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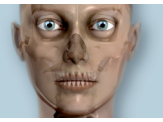

ORIGINAL ARTICLE

M. V. Angelopoulou
V. Vlachou
D. J. Halazonetis

Pharmacological management of pain during orthodontic treatment: a meta-analysis

Authors' affiliations:
M. V. Angelopoulou, Department of Paediatric Dentistry, School of Dentistry, University of Athens, Athens, Greece
V. Vlachou, Private Dental Practice, Athens, Greece
D. J. Halazonetis, Department of Orthodontics, School of Dentistry, University of Athens, Athens, Greece

Correspondence to:
Matina V. Angelopoulou
Department of Paediatric Dentistry
School of Dentistry
University of Athens
2 Thivon Street
Goudi 115 27, Greece
E-mail: matinangelop@yahoo.gr

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Structured Abstract

Objectives – To evaluate the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in managing pain arising from orthodontic interventions, such as archwire or separators placement.

Data Sources – Medline and Cochrane databases searched in February 2010 and updated in July 2010 using orthodontics and pain as the search terms. Additional studies located from Google Scholar, Clinical Trials and the reference lists of retrieved articles.

Study Selection – Randomized controlled trials comparing NSAID to placebo using visual analogue scale (VAS) scores.

Data Synthesis – Of the 1127 studies identified through database searches, seven were included for meta-analysis. Treatment effects (Hedges' g using random effects model) and 95% confidence intervals (CI) of the pain VAS scores were evaluated at 2, 6 and 24 h after intervention, during chewing and biting activities. Pain level at 2 h differed between the ibuprofen and placebo groups during biting (95% CI: −0.178 to −0.046), but not during chewing (95% CI: −0.551 to 0.148). At 6 h, the ibuprofen group exhibited lower pain levels during both activities (chewing 95% CI: −0.640 to −0.123, biting 95% CI: −0.857 to −0.172). At 24 h, no statistically significant difference could be detected between ibuprofen and placebo (chewing 95% CI: −0.642 to 0.112, biting 95% CI: −0.836 to 0.048). No statistically significant difference was found between ibuprofen and acetaminophen at any time point.

Conclusion – Ibuprofen appears to lower orthodontic pain compared to placebo at 2 and 6 h after separators or archwire placement, but not at 24 h, when pain peaks.

Key words: analgesics; meta-analysis; orthodontics; pain

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Introduction

Pain and discomfort are potential side effects of orthodontic treatment (1–4), occurring in 91–95% of patients undergoing fixed

orthodontic treatment (3, 5, 6); it may discourage patients from treatment (7–9) or reduce their compliance (10).

Pain has been reported after separator placement (11–14), initial archwire placement (2, 3, 11, 12, 15–18), headgear use (19), rapid palatal expansion (20) and chin cup therapy (21). Pain may also be induced during debonding (22) or because of traumatic ulcers to the cheeks, lips or tongue (5). No difference has been found in pain levels in patients treated with self-ligating, lingual or conventional brackets (23–27). Higher pain levels have been reported in the anterior region than in the posterior (3, 11, 18) and in the lower rather than in the upper jaw (16). Concerning the influence of gender on pain perception, some studies report higher pain levels in females (3, 28), whereas other studies find no differences between genders (11, 15, 18, 23, 25, 27, 29, 30). Age may also be a factor (3, 15, 16, 31), but findings are controversial (11, 23, 25, 27).

Pain during orthodontic treatment is related to changes in the periodontal ligament (PDL) that increase the number of multinuclear osteoclasts, promote osteoclastic bone resorption and thereby allow tooth movement (1, 26, 32–35). Orthodontic force produces pressure to the PDL that leads to ischaemia, inflammation and oedema (36). As a result of inflammation, high levels of prostaglandins, histamine, serotonine, bradykinin, substance P and cAMP are released to the PDL (12, 13, 33, 37–39). Pain may also be induced by pulp irritation during orthodontic tooth movement (40).

Various methods have been proposed to manage orthodontic pain. The most commonly used is the administration of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, acetaminophen (paracetamol), ibuprofen, flurbiprofen, naproxen sodium and tenoxicam (4, 12–14, 34, 37, 41–44). Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and reduce inflammation to the PDL thus minimizing pain (12, 13, 42). However, NSAIDs may have side effects (14, 45, 46), such as gastric or duodenal ulceration, bleeding disorders, renal insufficiency, asthma, allergy, hypertension, congestive heart problems and atherosclerosis (43), even though their occurrence may be low (12). Ibuprofen is contraindicated for pregnant and lactating women, and for persons with nasal polypods, angioedema and ocular reactions (13). Aspirin, ibuprofen (35, 47) and indomethacine have been found to delay tooth movement (48). However, as some studies indicated, low doses and specific drugs, such as tenoxicam and acetaminophen, do not seem to interfere with tooth movement (33, 34, 49). Acetaminophen reduces pain by inhibition of cycloxogenase-3 in the brain and the spinal cord and by weak inhibition of peripheral prostaglandin synthesis (4, 34).

Although a multitude of studies has been published on the topic of orthodontic pain management, there seems to be lack of consensus concerning the effectiveness of the suggested interventions. In recent years, orthodontic pain-related research seems to have reached adequate volume for performing a reliable meta-analysis. Xiaoting et al. (50) reported the results of such a study for drug interventions only. However, the results of their meta-analysis include all pain relief methods, do not include all the relevant studies and do not follow the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (51, 52).

The aim of this study was to evaluate the effectiveness of pharmacological interventions on pain experienced by patients undergoing orthodontic treatment, by reviewing randomized controlled trials (RCT) that report the efficacy of the most commonly used drugs (ibuprofen and acetaminophen) and to compare these two drugs to each other and to placebo.

