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Comparative effectiveness of pharmacological and non-pharmacological interventions for orthodontic pain relief at peak pain intensity level – A Bayesian network meta-analysis

Abstract

Introduction: Objective of this network meta-analysis (NMA) was to synthesize the evidence of comparative effectiveness for various interventions used for orthodontic pain relief during peak pain intensity level.

Methods: The MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases were searched till 31st December 2014 to identify the relevant studies. Additional studies were identified by hand searching of journals and reference lists. Unpublished literature was also searched. Eligible studies were randomised-controlled trials (RCTs) evaluating the effectiveness of pharmacological or non-pharmacological interventions for pain relief after placement of separator or initial aligning arch wire. A covariate adjusted arm-based three level hierarchical Bayesian random effects model was used for this NMA.

Results: 24 RCTs (2,273 participants; male/ females 997/1276; mean age 18.2 years, SD 4.4) were included in this NMA. Total 26 interventions were identified which were classified into 6 classes based on their mechanism of actions. Compared to placebo, 'NSAIDs' analgesics and lasers were most effective intervention classes with shared median rank of 2 (95% CrI 1 to 3); followed by 'other' analgesics (median rank 3; 95% CrI 1 to 4); behaviours therapy (median rank 4; 95% CrI 3 to 6); and miscellaneous (median rank 5; 95% CrI 3 to 6). The most effective individual interventions in 'NSAIDs' analgesics and lasers classes were etoricoxib (median rank 1; 95% CrI 1 to 3) and GaAs super-pulsed lasers (median rank 3; 95% CrI 1 to 13) respectively. Assessment of transitivity and consistency assumption revealed no threat to the NMA estimates. There was no evidence for significant publication bias. Heterogeneity was mild to moderate (τ^2 0.044, 95% CrI 0.040 to 0.055).

Conclusion: Results show that analgesics and lasers are effective in management of orthodontic pain at peak pain intensity level. Further research is required to improve the quality of evidence, especially for analgesic interventions.

Introduction

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 fact that placement of orthodontic separators[3,4] and initial aligning arch wires[1,2] induces pain which reaches at peak intensity after 24 hours/ day 1 of orthodontic force application.[1-3,5] Therefore, management of orthodontic pain at peak intensity level is of paramount clinical importance.

Recently, pairwise meta-analyses (PMAs) were conducted to provide answers related to the effectiveness of pharmacological[6] and laser[7] interventions for orthodontic pain management after separators or initial arch wire placement. However, PMAs have an inherent limitation in terms of not utilizing all the available evidence if direct comparisons are not provided by all studies included in the PMAs.[8] Further, many interventions such as Cognitive Behavioural Therapy (CBT), structured phone call and text messages etc., which are used in the management of orthodontic pain, have never been included in any of the previous PMAs.

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

The statistical methods for conducting NMA are broadly classified into two groups- Bayesian and Frequentist. Recently, Pandis et al[11] have introduced the Frequentist models of NMA in the orthodontic field. Both Bayesian and Frequentist models can be effective in

conducting NMA, however, Bayesian methods offer certain advantages over the Frequentist method. For example, compared to Frequentist method, Bayesian methods allow greater flexibility in fitting diverse and complex network of interventions; directly estimates the uncertainty in heterogeneity and the associated credible intervals based on the prior distribution; and ranking each intervention included in the network as best, second best etc. is straightforward based on the joint posterior distribution of all relative treatment effects.[8,10,12,13] Further, the most recent development of a three-level hierarchical modelling approach in Bayesian NMA allows inclusion of sparse data wherein even a single study for any given comparison can be included in the NMA without compromising the precision of estimates.[14,15] This approach allows strength to be borrowed within the classes of interventions and potentially reducing the uncertainty around the individual intervention effects, and consequently allowing the ability to rank the interventions and classes independently and inform decision-making frameworks.[14]

This NMA was undertaken with an objective to assess the comparative effectiveness of different interventions and interventions classes used for orthodontic relief after orthodontic separator or initial arch wire placement by combining direct and indirect evidence in an arm-based covariate adjusted three-level hierarchical Bayesian network meta-analysis model. A motivation to apply a three level hierarchical modelling is the scarcity of data due to a large number of interventions of interest and a relatively smaller number of trials which could compromise the precision of the effect estimates and the estimation of heterogeneity.

