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REVIEW ARTICLE

Ibuprofen and Low-level Laser Therapy for Pain Control during Fixed Orthodontic Therapy: A Systematic Review of Randomized Controlled Trials and Meta-analysis

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ABSTRACT

Introduction: To systematically review high-quality randomized controlled trials (RCTs) and meta-analysis on the effectiveness of use of ibuprofen and low-level laser therapy (LLLT) for pain control during fixed orthodontic appliance therapy.

Materials and methods: A web-based systematic search of PubMed and Medline database using relevant keywords was performed in August 2016 limited to the English language studies. Based on inclusion and exclusion criteria, RCTs utilizing blind approach were selected. The quality of studies was analyzed and only high-quality studies were included. Following data extraction, meta-analysis was performed by standardized mean difference Hedges' (adjusted) g with 95% confidence interval.

Results: A total number of six studies (four ibuprofen and two LLLT) comprising 315 patients were included. Heterogeneity among ibuprofen studies was small, while large heterogeneity was found among LLLT studies. The results showed that both ibuprofen and LLLT could reduce pain intensity during fixed orthodontic therapy and during 17 days follow-up period. However, this reduction was statistically significant only at 6 to 24 hours postoperatively for ibuprofen and 2 hours and 3 to 7 days for LLLT ($p < 0.05$).

Conclusion: Considering the limitations of the current meta-analysis, ibuprofen could alleviate orthodontic archwire activation pain during the 1st day with relatively high level of evidence. Low-level laser therapy could reduce this pain in the long term with limited evidence. Further well-designed RCTs are required to provide more evidence.

Keywords: Ibuprofen, Low-level laser therapy, Orthodontics, Pain, Randomized controlled trials, Review.

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INTRODUCTION

Orthodontic pain is a common symptom that occurs 2 to 4 days following placement of fixed orthodontic appliances.[1,2] Such discomfort is described as "tearing" in some patients and could hinder them to continue therapy.[3] Some patients may stop toothbrushing due to the pain. Such pain increases during the 1st day and degrades after 1 week.[2]

The pain during orthodontic tooth movement is believed to be due to changes in periodontal compression, changes in blood flow, and resulted ischemia and inflammation.[4] When periodontal tissues are compressed, inflammatory ligaments, such as histamine, bradykinin, prostaglandins, serotonin, and substance P are released and they start inflammatory reactions, resulting in patient pain.[5]

Factors influencing intensity of experienced pain include sex,[6,7] age,[6,7] cultural differences,[6,7] and state of emotions[7] in addition to pain history.[7] Some authors have questioned the role of sex on pain intensity and suggested that such difference is more likely due to cultural differences rather than physiological reasons.[6,8]

The application of nonsteroidal anti-inflammatory drugs (NSAIDs) is one of the preferred methods for pain

control during fixed orthodontic therapy. They could inhibit cyclooxygenase and prevent prostaglandins biosynthesis from arachidonic acid.[9] The first report on use of ibuprofen for orthodontic tooth movement pain relieve by Ngan et al[10] showed the analgesic efficacy of ibuprofen compared to placebo and aspirin. The NSAIDs could be used both pre- and postoperatively.

On the contrary, low-level laser therapy (LLLT) has been increasingly applied in dentistry due to its regenerative, analgesic, and anti-inflammatory features as well as enamel conditioning.[11-13] Its low output energy does not cause temperature rise above 36.5°C. Mechanism of LLLT pain control has not been explained, yet. Some suggested that the effect of LLLT on neuronal and inflammatory cells is responsible for pain relief.[14] Although the positive effect of LLLT on pain reduction during fixed orthodontic therapy has been demonstrated in some studies,[3,13] Lim et al[15] found no significant difference in pain following application of LLLT.