Methods

In the preparation of this meta-analysis, we followed the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (51, 52). Methods of analysis, exclusion and inclusion criteria and the main outcome measure [pain as evaluated on a visual analogue scale (VAS)], as well as the 24-h time point of pain recording, were specified in advance of the study. The activity during which pain would be evaluated (e.g. biting, chewing, fitting teeth together,

etc.) as well as additional time points of pain recording was specified after the eligible studies had been collected, based on study availability. The protocol was not published, nor was the study registered.

Randomized controlled trials evaluating pharmacological management of pain during orthodontic treatment were investigated. Trials were retrieved with no date, language or publication status restriction and limited to human subjects. The exclusion criteria were the following: 1) trials irrelevant to orthodontics; 2) studies concerning orthodontics but irrelevant to pain; 3) articles referring to temporomandibular joint disorders and orofacial pain; 4) studies referring to pain because of oral surgery procedures, even if these were conducted for orthodontic reasons; 5) author's replies; 6) reviews; 7) articles presenting techniques to manage orthodontic pain; and 8) clinical trials reporting the amount of orthodontic pain without management of this pain.

Inclusion criteria were as follows: 1) randomized controlled trials comparing the efficacy of NSAIDs to placebo; 2) prospective studies; 3) use of a control group; 4) use of VAS to report pain levels; and 5) participants undergoing orthodontic treatment with fixed appliances, including separator placement without age or gender restrictions.

The main outcome was pain level during chewing and biting, as measured on a VAS, at 2, 6 and 24 h after orthodontic intervention. These activities and the 24-h time point were chosen to evaluate the effectiveness of NSAIDs at the peak of orthodontic pain (2, 3, 9, 11–13, 18, 19, 23, 25, 28, 29, 42, 44). The 2- and 6-h time points, which have been commonly assessed in the literature, were added for a more comprehensive evaluation. The VAS system was considered a prerequisite, because it has been found a reliable tool to evaluate patients' pain level, with good sensitivity and high reproducibility (3, 12, 17, 18, 29, 43).

Relevant studies were located by searching the Medline and Cochrane databases. The main search was conducted in February 2010 and updated in July 2010. We used Google Scholar and Clinical Trials to retrieve additional studies (un-published reports and ongoing trials). The reference lists of the retrieved articles were searched to identify studies that might not have been included. The search term 'orthodontics AND pain' was used. Wild-card characters (e.g. 'orthodont*') did not produce additional records.

As a first step, the titles and abstracts of the articles were checked independently by two reviewers (MA, VV). If the reviewers could not decide on a study's eligibility by examining the title and the abstract, its full text was retrieved; any disagreements were resolved by discussion. Duplicate studies were identified by comparing authors' names, title and results and removed from the final count.

From each included study, we extracted the study's publication data (journal, title, authors, date), sample characteristics (sample size, gender, age), relevant results (VAS score, standard deviation) and details of the intervention (time, drug type and dosage). The data were extracted by one author (MA) and checked by a second author (DH). Disagreements were resolved by discussion between the authors. Authors of six studies that provided insufficient data for meta-analysis were contacted but only one responded and returned the requested information. In two studies, the results were presented as graphs only (12, 13). We retrieved numerical values by measuring directly from the graphs, as the authors did not respond to our query.

Risk of bias was evaluated by considering specific criteria: 1) randomization method; 2) blinding; 3) report of drop-outs; 4) intention-to-treat analysis; 5) selective reporting; and 6) incomplete reporting. Each study was evaluated jointly by all authors and consensus was reached.

The data were analysed with the META-ANALYST statistical package (version 3.13, Tufts, Boston, MA, USA). The standardized mean difference (SMD) and 95% confidence intervals (CI) of the main outcome were estimated by the random effects model, as proposed by DerSimonian and Laird (53). Hedges' g was chosen as estimator of the effect size. Heterogeneity was evaluated by I^2. Risk of bias across studies was evaluated by visual inspection of the funnel plot, and leave-one-out analysis was performed to check the sensitivity of the results.

Results

The electronic search produced 1127 articles (Fig. 1). Application of the exclusion and inclusion criteria reduced these to 77 articles that were evaluated in their full-text form. Of these, 14 concerned the use of NSAIDs for orthodontic pain management, but only seven studies fulfilled all inclusion criteria, including the use of VAS scores and a control group, and these were used for the meta-analysis (Tables 1 and 2).

The finally selected studies were randomized controlled clinical trials evaluating pain relief using NSAIDs during fixed orthodontic treatment. Three studies evaluated pain after separator placement (4, 13, 30), three studies after initial archwire placement (34, 43, 44) and one study after both separator and archwire placement (12). In six studies, pain was evaluated for 7 days (4, 12, 13, 34, 43, 44), whereas one evaluated pain for the first 24 h only (30).

The included studies involved a total of 621 participants and had a mean age of participants between 13 to 18 years and various gender distributions. The agents administered were lactose, as placebo, for the control group (12, 13, 30, 34, 43, 44), 400 mg ibuprofen (4, 12, 13, 30, 34, 43) or 600 mg ibuprofen (44) and acetaminophen-paracetamol in various dosages (4, 34, 44) (Table 1). Three studies included groups receiving aspirin, naproxen sodium or flurbiprofen, but these groups were not comparable to other studies and were not included in the meta-analysis (12, 43, 44). Time of administration differed between studies. In three studies, medication was given after orthodontic intervention (12, 13, 34), in one study medication was given before archwire application (43), and three trials included both pre- and post-visit medication (4, 30, 44).