Methods

We followed a standard systematic review protocol according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines and its recent adaptation for NMA.[16,17] keeping in mind the fact that excluding treatments from network

meta-analyses can adversely affect the findings of NMA;[18] the eligibility criteria and search strategy were designed to ensure that studies included in this NMA would enable us to compare all possible interventions used for orthodontic pain management at peak pain intensity level.

Eligibility criteria (PICOT)

We considered the population (patients), interventions, comparator, outcomes and type of study (PICOT) to define the eligibility criteria for studies to be included in this NMA. Eligible studies were prospective randomised-controlled trials (RCTs) evaluating the effectiveness of any pharmacological or non-pharmacological interventions for pain relief. The quality of evidence derived from the RCTs is considered as 'gold standard' in evaluating the interventions effects.[19] We did not specify a minimum sample size for inclusion and therefore, studies of all sample sizes were included.

To safeguard against violation of transitivity assumption in NMA, we included studies with comparable design characteristics and plausible range of covariate distribution.[12,20] The target population was defined as the children and adults of both sexes (males and females) with orthodontic separator or initial arch wire placement as a part of fixed orthodontic treatment procedure. We decided to include studies with orthodontic separator or initial arch wire because the patterns and magnitude of pain after placement of separator and initial arch is similar.[1-3,5,21] The index for comparative effectiveness (outcome) was the pain intensity at 24 hours/day 1, after separator or initial arch wire placement. Control group (no treatment) was considered reference group for comparisons of effectiveness of interventions. Considering the diversity of interventions included in this NMA, the interventions would be classified based on the mechanism of action. Details are provided in the method and results section of manuscript.

Search strategy

The MEDLINE, The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), and EMBASE databases were searched to identify the randomized controlled trials (RCTs). These databases were searched till December 31, 2014 without any restriction for starting date of search or publication language.

In order to eliminate the possibility of excluding any intervention used for orthodontic pain relief and its impact on the NMA findings,[18] we did not use interventions as search item, rather we searched all studies which had a keyword pain or discomfort in the title and/or abstract. All such retrieved studies were then searched to find whether these studies used any intervention for orthodontic pain relief.

Additional studies were identified by hand searching of four major orthodontic journals (1980 to December, 2014): American Journal of Orthodontics and Dentofacial Orthopaedics, The Angle Orthodontist, the European Journal of Orthodontics and the Journal of Orthodontics. Reference lists of the included studies and previously published systematic reviews/meta-analysis related to the topic were screened for identification of any additional study.

Unpublished literature was searched by electronically searching Pro-Quest Dissertations & Theses database, ClinicalTrials.gov, and National Research Register using "orthodontic" and "pain" as search term. Conference proceedings and abstracts were also accessed, where possible.

Study selection and data extraction

The titles and abstracts of all studies identified by the search strategies were independently screened by the first author for removal of duplicate entries and studies which failed to meet the objectives of this NMA. Full-text articles of reaming studies were assessed independently by two other authors for eligibility based on the predefined eligibility criteria.

When disagreement occurred, the article was re-read and discussed until a consensus was obtained amongst the authors. A record of all decisions made about the identified studies was kept. The review authors were not blinded to author(s), institution or site of publication of studies.

Study characteristics data was extracted using a pilot tested data extraction form. The data extracted was: 1) study identification: first author's name and year of publication 2) study design 3) population (participants): sample size, mean age, number of male and female participants, and female proportion 4) interventions: details of pharmacological/non-pharmacological interventions including the dose; frequency; mode and timing of administration 5) comparator and 6) outcome assessment.

Data was also extracted for potential confounder/s and effect modifier/s which would be included in the NMA. Based on the recent evidence available, we identified three effect modifiers (age, sex, and baseline pain) which could have affected the estimates, and therefore included as priori covariates in our NMA.[22,23] Further, we also decided to include another potential confounder, orthodontic procedure (separator vs initial arch wire) as covariate to adjust for the possible effect of orthodontic procedure on NMA estimates. Hereafter, all four would be referred as 'covariate/s'.

