and control groups, the ibuprofen group's significant decreases in SP levels on days 0 and 1 and the decreased pain intensity at baseline might be mainly due to ibuprofen's pre-emptive anti-inflammatory effect, as well as its analgesic effect. Orthodontic pain is an inflammatory process that includes the release of high levels of histamine, serotonin, dopamine, glycine, cytokines, leukotrienes, prostaglandins, and SP [2, 4, 17]. When ibuprofen is administered before the application of a force, the inflammatory response and associated pain decreases because the body has time to absorb and distribute the medication before the tissue injury [5, 6, 20, 22, 29]. In addition, the lack of subsequent doses might have led to insignificant differences at other time points.

This study's main limitation is its comparison of a single pre-emptive 400 mg dose of ibuprofen with a single 810 nm LLLT irradiation session. Therefore, further studies are recommended in which the number of ibuprofen doses and laser irradiation sessions are increased.

Conclusion

- Compared to the laser and control groups, the ibuprofen group experienced a significant decrease in substance P levels on days 0 and 1, as well as in pain intensity at baseline.
- Visual analog scale scores indicated a significant increase in pain intensity from baseline to a peak level on day 1, followed by a significant decrease on days 3 and 7, in all groups.

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Compliance with ethical guidelines

Conflict of interest Y. Kaya, Ö. Alkan, A.U. Kömüroglu and S. Keskin declare that they have no competing interests.

Ethical standards Ethical approval was obtained from the research ethics committee of Van Yüzüncü Yıl University's Faculty of Medicine (26.07.2017/04). Written informed consent was obtained from all individual participants included in the study after they were provided a detailed description of the study. All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

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