The Polat et al. (43) publication had errors in the results, but these were later corrected with an erratum. Because of high similarities of this study to another study (44), the leading author, common to both studies, was contacted to ensure that the subjects did in fact differ between the two publications. Upon confirmation, we retained both studies, in contrast to a previously published review (50). In the Bradley et al. (4) study, discomfort was not differentiated between chewing and biting, but a single VAS value was taken; we used this measurement for both chewing and biting, considered the 'day 1' value as the 24-h measurement and used the 'per-protocol' values in the analysis. In the Salmassian et al. (34) study, there was no discrimination of discomfort between any activities; the mean VAS scores and standard deviations (SD) for the 2- and 6-h time intervals were retrieved from the 3- and 7-h measurements. In the Minor et al. (30) study, biting results were not published, whereas chewing results were the sum of pain during chewing on both sides. In addition, this study does not mention whether patients were excluded if additional medication was taken. Two studies did not report mathematical data, and their results were retrieved from graphs (12, 13). In the study of Ngan et al. (12), no discrimination between pain levels of different activities could be obtained from the graphs. Finally, Steen Law et al. (13) included patients who took additional medication in the analysis; however, the authors mentioned that there was no difference between groups regarding the

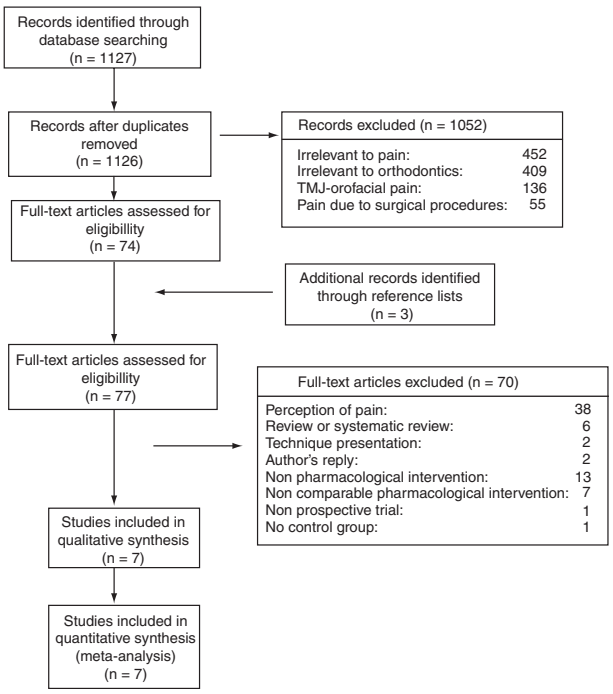

Fig. 1. Flow chart of studies selection.

Table 1. **Studies included in the meta-analysis (n: sample size, h: hours, d: days, ia: immediately after)**

Study	n	Gender distribution	Mean age (years)	Time pain evaluated	Orthodontic procedure	Groups (sample size) and medications administered
Ngan et al. (12)	77	44% ♀ 56% ♂	16.6 ± 6.8	2, 6, 24 h 2, 3, 7 d	Separators Archwire	Group A (n = 23) 400 mg ibuprofen (ia) Group B (n = 28) 650 mg aspirin (ia) Group C (n = 26) placebo (ia)
Steen Law et al. (13)	63	60% ♀ 40% ♂	13.4 ± 1.7 13.3 ± 1.4 13.1 ± 1.8	2, 6, 24 h 2, 3, 7 d	Separators	Group A (n = 22) 400 mg of ibuprofen (1 h before) / placebo (IA) Group B (n = 19) placebo (1 h before) / 400 mg of ibuprofen (IA) Group C (n = 22) placebo (1 h before) / placebo (IA)
Polat et al. (43)	60	38% ♀ 42% ♂	16.0 ± 6.1 17.0 ± 7.0 15.0 ± 2.2	2, 6 h At bedtime 24 h, 3, 7 d	Archwire	Group A (n = 20) placebo (1 h before) Group B (n = 20) 400 mg ibuprofen (1 h before) Group C (n = 20) 550 mg naproxen sodium (1 h before)
Polat & Karaman (44)	120	36% ♀ 64% ♂	16.0 ± 6.1 15.0 ± 2.8 15.0 ± 4.5 16.0 ± 4.6 15.0 ± 2.9 15.0 ± 3.7	2, 6 h At bedtime 24 h 2, 3, 7 d	Archwire	Group A (n = 20) placebo(1 h before) / placebo (6 h after) Group B (n = 20) 600 mg ibuprofen (1 h before) / ibuprofen (6 h after) Group C (n = 20) 100 mg flurbiprofen (1 h before) / flurbiprofen (6 h after) Group D (n = 20) 500 mg acetaminophen (1 h before) / acetaminophen (6 h after) Group E (n = 20) 550 mg naproxen sodium (1 h before) / naproxen sodium (6 h after) Group F (n = 20) 300 mg aspirin(1 h before) / aspirin (6 h after)
Bradley et al. (4)	159	64% ♀ 36% ♂	12–16	2, 6 h At bedtime Next morning 2, 3, 7 d	Separators	Group A (n = 82) 400 mg ibuprofen (1 h before, 6 h after) Group B (n = 77) 1 g paracetamol (1 h before, 6 h after)
Salmassian et al. (34)	60	48% ♀ 52% ♂	12–18	3, 7, 19, 24, 31, 48 h 3, 4, 7 d	Archwire	Group A (n = 21) 600 mg acetaminophen (ia, 3, 7, 19, 24, 31, 48 h after, 3, 4, 7 d after) Group B (n = 19) 400 mg ibuprofen (ia, 3, 7, 19, 24, 31, 48 h after, 3, 4, 7 d after) Group C (n = 20) placebo (ia, 3, 7, 19, 24, 31, 48 h after, 3, 4, 7 d after)
Minor et al. (30)	52	58% ♀ 42% ♂	17.6 ± 5.0 14.9 ± 2.71 6.4 ± 3.6	2, 6 h At bedtime Next morning 24 h	Separators	Group A (n = 16) 400 mg ibuprofen (1 h before) / 400 mg ibuprofen (3 h after) / 400 mg ibuprofen (7 h after) Group B (n = 17) placebo (1 h before) / 400 mg of ibuprofen (3 h after) / 400 mg ibuprofen (7 h after) Group C (n = 18) placebo (1 h before) / placebo (3 h after) / placebo (7 h after)