Primary outcome assessment

The predefined primary outcome of interest was the patient reported pain intensity at 24 h/ day 1 after orthodontic procedure. For statistical analysis, we required a mean pain score and a level of precision (standard deviation, standard error or 95% confidence interval) estimate. If a trial did not report these summary measures, we contacted trial authors for these data. Where data was reported only graphically, we contacted the corresponding author for numerical data. If this was unsuccessful, the corresponding numerical data was extracted by

using the Windows- based digitizing computer program UnGraph (Biosoft, version 5.0, 2004). The data extraction by using UnGraph has good reliability and validity.[24]

We included trials which assessed pain intensity by using 100 mm Visual Analogue Scale (VAS), 10 cm VAS scale or 10 points Numeric Rating Scale (NRS). To standardise to a single scale, we assumed that NRS (0-10) and VAS (0-10 cm) were equivalent and these scales were converted to VAS (0-100mm) by multiplying pain scores by ten. This method of combining 100 mm VAS, 10 cm VAS and 10 points NRS has been used in the recent meta-analysis.[25] If a trial reported multiple effect sizes (e.g. at rest, during fitting teeth together etc.), we combined these effect size to get a single estimate, as recommended.[26]

Assessment of quality of included trials

Risk of bias was assessed independently by two authors and all disagreements were resolved by discussion. The Cochrane Collaboration risk of bias tool[26] was used to assess the risk of bias based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting of outcomes and 'others' sources of bias. The 'others' source of bias was based on the assessment whether male and female participants were similar with respect to the mean age. This 'others' sources of bias was in relation to assess the clinical heterogeneity.

Grading the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach recently extended to the NMA was used to grade the quality of evidence.[27] Quality of evidence was synthesized for the comparative effectiveness of each intervention as compared to the reference group i.e. control. Although GRADE can be, rather should be applied for all comparisons, however depending on the objective of the NMA, it can be applied only for the comparisons of interventions as compared to reference group such as control group

in our NMA.[16] The domains considered for evaluating the quality of evidence were study limitations (risk of bias); intransitivity; inconsistency/indirectness; statistical heterogeneity; imprecision (wide credible intervals) and publication bias.[27]

Statistical analysis

A conventional pairwise meta-analysis (PMA) was undertaken to compare the interventions if two or more studies included the same pair of interventions as head-head comparison. A random effects model (DerSimonian and Laird method) was applied using the R 'meta' (version 4.3-0) package.[28] The statistical heterogeneity was assessed by the Cochran's Q test and the I^2 statistic.[26] The I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high level of heterogeneity.[26] If more than 10 studies contribute to same pairwise comparison, a funnel plot would be drawn to assess the publication bias.[26]

For NMA, a recently developed arm based three-level hierarchical Bayesian random effects model with ordering constraints[14] was used which fully accounts for the correlation between comparisons within multi-arm trials.[20] Four priori covariates (mean age, proportion of females, mean baseline pain and orthodontic procedure) were incorporated into the NMA as study level covariates within a network meta-regression framework. The statistical model including assumptions employed, inclusion of covariate as part of network meta-regression, model run-in/fit evaluation, and the prior distribution and its sensitivity analysis is described in detail in the Appendix 1 (online supplementary material).

NMA was implemented using the WinBUGS software (version 1.4.3), calling it from within the R software (version 3.1.2) using the 'R2WinBUGs' package.[29] Four individual chains with disparate starting values were analysed and convergence was assessed using Brooks Gelman Rubin (R_{hat}) statics.[29] The results are based on 100,000 samples, where the first 40,000 samples were discarded from the analyses as a "burn-in." The graphical presentation

for ranking the interventions and intervention classes was done using the Surface Under the Cumulative Ranking (SUCRA) values and Rankograms.[13] SUCRA allows for ranking the intervention based on the overall per cent of surface under the curve. SUCRA would be 1 (or 100%) when an intervention is certain to be the best (that is always ranks first) and 0 (or 0%) when an intervention is certain to be the worst. For presenting the probability that each intervention/intervention class is best, 2nd best, 3rd best, etc, Rankogram were used.

