Comparative effectiveness of pharmacologic and nonpharmacologic interventions for orthodontic pain relief at peak pain intensity: A Bayesian network meta-analysis

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Introduction: The objective of this network meta-analysis was to synthesize the evidence of the comparative effectiveness for various interventions used for orthodontic pain relief during peak pain intensity. **Methods:** MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched to December 31, 2014, to identify relevant studies. Additional studies were found by hand searching of journals and reference lists. Unpublished articles were also searched. Eligible studies were randomized controlled trials evaluating the effectiveness of pharmacologic or nonpharmacologic interventions for pain relief after placement of separators or an initial aligning archwire. A covariate-adjusted arm-based 3-level hierarchical Bayesian random-effects model was used for this network meta-analysis. **Results:** Twenty-four randomized controlled trials (2273 participants; 997 male, 1276 female; mean age, 18.2 years; SD, 4.4 years) were included in this network meta-analysis. A total of 26 interventions were identified and classified into 6 classes based on their mechanism of action. Compared with placebo-class, nonsteroidal anti-inflammatory drug analgesics and lasers were the most effective intervention classes with a shared median rank of 2 (95% credible interval [CrI], 1-3), followed by "other" analgesics (median rank, 3; 95% CrI, 1-4), behavior therapy (median rank, 4; 95% CrI, 3-6), and miscellaneous (median rank, 5; 95% CrI 3-6). The most effective individual interventions in the nonsteroidal anti-inflammatory drug analgesics and lasers classes were etoricoxib (median rank, 1; 95% CrI, 1-3) and gallium-arsenide superpulsed lasers (median rank, 3; 95% CrI, 1-13), respectively. Assessment of transitivity and consistency assumption showed no threat to the network meta-analysis estimates. There was no evidence of significant publication bias. Heterogeneity was mild to moderate (tau-square, 0.044; 95% CrI, 0.040-0.055). **Conclusions:** The results show that analgesics and lasers are effective in the management of orthodontic pain at its peak intensity. Further research is required to improve the quality of evidence, especially for analgesic interventions. (Am J Orthod Dentofacial Orthop 2016;150:13-32)

The prevalence of pain during fixed orthodontic treatment is high,[1] and fear of pain is a major concern for many prospective orthodontic patients.[2] It is well known that the placement of orthodontic separators[3,4] and initial aligning archwires[1,2] induces pain that reaches peak intensity at 24 hours, or 1 day, after orthodontic force application.[1-3,5] Therefore, management of orthodontic pain at its peak intensity is of paramount clinical importance.

Recently, pairwise meta-analyses were conducted to provide answers related to the effectiveness of pharmacologic[6] and laser[7] interventions for orthodontic pain management after placement of separators or initial archwires. However, pairwise meta-analyses have an inherent limitation in terms of not using all the available evidence if direct comparisons are not provided by all studies included in the pairwise meta-analyses.[8] Furthermore, many interventions such as cognitive behavioral therapy, structured phone calls, and text messages, which are often used in the management of orthodontic pain, have never been included in any previous pairwise meta-analyses.

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Comparative effectiveness research relies on the accurate assessment of the treatment effectiveness of all possible interventions to provide evidence to inform health care decision makers.[9,10] The network meta-analysis, also called mixed treatment comparison, has extended this concept of comparative effectiveness research by providing estimates for comparative effectiveness of all competing treatments even when no head-to-head comparisons are available.[8-10] Synthesizing all available evidence (direct and indirect) also usually improves the precision of the estimates. Therefore, it is recommended that even when pairwise meta-analyses exist for any condition, the results obtained from network meta-analyses are more precise.[8]

The statistical methods for conducting a network meta-analysis are broadly classified into 2 groups: Bayesian and frequentist. Recently, Pandis et al[11] introduced the frequentist models of network meta-analyses in orthodontics. Both Bayesian and frequentist models are well-accepted for conducting network meta-analyses; however, Bayesian methods offer certain advantages over the frequentist method. For example, compared with the frequentist method, Bayesian methods allow greater flexibility in fitting diverse and complex networks of interventions, estimating the uncertainty in heterogeneity and the associated credible intervals based on prior distributions, and ranking each intervention included in the network as best, second best, and so on. In Bayesian methods, ranking is straightforward, based on the joint posterior distribution of all relative treatment effects.[8,10,12,13] Furthermore, the most recent development of a 3-level hierarchical modeling approach in Bayesian network meta-analyses allows inclusion of sparse data in which even 1 study for any comparison can be included in the network meta-analyses without compromising the precision of the estimates.[14,15] This approach allows strength to be borrowed within the classes of interventions, potentially reducing the uncertainty around the individual intervention effects, and consequently allowing the ability to rank the interventions and classes independently and inform the decision-making frameworks.[14]

This network meta-analyses was undertaken with the objective to assess the comparative effectiveness of different interventions and intervention classes used for pain relief after orthodontic separator or initial archwire placement by combining direct and indirect evidence in an arm-based covariate-adjusted 3-level hierarchical Bayesian network meta-analysis model. The motivation to apply a 3-level hierarchical modeling is the scarcity of data because of the large number of interventions of interest and relatively few trials, which could compromise the precision of the effect estimates and the estimation of heterogeneity.

MATERIAL AND METHODS

We followed a standard systematic review protocol according to the PRISMA guidelines and its recent adaptation for network meta-analyses.[16,17] Excluding treatments from network meta-analyses can adversely affect the findings.[18] Therefore, the eligibility criteria and search strategy were designed to ensure that studies included in this network meta-analyses would enable us to compare all possible interventions used for orthodontic pain management at the peak pain intensity level.

Eligibility criteria (PICOT)

We considered the population (patients), interventions, comparators, outcomes, and types of study (PICOT) to define the eligibility criteria for studies to be included in this network meta-analyses. Eligible studies were prospective randomized controlled trials (RCTs) evaluating the effectiveness of any pharmacologic or nonpharmacologic interventions for pain relief. The quality of evidence derived from RCTs is considered the gold standard in evaluating intervention effects.[19] We did not specify a minimum sample size for inclusion; therefore, studies with all sample sizes were included.

To safeguard against violation of the transitivity assumption in network meta-analyses, we included studies with comparable design characteristics and plausible range of covariate distribution.[12,20] The target population was defined as children and adults of both sexes with orthodontic separators or an initial archwire placed as a part of fixed orthodontic treatment. We decided to include studies with orthodontic separators or initial archwires because the pattern and magnitude of pain after their placement are similar.[1-3,5,21] The index for comparative effectiveness (outcome) was the pain intensity at 24 hours, or 1 day, after separators or initial archwire placement. A control group (no treatment) was considered the reference group for comparisons of the effectiveness of interventions. Considering the diversity of interventions included in this network meta-analyses, the interventions would be classified based on the mechanism of action. Details are provided in the "Results" section.

Search strategy

The MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE databases were searched to identify the RCTs. These databases were searched until December 31, 2014, without restrictions for starting date of search or publication language.