Table 2. **Quality measures of randomized clinical trials included in the meta-analysis**

Study	Randomization	Placebo group	Patients blinded	Clinician blinded	Report of drop-outs	Per protocol	Selective reporting
Ngan et al. (12)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Steen Law et al. (13)	Yes	Yes	Yes	Yes	Yes	No	Yes
Polat et al. (43)	Yes	Yes	Yes	Yes	Yes	Yes	No
Polat & Karaman (44)	Yes	Yes	Yes	Yes	Yes	Yes	No
Bradley et al. (4)	Yes	No	Yes	Yes	Yes	Yes	Yes
Salmassian et al. (34)	Yes	Yes	Yes	Yes	Yes	Yes	No
Minor et al. (30)	Yes	Yes	Yes	Yes	No	Yes	Yes

number of patients who took additional medication.

Minor et al. (30) found that the group receiving ibuprofen before and after separator placement experienced less pain ($p < 0.05$) at 6 h, at bedtime, and at awakening on the second day, but not at 24 h. Steen Law et al. (13) also found lower levels of pain 2 h after intervention in the group receiving preoperative ibuprofen, when compared to subjects who had taken preoperative placebo and post-operative ibuprofen, or the placebo medication both preoperatively and post-operatively, but there was no significant difference in pain levels between groups at any of the subsequent post-operative times. Salmassian et al. (34) found that acetaminophen, ibuprofen and placebo were equally effective at all time points. Bradley et al. (4) found no statistically significant difference in pain scores between ibuprofen and paracetamol at 24 h. Polat et al. (43) did not find any significant differences between the placebo and ibuprofen groups, while naproxen sodium (550 mg) taken 1 h before archwire placement significantly decreased the severity of pain at 2, 6 h and at night-time. Polat and Karaman (44) reported that patients receiving acetaminophen had significantly less pain than those receiving placebo both at 6 and 24 h, while ibuprofen proved better than placebo at 24 h after intervention. Finally, Ngan et al. (12) found that the placebo group had significantly more discomfort than either the ibuprofen or the aspirin group at all time points tested.

Detailed data for each study and meta-analysis results are presented in Tables 3 and 4. Meta-analysis of the six studies comparing the effect of ibuprofen vs. placebo in pain levels during chewing, 24 h after intervention, revealed no statistically significant difference. The treatment effect (Tx effect) was −0.265 and the 95% confidence interval (CI) was −0.642 to 0.112 (Fig. 2). The results did not differ when evaluating pain levels during biting, using the same medications (ibuprofen vs. placebo) and time of measurement (24 h). Tx effect was −0.394 and 95% CI ranged from −0.836 to 0.048 (Fig. 3).

However, when comparing ibuprofen to placebo during chewing and biting at an earlier time (6 h), we found a statistically significant effect. Tx effect for chewing was −0.381 and the 95% CI was −0.640 to −0.123 (Fig. 4), whereas the Tx effect for biting was −0.515 and the 95% CI was −0.857 to −0.172 (Fig. 5). At 2 h after intervention, pain levels between ibuprofen and placebo differed significantly during biting (Tx effect: −0.562, 95% CI: −0.178 to −0.046, Fig. 6), but did not differ significantly during chewing (Tx effect: −0.202, 95% CI: −0.551 to 0.148, Fig. 7).

When comparing acetaminophen to ibuprofen, no statistically significant differences were found either for biting or for chewing, for any of the three time points (2, 6 and 24 h).

Significant evidence of heterogeneity between studies was observed in biting, between placebo and ibuprofen 2 h after intervention (Table 4, $I^2 = 69\%$, $p < 0.05$) and 24 h ($I^2 = 59\%$, $p < 0.05$), as well as in the acetaminophen vs. ibuprofen measurements at 2 h (chewing, $I^2 = 71\%$, $p < 0.05$) and at 6 h (chewing, $I^2 = 68\%$, $p < 0.05$; biting, $I^2 = 80\%$, $p < 0.05$). Funnel plots confirmed evidence of

Table 3. **Mean visual analogue scale scores (cm on a 10-cm scale) and standard deviations (in parentheses) for studies included in the meta-analysis (n: sample size, h: hours)**