Transitivity and consistency are the important assumptions related to the validity of indirect and mixed estimates in NMA.[30] The plausibility of transitivity assumption was evaluated based on the design characteristics and the methodology of studies included in the NMA, as recommended.[30] The covariates distribution was assessed at study level as well as for the loop specific comparisons and direct comparisons involved in the indirect and mixed estimates. The consistencies between direct and indirect comparisons for all closed loops were evaluated using the 'node-splitting' method.[14,31] 'Node-splitting' method is based on the calculation of two posterior distributions, one of which is derived from trials that directly compare the interventions (e.g. interventions X and Y), d^{Dir}_{xy}, whereas the other is indirectly derived from the remaining trials $d^{Ind}_{xy.}$ To test for consistency between direct and indirect estimates i.e. probability that the direct estimate surpasses that of the indirect estimate, a Bayesian p value was calculated.[14]

The heterogeneity was estimated from the median of the posterior distribution of the between trial variance, tau square (τ^2). The tau square is a valid parameter to assess and quantify the magnitude of heterogeneity in a random effect meta-analysis.[26,32] The square root of tau square i.e. tau (τ) shows the standard deviation of underlying effects across studies study.[7,26] In the Bayesian hierarchical random effect models, the definition and interpretation of τ^2 is similar to conventional random effect models.[33] Similar to recently published NMA[34], we defined heterogeneity to be mild if $\tau^2 <$ 0.04, moderate if τ^2 0.04-0.14, and severe if $\tau^2 >$ 0.40.

Small study effect was assessed using the meta-regression based approach recently introduced to Bayesian framework NMAs.[20,35] This approach is based on the assumption that biases are exchangeable across the network, i.e. biases, if present, operate in a similar way in trials across the network.[35,36] Therefore, we extracted the pairwise estimates from the NMA in a way which would reflect that in trials comparing active and inactive treatments (e.g., placebo, control group), it could be reasonably assumed that the active treatment would be favoured by small-study bias.[35] Similar approach was used to extract pairwise estimates to draw the comparison-adjusted funnel plot to assess the small study effects. The comparison-adjusted funnel plot was drawn by using the 'netfunnel' command[37] in Stata software (version 13). Considering the fact that interventions in our NMA were beneficial in nature, therefore, funnel plot asymmetry with fewer studies lying on the left side of zero would indicate that small-study effects favour the active treatments.[37]

Results

Search results and characteristics of studies included in the NMA

The search strategy details are provided in the Appendix 2 (online supplementary material). Total 236 RCTs were identified from the search strategy. After removing duplicates, a total of 99 RCTs remained, from which we identified 24 RCTs[38-61] relevant for our review. The PRISMA flow diagram is shown as Figure 1.

The characteristics of studies included in the NMA are presented in the Appendix 3 (online supplementary material) and summarised in Table 1 and Table 2. Total 2,273 participants (male=997, 43.86%; females=1276, 56.14%) were included with mean age of 18.22 years (SD=4.40), female proportion of .54 (SD=.05), mean baseline pain VAS score 2.56 (SD=3.17). 14 RCTs used orthodontic separator as orthodontic procedure whereas remaining 10 RCTs used initial arch wire as orthodontic procedure. VAS was used for assessment of pain

across all studies. Two RCTs were of split-mouth design[42,47] and one RCT was of cross-over design.[52] We followed the recommended procedure[26] to extract the relevant data so that these three non-parallel design RCTs could also be included in the NMA along with the rest of the parallel design RCTs.

The evidence network plot is shown in Figure 2. Total 26 different interventions were identified across all 24 RCTs which were further classified into following six classes based on their mechanism of action: These were 1) placebo, 2) 'NSAIDs' analgesics, 3) 'others' analgesics, 4) lasers, 5) behaviours therapy, and 6) miscellaneous. The detail of individual intervention and respective intervention classes is provided in Table 1. The rationale and justification of interventions classification is provided in the Section C of Appendix 1 (online supplementary material).

Risk of bias assessment

Risk of bias assessed for each individual study is shown in Figure 3. For two studies, risk of bias was high for randomization process.[38,55] There was no evidence for high risk of bias for any other domain, though few studies did not provide relevant information; and thus assigned unclear risk of bias. Considering the fact that many studies used non-pharmacological interventions and it could have been impossible for the investigators to design double blind trials, therefore a judgement based on the consensus amongst authors was used to assess the risk of bias for two domains related to the blinding process.

Pairwise meta-analysis (PMA) findings

The results of random effect PMAs for 10 pairwise comparison (for which two or more studies studied the same comparison) is presented in the Appendix 4 (online supplementary material). The heterogeneity (I^2) varied from 0% to 69% and all effect sizes were associated

with wide 95% CI. Since number of studies for each comparison were few (maximum 5 studies per comparisons), therefore we did plot conventional funnel plot to assess small study effect.