Systematic reviews on randomized controlled trials (RCTs) could determine the level of evidence for use of interventions in human. Previous literature reviews demonstrated the effectiveness of analgesic drugs in pain reduction during fixed orthodontic therapy[16] while on the effectiveness of LLLT, the evidence is limited.[13] The aim of this study was to systematically review high-quality RCTs and meta-analysis on the effectiveness of use of ibuprofen and LLLT for pain control during fixed orthodontic therapy.

MATERIALS AND METHODS

Study Design

In this review, RCTs evaluating the effectiveness of use of single-dose ibuprofen or LLLT in pain management of fixed orthodontic therapy in humans were included. Only studies which used visual analog system (VAS) for assessment of pain degree were included and other methods were excluded. Moreover, studies that did not mention when the pain intensity was assessed (during chewing) were excluded. Studies on fixed orthodontic therapy were included and craniofacial syndromes, orthosurgery, removable orthodontic therapy, and elastic separator placement were excluded. In addition, other methods for pain control apart from ibuprofen and LLLT were excluded. The drug or laser administration protocol varied among studies, and therefore, it was not considered as an inclusion/exclusion criteria.

Electronic Search and Study Selection

An electronic search was performed using PubMed and Medline until August 2016 limited to English language and human studies. A combination of relevant keywords was used according to PICO: Problem/Patient/Population Intervention/Indicator Comparison Outcome of Interest:

Patient:

"Orthodontics"[Mesh] OR orthodontic*

AND Intervention and Control:

"Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR NSAID* OR "Ibuprofen"[Mesh] OR "Laser Therapy"[Mesh] OR "Lasers"[Mesh] OR "Low-Level Light Therapy"[Mesh]

AND Control:

"Randomized Controlled Trial" [Publication Type] OR random* OR control* OR Placebos"[Mesh]

AND Outcome:

"Pain Measurement"[Mesh] OR "Pain"[Mesh] OR "Visual Analog Scale"[Mesh]

In addition, the references of the included studies were searched for further relevant studies. Initial screening of titles and abstracts was carried out and full texts of the potentially eligible studies were obtained for further evaluation. Studies were included based on established inclusion/exclusion criteria by two reviewers separately. Disagreements were discussed with the third reviewer.

Quality Assessment

To reduce meta-analysis bias, two reviewers assessed the quality of included studies based on Jadad et al[17] and only studies with low risk of bias (score ≥ 2) were included. Jadad criteria (maximum 5 scores) include randomization (1 score), appropriate method of randomization (1 score), blinding (1 score), appropriate method of blinding (1 score), and handling dropouts (1 score).[17]

Data Extraction and Meta-analysis

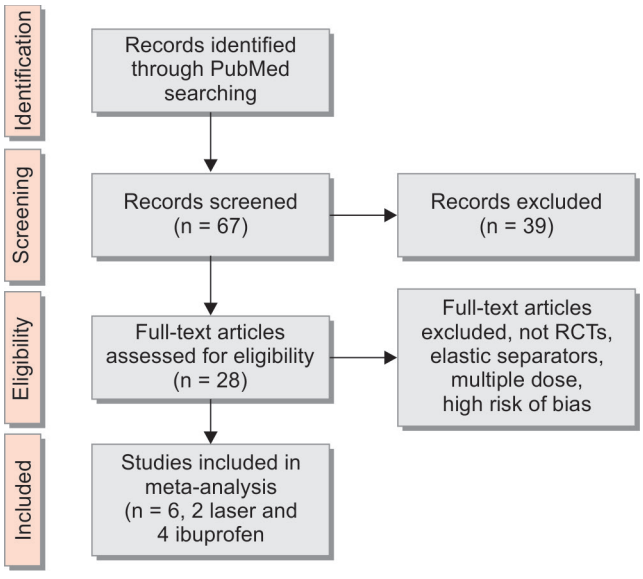
Relevant data including number of patients, mean age, and mean VAS of each group (test and control), as well as drug or laser administration protocol,were extracted from each study.