		Ibuprofen				Placebo				Acetaminophen			
Study	Activity	n	2 h	6 h	24 h	n	2 h	6 h	24 h	n	2 h	6 h	24 h
Ngan et al. (12)	Sum of all activities	23	4.18 (1.18)	4.27 (1.44)	4.60 (1.32)	26	4.61 (1.26)	4.93 (1.21)	5.30 (1.31)				
Steen Law et al. (13)	Chewing	22	0.95 (1.21)	2.92 (2.37)	5.30 (2.82)	22	2.55 (2.67)	3.56 (2.77)	5.11 (3.12)				
	Biting	22	0.96 (1.06)	2.43 (2.62)	4.56 (3.43)	22	2.68 (3.23)	4.24 (3.07)	4.31 (3.12)				
Polat et al. (43)	Chewing	20	2.18 (2.68)	3.49 (3.04)	5.46 (3.82)	20	3.92 (3.18)	5.18 (3.07)	4.47 (2.97)				
	Biting	20	2.15 (2.44)	4.56 (3.50)	6.08 (3.38)	20	5.41 (2.78)	5.73 (3.71)	6.69 (2.84)				
Polat & Karaman (44)	Chewing	20	3.70 (2.75)	2.73 (3.18)	2.45 (3.26)	20	3.81 (3.28)	5.19 (3.31)	5.94 (3.12)	20	2.28 (2.65)	2.13 (2.94)	1.31 (2.47)
	Biting	20	1.30 (2.07)	2.37 (3.08)	2.62 (3.29)	20	3.91 (3.42)	6.05 (3.27)	6.66 (2.96)	20	1.00 (2.01)	1.03 (1.51)	2.64 (3.46)
Bradley et al. (4)	Chewing and biting	74	1.84 (1.89)	2.52 (2.14)	3.15 (2.27)*					80	2.56 (2.04)	3.57 (2.21)	3.41 (2.33)**
Salmassian et al. (34)	Not specified	19	3.41 (2.61)	4.25 (2.71)	3.63 (3.01)	19	2.51 (2.81)	4.40 (2.50)	4.07 (2.75)	21	2.98 (2.66)	3.60 (2.73)	3.59 (2.77)
Minor et al. (30)	Chewing (sum of both sides)	17	5.90 (5.77)	7.20 (5.36)	10.30 (7.01)	18	4.80 (4.12)	8.50 (5.52)	11.90 (4.67)				

*n = 67, **n = 76.

asymmetry, perhaps signifying publication bias, although other factors cannot be excluded.

Leave-one-out analysis was conducted for the comparisons between ibuprofen and placebo only, because of the small number of studies comparing ibuprofen to acetaminophen. Removing the Salmassian et al. (34) study caused the 2-h chewing effect of ibuprofen to become significantly different from placebo. In contrast, removing any other study, except the Salmassian et al. (34) study, caused the 2-h biting effect to revert to a non-significant difference. The 6-h data were insensitive to study removal. The 24-h data for biting exceeded the significance limit by removing the Steen Law et al. (13) study.

Discussion

Overall, meta-analysis showed that ibuprofen is more effective than placebo at 2 and 6 h, but it has no statistically significant effect in reducing pain 24 h after separators or archwire placement. Acetaminophen was found to be equally effective to ibuprofen at all time points and activities. These conclusions are based on a total of seven randomized trials of similar design. Areas of non-matching included time of intervention, dosage and timing of drug administration, activity measured (chewing, biting) and orthodontic appliance used (separators, archwire). It was not possible to select completely homogeneous studies, and therefore, subgroup analysis was not performed.

In addition, some of the studies (12, 13) did not include numerical data, and the information was retrieved from graphs, probably accompanied by measurement error. Moreover, results may be influenced by the difference in gender ratio of the samples between studies. Another limitation stems from the small sample size (around 20 subjects in each group) of most of the studies, which reduces the confidence of the results and may not allow detection of a true effect. Finally, publication bias may have affected the results of the meta-analysis, because asymmetry was found on some occasions between studies.

Sensitivity analysis of the results places more confidence on the 6- and 24-h conclusions. The

Table 4. **Meta-analysis results: Standardized treatment effect (Tx effect), calculated as Hedges' g, 95% Confidence Interval (CI), using random effects model and I^2 values**

		Ibuprofen vs. Placebo (six studies)			Ibuprofen vs. Acetaminophen (three studies)		
Activity	Time	Tx effect	95% CI	I^2	Tx effect	95% CI	I^2
Chewing	2 h	−0.206	−0.550 to 0.138	0.456	0.049	−0.507 to 0.606	0.711*
	6 h	−0.386	−0.638 to −0.133	0.000	−0.076	−0.600 to 0.447	0.679*
	24 h	−0.270	−0.642 to 0.102	0.532	−0.003	−0.266 to 0.261	0.000
Biting	2 h	−0.560	−1.065 to −0.056	0.691*	−0.106	−0.488 to 0.276	0.421
	6 h	−0.513	−0.847 to −0.179	0.313	0.054	−0.617 to 0.725	0.801*
	24 h	−0.395	−0.828 to 0.037	0.592*	−0.072	−0.335 to 0.191	0.000

*$p < 0.05$.