Network meta-analysis (NMA) findings

Tables 3 show the summary of NMA results. The covariate adjusted model had substantially better fit as compared to the non-adjusted model as shown by the DIC (Deviance Information Criterion) value which was smaller by approximately 68 units. The distribution of study level covariates included in the NMA as presented in Table 2. The models incorporating ordering constraints were of a better fit as compared to the non-constrained models and thus, the results presented are based on estimates derived from the constrained NMA. The summary of NMA estimates with and without the ordering constraints are presented in Appendix 5 (online of supplementary material).

The pair-wise summary forest plot for each intervention is shown in Appendix 6 (online supplementary material). Interestingly, the NMA derived direct estimates are more precise as compared to the corresponding direct estimates available from the PMAs. This was particularly true where heterogeneity was large in the PMAs. For example, the Placebo_Pharmacological Vs Naproxen_Premptive_Postoperative with moderate to high heterogeneity (I^2 69.1%) had wide 95% CI for PMA (estimate -19.62; 95% CI -38.05 to -1.20) as compared to the narrow 95% CrI in NMA (estimate -17.96; -28.53 to -8.12). This probably is due to the fact that the estimates from NMA are adjusted for the covariates.

Interestingly, the direct estimates within the NMA were more precise than the indirect/mixed NMA estimates. A reason for this paradox could be the common heterogeneity assumption in the model used for NMA. Under the assumption of common heterogeneity, comparisons with little or no heterogeneity share the same heterogeneity with comparisons

with large heterogeneity and as a result the NMA estimates appear to be less precise than the respective direct estimates.[30]

Table 3 summarizes the median rank and SUCRA values for each individual intervention and interventions classes. Figures 4 summarizes the pair-wise estimates of interventions as compared to the reference i.e. control group. The etoricoxib was the most effective intervention as compared to the control (estimate -41.96; 95% CrI -52.85 to -30.69) with a median rank of 1; followed by GaAs super-pulsed laser (estimate -34.01; 95% CrI -42.57 to -25.66) and pre-emptive piroxicam (estimate -33.72; 95% CrI -45.17 to -21.82) with a shared median rank of 3. Figure 5 show the SUCRA plot for all interventions. The Rankograms for each individual intervention are shown in Appendix 7 (online supplementary material).

Compared to placebo, 'NSAIDs' analgesics (estimate -19.67; 95% CrI -28.81 to -10.71) and lasers (estimate -19.66; 95% CrI -30.15 to -9.15) were the most effective intervention classes with shared median rank of 2; followed by 'others' analgesics class (estimate -15.26; 95% CrI -25.44 to -5.41) with median rank of 3. The behaviours therapy and miscellaneous intervention classes were not significantly effective as compared to placebo class (Figure 6). Figure 7 show the SUCRA plot for all intervention classes. The Rankograms for each intervention classes are shown in Appendix 8 (online supplementary material).

Sensitivity analysis for priors

Sensitivity to the prior distribution for the between-study variance and the intervention class variances showed little evidence of an impact on the overall effect estimates and precision, as shown in Appendix 9 (online supplementary material). This suggests that all sets of analyses are insensitive to the choice of the prior distributions and NMA estimates are not effected by prior distribution.

Transitivity and inconsistency assessment

The transitivity assessment, based on the recent recommendation,[30] revealed no major threat to transitivity assumption from study design characteristics. We adjusted the NMA estimates by including covariates as part of network meta-regression which further improve the plausibility of the transitivity assumption.[30] The covariate distribution for loop specific comparison as well as direct pairwise comparisons is presented in the Appendix 10 (online supplementary material).

Results from 'Node split' method to estimate the inconsistency shows no substantial evidence for inconsistency (Table 5). Out of total 41 comparisons which provided both direct and indirect estimates and eventually included in the node split method inconsistency estimation, three comparison namely, acetaminophen (pre-emptive and postoperative) vs etoricoxib (pre-emptive and postoperative); placebo (pharmacological) vs aspirin (pre-emptive and postoperative); and placebo (pharmacological) vs etoricoxib (pre-emptive and postoperative) which constitutes 7.3% of total evidence examined (3/41=0.0731), showed significant inconsistency. Results show that covariate adjustments improved the consistency of NMA. For example, the number of comparisons with significant inconsistency (Bayesian p value < 0.05) was eight (19.5%) for unadjusted NMA whereas only three comparisons (7.3%) were inconsistent when covariates were included in the NMA. Further even for three comparisons which showed inconsistency in covariate adjusted NMA, the inconsistency estimate was less as compared to the non-adjusted NMA. The results for the 'Node split' method to estimate the inconsistency without covariate adjustment is shown as Appendix 11 (online supplementary material).