Meta-analysis was carried out by Stata 13 (College Station, TX, USA). For every pair-wise comparison standardized mean difference (SMD) Hedges' (adjusted) g with confidence interval 95% was obtained. Heterogeneity between studies was measured by I^2 which ranges between 0 and 100%. For values more than 50% showing large heterogeneity[18] random effects model was used. If I^2 was < 50%, fixed effects model was applied. Cochran's Q was also calculated, but only its significance was considered. The level of significance was set at 0.05.

This study was performed in compliance with the preferred reporting items for systematic reviews and meta-analyses statement.[19]

RESULTS

The electronic literature search identified 92 studies (Graph 1), of which full-text of 28 studies were assessed



Graph 1: Review flow diagram

for eligibility. No further publication was provided by the hand search. A total of six studies met the inclusion criteria and were included in the meta-analysis (Table 1). The included studies comprised a total number of 315 patients (157 received interventions and 158 received placebos).

Low-level Laser Therapy *vs* Placebo

A total number of two studies comprising 196 patients compared the analgesic effect of LLLT *vs* placebo. The SMD at different time points within 7 days after activation of fixed orthodontic treatment was in favor of LLLT (Table 2). As apparent in forest plot (Graph 2A–F), however, the analgesic effect of LLLT compared to placebo reached significant level only at 2 hours and 3 and 7 days, showing that LLLT could control pain mostly in long term. The SMD was −8.094 (95% confidence interval [CI] = −9.213 to −6.975, p < 0.001), −6.126 (95% CI = −14.921 to 1.373, p < 0.001), and −2.846 (95% CI = −3.363 to −2.329, p < 0.001) at hours and 3 and 7 days respectively. Heterogeneity among studies was high (I^2 > 99% when both studies were included).

Ibuprofen *vs* Placebo

One hundred and nineteen patients were enrolled in four studies comparing pain relief effect of ibuprofen *vs* placebo. The SMD at different time points within 7 days after activation of fixed orthodontic treatment was in favor of ibuprofen (Table 3). Forest plot shows that ibuprofen is significantly more effective for pain management compared to placebo from 6 hours after until 24 hours (Graph 3A–G). The SMD was −0.450 (95% CI = −0.817 to −0.083, p = 0.016), −0.629 (95% CI = −1.086 to −0.173, p = 0.007), and −0.433 (95% CI = −0.804 to −0.063, p = 0.022) at 6 hours, night, and 24 hours after activation of fixed orthodontic treatment respectively. Heterogeneity of included studies was < 50%.