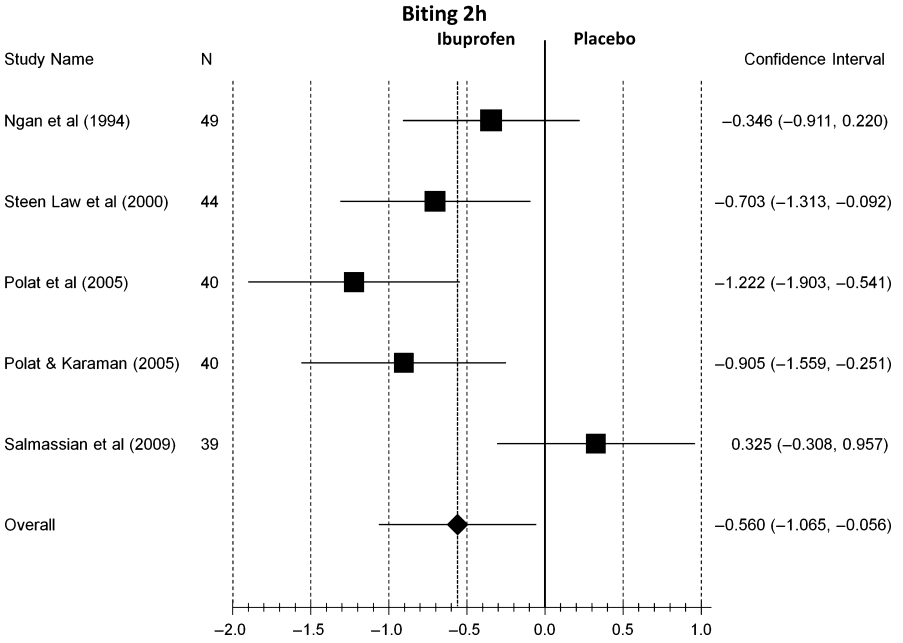

Fig. 2. Forest plot for effect of ibuprofen vs. placebo at 2 h (biting).

standardized effect size at 6 h was approximately −0.4 to −0.5, which translates to a reduction of slightly <1.5 cm in the VAS. At 24 h, no statistically significant treatment effect could be detected, but the confidence interval extended towards the pain reduction direction, and, for the biting activity, it reached the significance limit when removing one study. Therefore, it is conceivable that a small clinical effect may be present, but the included studies may be too few or contain samples too small to provide adequate power to the meta-analysis for detection of this effect. Statistical power is a test's ability to detect an effect, when one exists. Power is determined by, among other factors, sample size and the magnitude of the effect under investigation. Estimation of the appropriate sample size by a power analysis is important in clinical trials to assess the probability of Type II error. Investigators are strongly encouraged to include such information.

A possible explanation for the lack of efficacy of NSAIDs to control orthodontic pain at 24 h may be the inadequate dose of medication, because most of the times NSAIDs were taken many hours before the peak time of pain, but the peak plasma concentration of ibuprofen is reached after 1–2 h (30). This explains the positive effect of NSAIDs on orthodontic pain at 6 h. However, Salmassian et al., (34) even with additional doses, did not find any statistical significant differences between

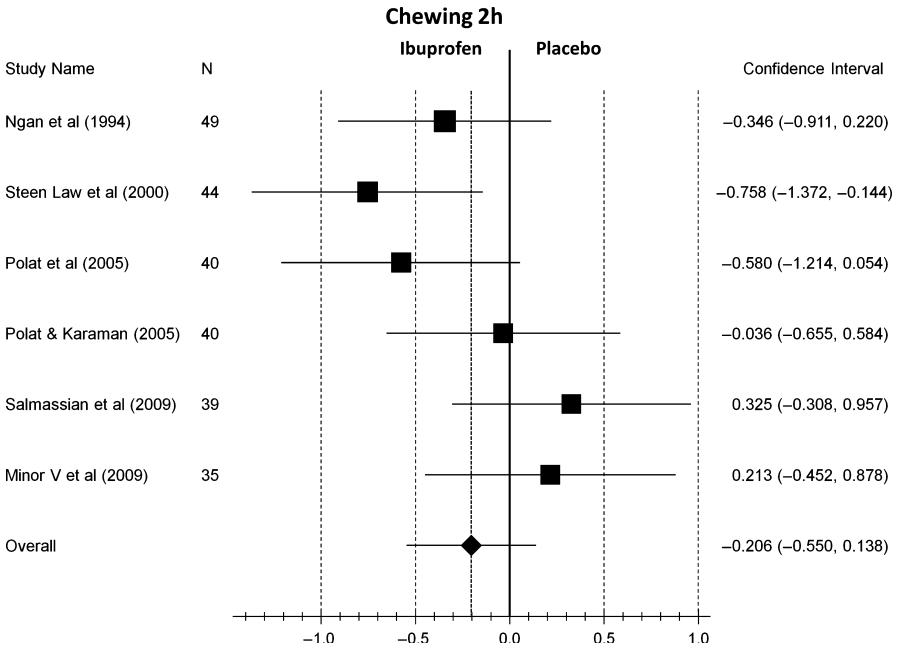

Fig. 3. Forest plot for effect of ibuprofen vs. placebo at 2 h (chewing).

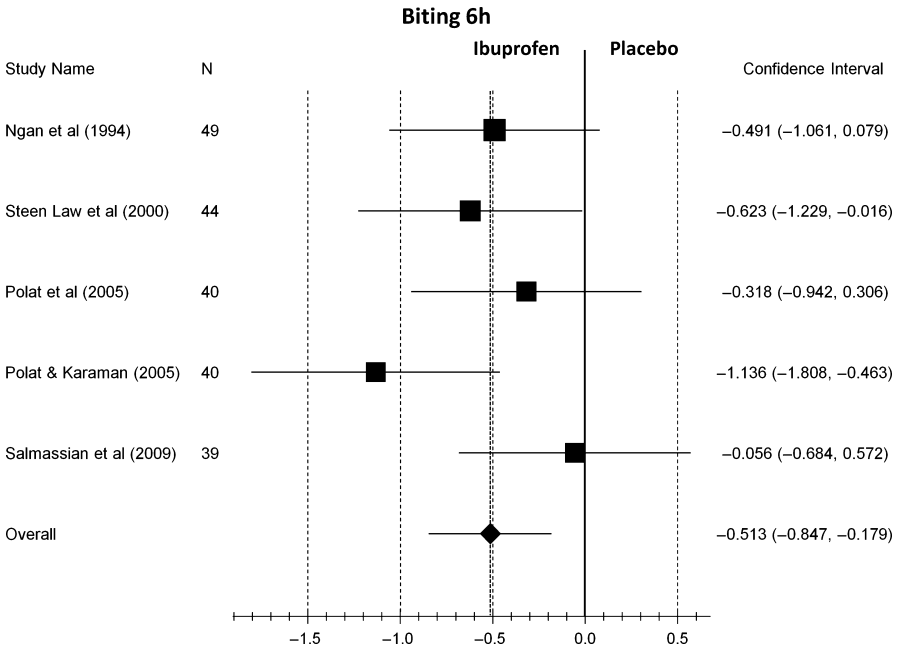

Fig. 4. Forest plot for effect of ibuprofen vs. placebo at 6 h (biting).