Heterogeneity and publication bias assessment

The NMA heterogeneity estimated from the median of the posterior distribution of the between trial study τ^2 was 0.044 (95% CrI 0.040 to 0.055), suggesting a mild to moderate heterogeneity.[33] The summary of NMA and heterogeneity estimate (τ^2) with and without adjustment for covariate/s is presented in the Appendix 12 (online supplementary material). The heterogeneity explained by covariate/s was calculated as the difference between the heterogeneity estimate after the inclusion of covariate/s (τ_a^2) and before the inclusion of covariate/s (τ_b^2). Thus, the difference $\tau_a^2 - \tau_b^2$ quantifies the amount of heterogeneity explained by covariate/s. A negative sign would indicate that heterogeneity decreased after inclusion of covariate/s. The amount of heterogeneity explained by inclusion of age, sex, baseline pain and orthodontic procedure was - 0.011 (0.088 - 0.099); - 0.030 (0.069 - 0.099); - 0.028 (0.071 - 0.099); and - 0.013 (0.086 - 0.099) respectively. The overall heterogeneity explained by including all four covariates in the NMA was - 0.055 (0.044 - 0.099).

The meta-regression model applied to Bayesian NMA estimates suggests an overall tendency for a small study effect in the network (mean slope estimate -9.73; 95% CrI −25.31 to 7.65), however this effect was not significant as the 95% CrI includes zero. This finding is substantiated by the comparison adjusted funnel plot (Figure 8) which shows no substantial asymmetry.

Quality of evidence

Quality of evidence varied from very low-to-high for direct comparisons, and very low to moderate for indirect comparisons and NMA estimates (Table 4). The quality of evidence for intervention classes can be inferred from the quality of evidence assigned to the constituting interventions. For example, the quality of evidence was very low-to-low for placebo class; low to moderate for the 'NSAIDs' analgesic classes and 'others' analgesics; moderate to high for

lasers; moderate to high for behaviour therapy; and very low to moderate for miscellaneous class.

Discussion

In general, our results substantiate the various claims made recently in relation to the NMA. Firstly, our findings support the fact that NMA estimates are more precise as compared to direct pairwise estimates obtained from the conventional PMAs.[8] Secondly, use of three level hierarchical structure and incorporating the ordering constraints does provide precise estimate even when number of interventions is large and few studies are available for each comparison. More importantly, this framework provides the ability for independent ranking of closely related interventions.[14] For example, in our NMA, the median rank of pre-emptive ibuprofen, postoperative ibuprofen and combined pre-emptive postoperative ibuprofen were 15, 12 and 8 respectively (Figure 4) despite the fact that these three interventions were same except for the timing of administration. Thirdly, the covariates adjusted models provide unbiased NMA estimates[10,20,23]; reduces the heterogeneity and inconsistency; and improves model fit.[10,20,23]

Although categorizing the interventions into their respective classes for the class-based NMA increased the precision of the effect estimates, however it restricts the interpretability of the result at an individual intervention level.[14] Therefore, for the inference purpose, we will be placing emphasis on the intervention class effect while discussing the contribution of each individual intervention in the respective class.

Results shows that compared to placebo (least effective intervention class with median rank 6), 'NSAIDs' analgesics and lasers were the most effective intervention classes, followed by the 'others' analgesics. The behaviour therapy and miscellaneous classes were not significantly better than placebo.

Etoricoxib (pre-emptive postoperative) was the most effective intervention in the 'NSAIDs' analgesics class. This finding is in agreement with previous studies which reported that etoricoxib is more effective in reducing the acute pain as compared to other commonly used NSAIDs.[62] Etoricoxib is a second-generation, highly selective cyclooxygenase 2 (COX-2) inhibitor with anti-inflammatory and analgesic properties.[63] It has a dose dependent inhibitory effect on COX-2 across the therapeutic dose range, and possesses a long plasma half-life duration of 22 h.[63] The high effectiveness of etoricoxib observed in our NMA could be attributed to the fact that there was an accumulative dose of 120 mg (60 mg pre-emptive and 60 mg post-operative within few hours) administered to participants as evident from the study characteristics data (Appendix B), thereby enhancing its effectiveness which is a dose dependent phenomenon.