DISCUSSION

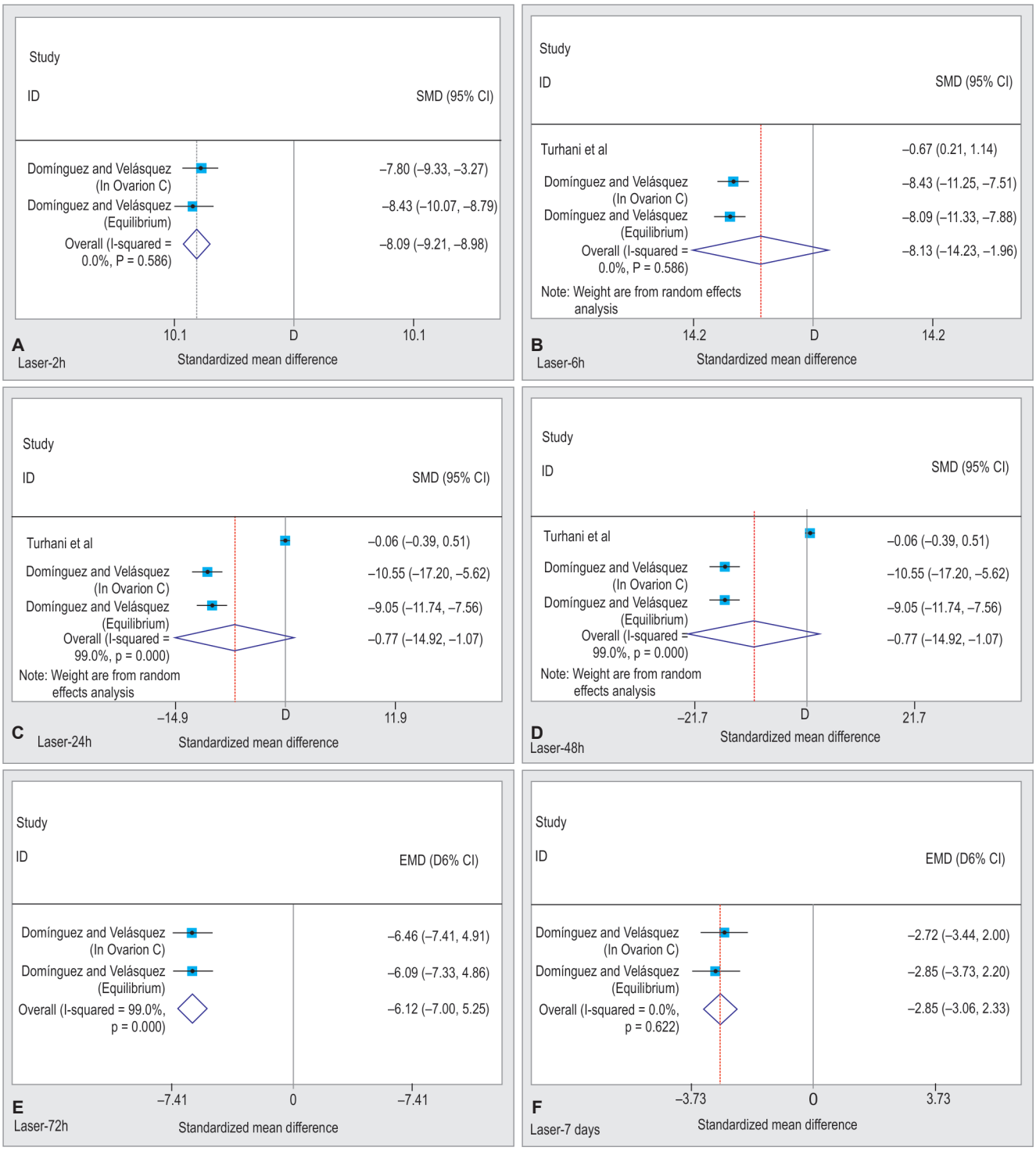
Since tooth movement could cause pain and discomfort, attempts have been performed to alleviate such pain and increase patient satisfaction. Previously, several reviews have analyzed the results of the clinical trials to find the most efficient method of fixed orthodontic treatment pain management.[13,16,24-27] However, they mostly did not consider several variables which could influence the results and cause bias. The number of included studies in this review was fewer compared to previous reviews as the aim of this review was to combine the results

Table 1: Data summary of six qualified trials and their quality assessment based on the Jadad score[17]

Study	*Number of treatment*	*Number of placebo*	*Intervention*	*Protocol*	*Jadad score*
Domínguez A, Velásquez[20]	60	60	LLLT	830 nm, 100 mW, 22 seconds, 80 J/cm^2	2
Turhani et al[3]	38	38	LLLT	670 nm, 75 mW, 30 seconds, 140 mW/cm^2	2
Polat and Karaman[21]	20	20	Ibuprofen	600 mg	2
Polat et al[5]	20	20	Ibuprofen	400 mg	3
Salmassian et al[22]	19	20	Ibuprofen	400 mg	4
Farzanegan et al[23]	10	10	Ibuprofen	400 mg	3