acetaminophen, ibuprofen or placebo. Thus, higher doses may be needed in addition to higher frequency of medication. Another explanation might be the differences in pain threshold and tolerance levels, because pain is subjective and depends on factors such as patient's previous pain experiences, emotional state and cultural background (30, 34, 44). Additionally, NSAIDs inhibit synthesis of prostaglandins, but are incapable of stopping their action once they have been produced (37). Thus, post-operative medication, arriving after inflammation has already begun, may not abort the pain experience (13). Preoperative use of acetaminophen (41) may prevent pain, because it reduces the formation of prostaglandins and blocks afferent nerve impulses before they reach the central nervous system (13, 42, 43). Preoperative, taken together with post-operative ibuprofen, was found to reduce pain, but pre- or post- only intervention did not

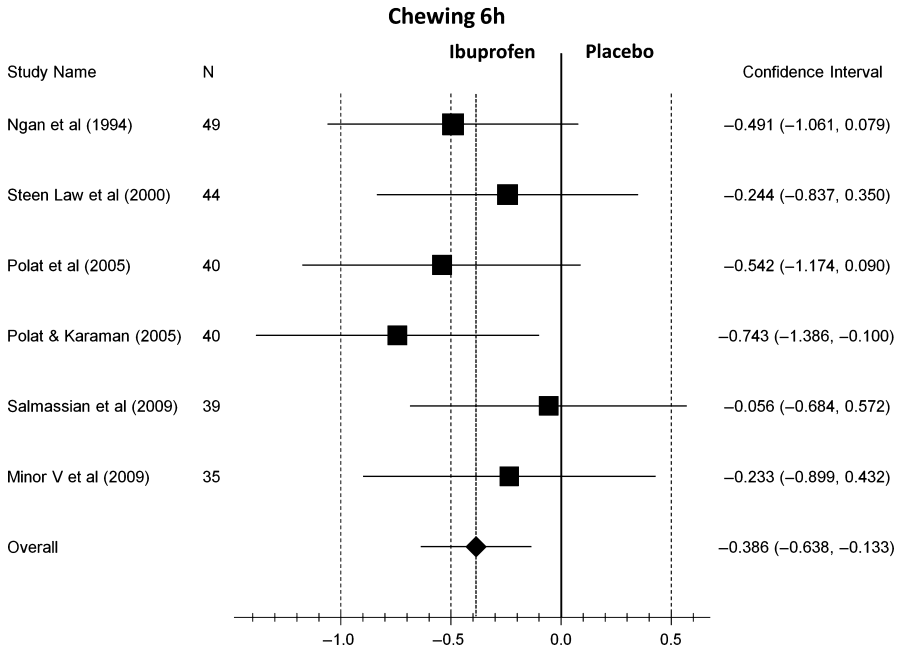

Fig. 5. Forest plot for effect of ibuprofen vs. placebo at 6 h (chewing).

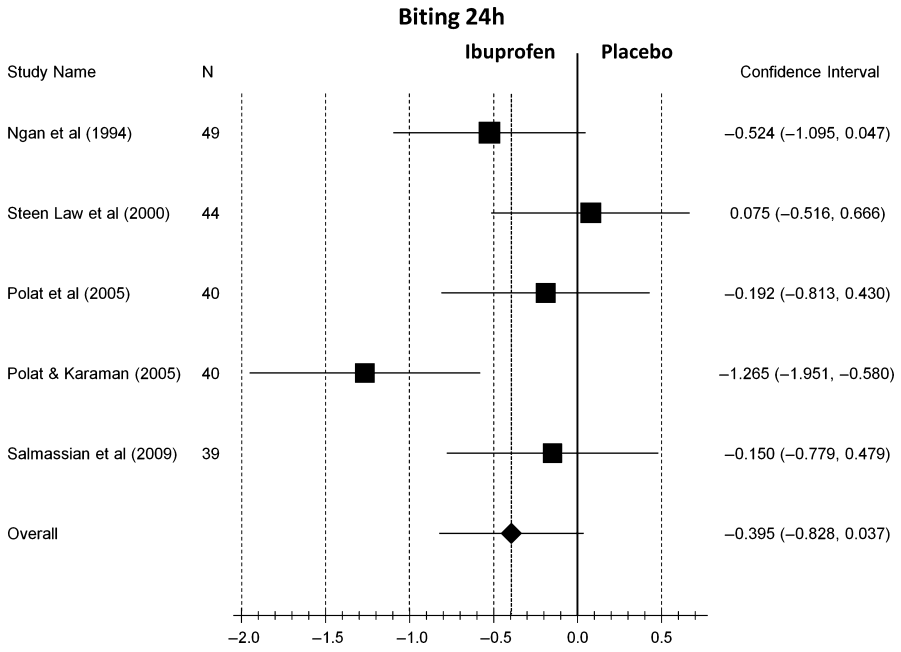

Fig. 6. Forest plot for effect of ibuprofen vs. placebo at 24 h (biting).

reduce pain adequately (42, 44). However, other studies using preoperative and post-operative medication did not report pain relief at peak pain time (4, 30).