Our finding suggests that the effectiveness of analgesics depends on the pharmacokinetics, and therefore, should be carefully considered during the selection of analgesics in terms of dose and timing of administration. For example, analgesics with long plasma half-life like pirocixam (18-20 h),[63] naproxen (approximately 15 h)[63] and lumiracoxib (12 h)[63] were effective (median rank within the 10 most effective interventions; and in the same order as their plasm half-life) when administered as only pre-emptive analgesic. However, the analgesics with shorter plasm half-life like ibuprofen (4-8 h)[63] and aspirin (approximately 6 h)[63] were in the top 10 interventions only when these analgesics were administered as combination of pre-emptive and post-operative analgesics. Acetaminophen was less effective in reducing pain perhaps because of its central mechanism of action which results in greater anti-pyretic effect as compared to its analgesic effect.[63] Further, the plasma half-life of acetaminophen is also short (2-5 h).[63]

Lasers were the second most effective intervention class. Several mechanisms have been proposed which could explain the analgesic efficacy of low-level laser therapy (LLLT)

for pain relieving such as, the gate theory, modulation of endorphin production, the anti-inflammatory effect, and the direct inhibition of neural activity.[64] Our results show that super pulsed gallium-arsenide (GaAs) laser is more effective compared to other lasers. This higher effectiveness of super pulsed GaAs laser could be attributed to the fact that the pulsed light is represented by pulse on and off periods, which allows LLLT therapy with higher peaks of power compared to those allowed in conventional lasers.[65] As a result, the super-pulsed lasers can achieve greater penetration depth without increasing the tissue temperature.[65] Interestingly, our findings supports this hypothesis of correlation between wavelength and effectiveness of lasers. In our NMA, wavelength used for the super pulsed GaAs laser (910 nm) was greater as compared to the AlGaInP laser (635 nm) and AlGaAs laser (670-830 nm); and the effectiveness of these lasers was in the order of their wavelength with the median rank of 3, 7 and 11 for super pulsed GaAs, AlGaInP and AlGaAs lasers respectively (Figure 4).

Amongst the behaviour therapy interventions, Cognitive Behavioural Therapy (CBT) was more effective compared to structured phone call and text messages. This could be due to the differences in the methodology of implementation of these procedure adopted in the studies included in our NMA. In both phone call and text message interventions, participants were asked about their pain and were reassured about their concerns regarding the pain, however no active psychological counselling was offered. However in CBT intervention, an active approach was adopted which involved guided relaxation training, assistance in tackling pain-related anxiety etc. Further, the therapists detailed the pain that might occur and patients were assured that pain will decrease gradually.[61]

For the miscellaneous intervention class, benzocaine local anaesthetic patch and TENS were more effective (shared median rank 20) as compared to vibrational appliance. Lesser effectiveness of vibration appliance could be attributed to the fact that vibration from the appliance could have negated the pain reliving ability of these appliances by actually causing

hurt to the already tender tooth owing to pain caused by orthodontic forces. The only conclusive evidence which supports the effectiveness of vibrational appliances in relieving dental pain has been provided by study wherein vibrations were applied to the skull and facial region, and not directly to the dentition.[66]

Our results, adjusted for covariates, suggests that there is no significant placebo effect at peak pain level after 24 h of orthodontic force application. This finding is in agreement with the recent meta-analysis which investigated placebo response.[25] Authors concluded that placebo response was significant only at the earliest time period (within 15-30 minutes) and there was no significant evidence of placebo response at any of the other time periods.[25]

Quality of evidence

Results revealed a great variation (very low to high) in the quality of evidence across comparisons. The factors which lowered the quality of evidence for various comparisons included risk of bias in few studies, inconsistency across few comparisons and intransitivity owing to the different types of interventions included in the estimation of indirect evidence. Lasers, as individual interventions and as intervention class, achieved the satisfactory quality for the direct, indirect as well as NMA estimates. This perhaps could be due to the fact that studies which investigated the efficacy of lasers in relieving orthodontic pain that were recently conducted, and thus were of higher quality.