Table 2: Meta-analysis data summary: Low-level laser therapy *vs* placebo

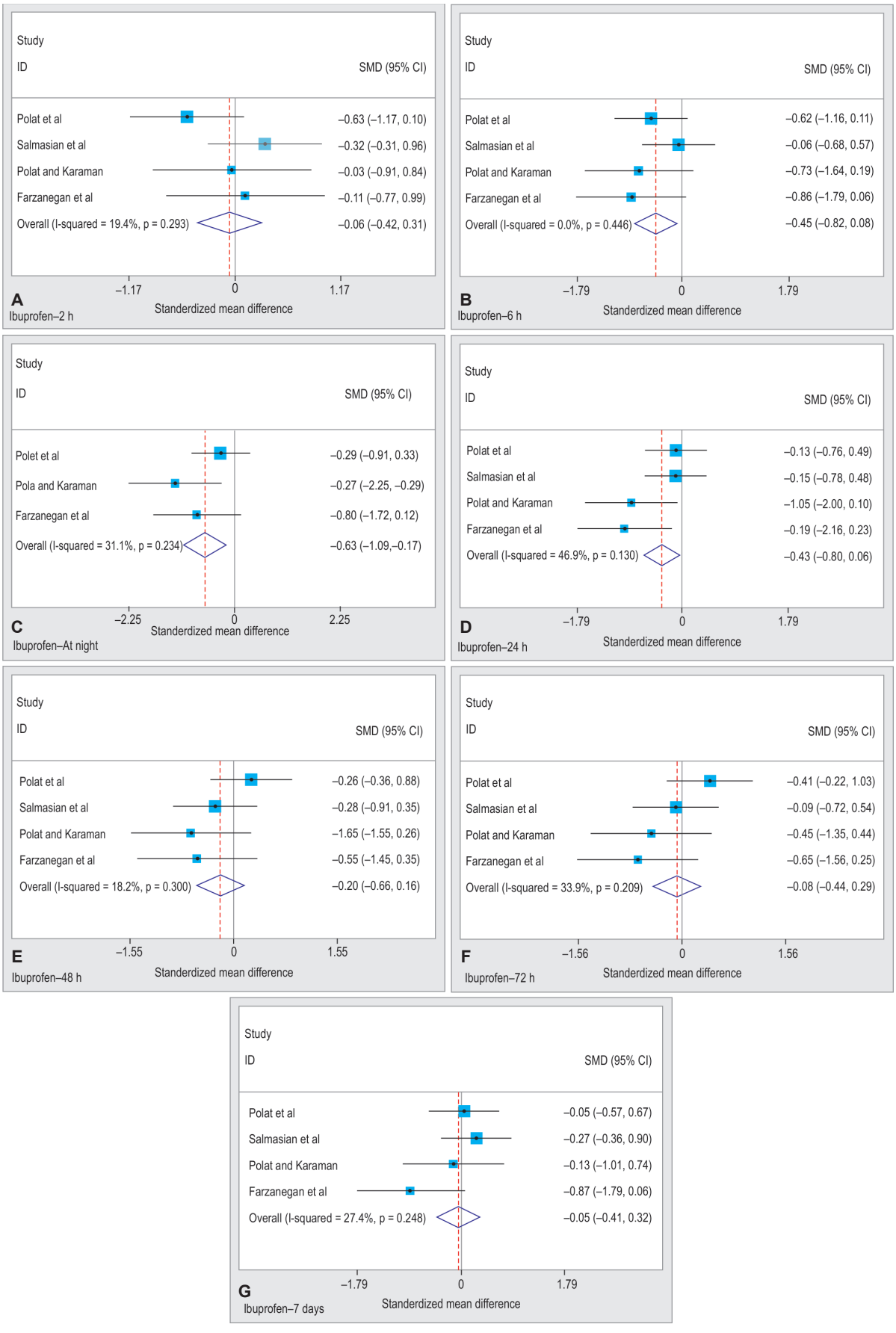
			Heterogeneity		
Time (hours)	*SMD*	*95% CI*	*I^2 (%)*	*p-value*	*p-value*
2	−8.094	−9.213 to −6.975	0	0.586	<0.001
6	−6.133	−14.228 to 1.961	99.1	<0.001	0.138
24	−6.774	−14.921 to 1.373	99.0	<0.001	0.103
48	−9.619	−21.675 to 2.437	99.1	<0.001	0.118
72	−6.126	−7.004 to −5.248	0	0.940	<0.001
7 days	−2.846	−3.363 to −2.329	0	0.622	<0.001