This study appears after the meta-analysis of Xiaoting et al. (50) on orthodontic pain. The present study differs in that: 1) it follows the PRISMA guidelines (51, 52), proposed as the most valid methodology for meta-analyses; 2) it focuses on pharmacological management of pain, and NSAIDs in particular; 3) it analyses pain during biting and chewing separately. The last point makes direct comparison of the results between the two meta-analyses difficult because the Xiaoting et al. (50) study does not specify which activity was used for analysis.

The clinically relevant question is whether we should prescribe medication for management of orthodontic pain in view of the potential side effects on our young patients. There is no easy

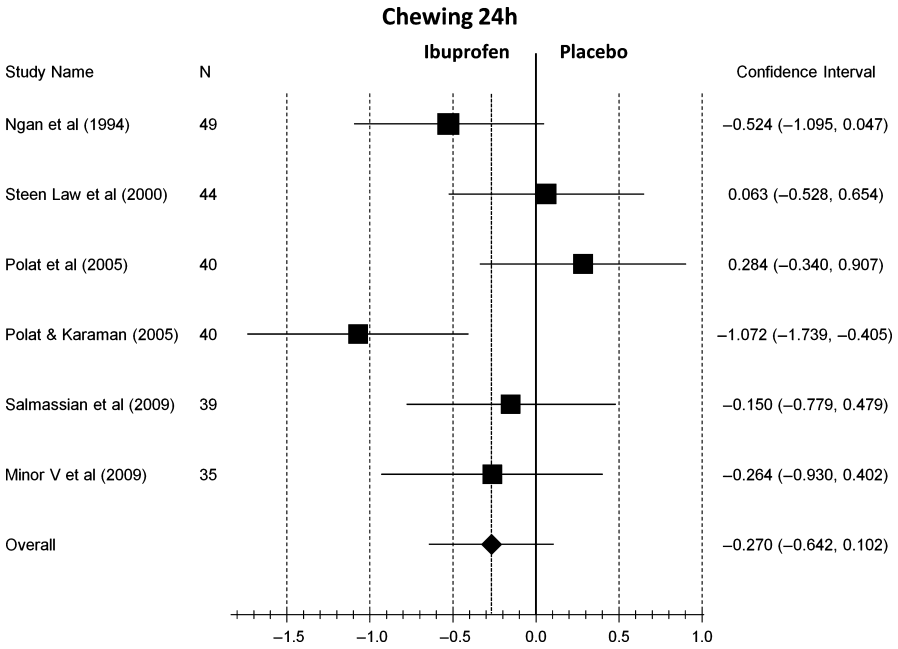

Fig. 7. Forest plot for effect of ibuprofen vs. placebo at 24 h (chewing).

answer and each clinician should weigh general and patient-specific factors for a final decision. Patient-specific factors are mainly related to each patient's sensitivity and past pain experiences, but also to dental status and to treatment specifics. No research is available in this area. General factors include the following: 1) the estimated treatment effect. The results of this meta-analysis show an average treatment effect of approximately 1.5 cm on the visual analogue pain scale at 6 h. This reduction has to be evaluated in comparison with the overall range of pain values reported. Although this differed greatly between studies, it was surprising to note that some very high values were recorded (the mean values and standard deviations reported in Table 3 can be used to infer the range of VAS scores). This seems contrary to the general belief that orthodontic pain is minimal for most patients. It is not clear in some studies how the extremes of the VAS line were described to the patients, but the customary 'worst pain imaginable' for the extreme right of the line was probably not followed, either by the investigators or the patients, or, the patients were lucky enough to not have experienced worse pain before. In any case, a 1.5-cm effect (on a scale of 10) seems moderate to low. 2) The timing of the treatment effect. Although pain was reduced at 6 h, no statistically significant effect was observed at 24 h, when pain is most intense. 3) The frequency of pain experiences. Orthodontic treatment requires regular appointments every few weeks for archwire adjustments. If pain management is justified for the first appointment, then it seems that it would be required at every subsequent appointment as well. This is usually not followed, and there are no data to show if pain diminishes during the course of treatment, if patients learn to accept it, or if orthodontists assume it is not an important issue anymore.

The trials evaluated here used a placebo group for comparison. This is considered essential because—stated perhaps too simplistically—it establishes the minimum pain level that can be achieved by suggestive means; any further reduction is considered purely pharmacological. However, the patients who took part in these studies were not experiencing any pain when recruited, or when receiving pre-treatment medication. It is conceivable that, merely the suggestion that orthodontic intervention might cause pain requiring analgesics, would increase patients' expectation of pain and thus pain itself. No data are available as to the level of pain produced by orthodontic intervention when no medication is given and when any inquiries about such pain are just dismissed by the orthodontist as unfounded.

Conclusions

Ibuprofen can reduce pain at 6 h after orthodontic procedure, whereas it has a statistically non-significant effect at 24 h, the peak pain time, after separators or archwire placement. There seems to be no difference in effectiveness between ibuprofen and acetaminophen, although the evidence is weak.

Clinical relevance

Pain has been reported as a common side effect during orthodontic treatment. Pharmacological management of pain using non-steroidal anti-inflammatory drugs (NSAIDs) is advocated but effectiveness is debatable. This meta-analysis shows that pain is reduced at 2 and 6 h after orthodontic intervention, but no significant effect is present at 24 h, when pain reaches its maximum value. Ibuprofen and acetaminophen seem equally effective, although the evidence is weak. The transient effect of NSAIDs and the moderate pain reduction they achieve may not justify analgesic prescription, at least according to the dosage scheme used in the reviewed studies.

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