Strength and limitation

The strengths of our NMA include: a) we were able to extract required data for the NMA from all 24 suitable trials identified by a comprehensive and inclusive search strategy; b) the three level hierarchical Bayesian model selected to perform NMA imparts confidence in our results because this model can handle complex network of evidence with sparse data, and yet provide precise estimates owing to the borrowing of strength across intervention. Further,

this model allowed us to have independent estimate and ranking of each individual intervention as well as intervention classes; c) our results are adjusted for all major covariates which could have affected the outcome; and d) there was no major threat to findings from any potential source of bias such as heterogeneity, inconsistency and publication bias.

However, there are several limitations. Perhaps the most important limitation pertains to the fact that we synthesized evidence only for peak pain intensity level at 24 h, and thus not utilized the data available for other time points. Our decision to include only the peak pain intensity level time was mainly based on the fact that studies included in this NMA provided pain data at varying time points, except for peak pain intensity level. For example, the timing for pain assessment varied from 4 h, 6 h, 8 h, 12 h, day 3, day 2, day 5 etc. Another limitation pertains to the fact that we combined multiple time point of pain assessment to define the baseline pain. Again this decision was based on the fact that there was no uniform timing of baseline pain assessment across trials included in this NMA. To minimize the influence of such limitation, we selected a window period of first 2 h for baseline pain assessment; and included baseline pain as a covariate in the NMA.

Implications for practice and research

This is perhaps the first comprehensive meta-analysis undertaken to evaluate the effectiveness of various interventions for orthodontic pain relief. Our findings show that selection of pharmacological interventions (analgesics) should be guided by appropriate knowledge of their mechanism of action as well as the pharmacokinetics such as plasma half-life period. Based on this knowledge, a clinician can build his/her own analgesic protocol using the multimodal analgesia approach which combines different classes of analgesics and methods of pain management to provide superior pain relief than any one class or method alone. The basic principle is that using various classes of medications will simultaneously and

synergistically inhibit the different pain receptor pathways. The combination reduces the dose of each analgesic and thereby decreases the incidence of side effects of any particular medication used.[63] An important component of multimodal analgesic therapy is the pre-emptive analgesia followed by adjuncts analgesics inform of post-operative analgesics. Pre-emptive analgesia is an anticipatory aesthetic approach that intends to prevent the pain and inflammatory response initiated by surgical incision and manipulation, and prevent the "wind-up phenomenon".[63]

We believe that our NMA will help in guiding the future research in area of orthodontic pain management. The detailed ranking of individual interventions along with the possible source of available evidence (direct, indirect or NMA) would guide the researchers to select appropriate comparative interventions while planning the research. This will fill the existing gap wherein no direct evidence is available for such comparisons. It will be interesting to see how multimodal analgesia could influence the orthodontic pain management.

Agreements and disagreements with other reviews

We are not aware of any other review/NMA of comparative effectiveness of pharmacological and non-pharmacological interventions for orthodontic pain relief. Our findings support the evidence provided by previously conducted PMAs which concluded that analgesics[6] and lasers[7] are effective in relieving orthodontic pain, and pre-emptive use is promising especially for long-acting non-steroidal anti-inflammatory drugs (NSAIDs).[6]

Conclusion

The result shows that analgesic and lasers are the effective interventions to manage orthodontic pain at peak pain intensity level. Etoricoxib seems to be most effective analgesic owing to its dose dependent analgesic effectiveness and long plasma half-life period. Amongst lasers, super-pulsed laser is more effective as compared to the continuous pulse lasers owing

to its deeper tissue penetration. Further, research is required to improve the quality of evidence especially for analgesic interventions. Placebo are least effective in managing orthodontic pain at peak pain intensity level.

Figure captions

Figure 1 PRISMA Flow Diagram

Figure 2 Evidence network plots showing the pharmacological and non-pharmacological intervention included in the network meta-analysis (please refer to Table 1 for more details). Thickness of nodes correspond to the total number of studies using this intervention. The edge thickness (showing numbers) shows the total number of studies making this comparison.

Figure 3 Risk of bias summary

Figure 4 Summary forest plot showing pair-wise estimates of each individual intervention as compared to the control group

Figure 5 Surface Under the Cumulative RAnking curve (SUCRA) for interventions

Figure 5 Summary forest plot showing all pair-wise estimates for interventions class

Figure 7 Surface Under the Cumulative RAnking curve (SUCRA) for interventions class

Figure 8 Comparison adjusted Funnel plot.

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