Graph 2A to F: Result of meta-analysis for LLLT and placebo, reported in standard mean difference (95% confidence interval) at different time points: (A) 2 hours; (B) 6 hours; (C) 24 hours; (D) 48 hours; (E) 72 hours; and (F) 7 days. Forest plot shows analgesic effect of LLLT compared with placebo at 2 hours and 3 and 7 days after activation of fixed orthodontic treatment

Table 3: Meta-analysis data summary: Ibuprofen *vs* placebo

	Standardized mean		*Heterogeneity*		
Time (hours)	*difference*	*95% CI*	*I^2 (%)*	*p-value*	*p-value*
2	−0.056	−0.419 to 0.306	19.4	0.293	0.760
6	−0.450	−0.817 to −0.083	0	0.445	0.016
At night	−0.629	−1.086 to −0.173	31.1	0.234	0.007
24	−0.433	−0.804 to −0.063	46.9	0.130	0.022
48	−0.200	−0.564 to 0.164	18.2	0.300	0.281
72	−0.076	−0.439 to 0.288	33.9	0.209	0.684
7 days	−0.048	−0.411 to 0.316	27.4	0.248	0.797



Graph 3A to G: Result of meta-analysis for ibuprofen and placebo reported in standard mean difference (95% confidence interval) at different time points: (A) 2 hours; (B) 6 hours; (C) night; (D) 24 hours; (E) 48 hours; (F) 72 hours; and (G) 7 days. Forest plot shows analgesic effect of ibuprofen compared to placebo from at 2 hours until 24 hours after activation of fixed orthodontic treatment

of studies with homogenous method. In the review of Xiaoting et al,[16] they included the study of Tortamano et al[28] for LLLT in which the authors assessed pain by a survey. He et al[13] and Ren et al[25] included all studies on LLLT not considering the frequency of laser treatment. This review only included high-quality studies which assessed pain alleviating effect of one-time application of laser with VAS.

In addition, several studies, such as Ngan et al,[10] Steen Law et al,[29] Bradley et al,[30] and Minor et al[31] who measured analgesic effect of ibuprofen following elastic separator insertion were included in previous meta-analyses,[16,24,26,27] while they were excluded from this review as the pain might vary with pain caused by archwire placement.

The results of this meta-analysis showed that ibuprofen could reduce pain intensity during the 1st day after activation of archwire. The level of evidence was high and included studies were homogenous. Previously, Angelopoulou et al[24] and Xiaoting et al[16] revealed analgesic effect of ibuprofen 2 to 6 hours and 6 hours to 3 days after archwire activation or separator insertion.

The two included studies on the effect of LLLT were heterogonous; hence, the risk of bias is high. The results showed that LLLT could alleviate pain after 2 hours, 3 and 7 days. Although it is believed that LLLT is a noninvasive method with no adverse effect for pain management, the long-time needed (32–37.5 minutes) for application to both dental arches prohibit its routine usage.[16]

One of the limitations of this study was the limited amount of comparative data. Hence, it seems that high-quality RCTs should further examine the effectiveness of pain management methods during fixed orthodontic treatment.

CONCLUSION

Ibuprofen can lessen pain at 6 hours after orthodontic archwire activation, while its effect is only statistically significant until 24 hours. The level of the evidence was relatively high.

Low-level laser therapy also could reduce pain after 3 to 7 days following archwire activation. However, the studies were heterogeneous.

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