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Brief Report

Short-term placebo response in trials of patients with symptomatic osteoarthritis: differences between hip and knee

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SUMMARY

Background: In placebo-controlled RCT of symptomatic treatment in osteoarthritis (OA) the extent of pain reduction is heterogeneous, the pooled effect size rather small. Pain reduction is typically higher in knee than in hip trials. The recommended trial duration is 3 months, but in knee OA the best treatment effect vs placebo is observed at 2 weeks. We hypothesized that the placebo response differs in knee vs hip OA.

Objective: We performed a meta-analysis to describe the time course of pain in placebo groups of trials in knee and hip OA over 3 months.

Methods: A systematic search of PubMed, MEDLINE and Google Scholar of placebo-controlled cox-2 inhibitor (coxib) RCT (from 1999 to 2007) of hip and knee OA was performed. Pain levels (visual analogue scale [VAS], Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) in the placebo groups at different measurement time points were extracted, expressed as weighted mean at weeks 2, 4, 6–8 and 12–13.

Results: Twenty-one studies included 3064 knee OA patients and 608 hip OA patients. For knee OA, pain (VAS) decreased from 15 mm at week 2, to 20 mm at week 6–8, and 21 mm at week 12–13. For hip OA patients, pain decreased by 12 mm, 14 mm and 14 mm, respectively.

Conclusion: Pain decreased in both knee and hip OA patients treated with placebo at 2 weeks, but further decreases up to week 12 occurred only in knee OA, especially for pain VAS, resulting in a time dependent impact on the magnitude of treatment outcome. Primary endpoint pain should be assessed at 2–4 weeks.

Introduction

Placebo-controlled trials are the reference standard to prove efficacy of a treatment. However, such proof is difficult in the presence of large placebo effects, as seen in the setting of symptomatic treatments for osteoarthritis (OA). For example, in most trials of nonsteroidal anti-inflammatory drugs (NSAID) for this indication differences with placebo were modest, effects heterogeneous and the pooled effect size for pain reduction rather small[1,2]. Most trials are 12 weeks in duration, and especially in knee OA trials placebo patients appear to gradually improve, in contrast to actively treated patients who show a rapid response that persists up to 12 weeks. Thus, the best contrast between treatment groups is seen after approximately 2 weeks[3]. Of interest, these findings appear to be less prominent in hip OA trials[4].

To further document these placebo effects we performed a meta-analysis of the placebo arms in published placebo-controlled randomized trials (RCTs) of selective cox-2 inhibitors (coxibs) in knee OA and hip OA patients, with special attention to the magnitude of effect on pain over time up to 3 months.

Method

Data source and search

The objective of the search was to include a large and representative sample of randomized placebo-controlled trials on oral coxibs in hip or knee OA patients (efficacy studies with celecoxib,

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etoricoxib, lumiracoxib, rofecoxib, valdecoxib). A complete coverage of all OA trials was not sought but to include trials providing the current status of study design with a highly comparable study population.

Literature search was performed on all coxib articles published between 1999 and 2007 in different electronic databases (PubMed, MEDLINE and Google Scholar).

In addition, cross-checking of reference lists in respective systematic reviews and meta-analyses was undertaken.

To amend the sparse number of hip data companies were required to provide placebo data; this applies also to the data of study 128 one of the few hip trials (mentioned in the review of Berenbaum, 2005).

Inclusion criteria

- Evaluation of pain intensity available (measured on 100 mm visual analogue scale [VAS] or Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain subscale)[5]
- Baseline values available
- Outcome measure separately available for knee and hip
- Flare design, or at least 50 mm mean baseline pain value on VAS scale
- Treatment duration of at least 6 weeks
- At least two post-baseline measurements of pain intensity
- Study design: randomized controlled trials (RCTs)
- Published in English language

Exclusion criteria

- Posters, abstracts

Data extraction and quality assessment

Data were extracted from tables and text or estimated from diagrams; additional data (for additional measurement time points and separated analyses for knee and hip patients) were requested from study sponsors.

For each study, we recorded the first author, year of publication, sample size, OA site, VAS, WOMAC pain scale (at baseline and change from baseline), study duration, measurement time points.

Statistical analysis of pain reduction

Pooled estimates of mean pain reduction were calculated based on a random effects meta-analysis by site (knee and hip). Heterogeneity of effect sizes is reported as I^2 statistic. Missing standard deviations were imputed based on a weighted mean of available standard deviations; however, as the standard deviations were generally homogeneous, possible bias due to imputation is probably small. The difference between mean pain reduction in knee and hip after week 12/13 was analysed by means of random effects meta-regression. All calculations were performed using R package metafor[6,7]. The weighted mean for WOMAC pain scale was determined from available values and their calculated standardized mean difference (SMD), standardized to a maximum pain scale of 20.

Results

Included studies

Figure 1 showed all studies which fulfilled the inclusion criteria and were analysed. We evaluated 33 RCT of the coxibs for knee OA and/or hip OA patients. Of these seven did not provide separated analyses of at least two post-baseline measurements pain scale data, three were too short and two were no efficacy studies.

Search results and baseline data

The final sample included overall 3672 patients from 21 studies: 18 knee OA (3064 patients) and six hip OA studies (608 patients); i.e., three studies included both hip and knee patients. Thirteen studies reported VAS and 15 WOMAC data; of these seven studies reported both data. Baseline demographics of patients and baseline pain severity between knee and hip patient groups were similar: VAS, both range 62–71 mm; WOMAC pain both range 10–15 mm (WOMAC pain subscale).

Results for VAS (range, 0–100 mm)

In hip trials pain decreased by 12 mm at week 2, to 14 mm at week 12–13 (Figs. 2 and 3). In contrast, results were similar in knee trials at week 2 (decrease, 14 mm) but further decreases up to 21 mm occurred up to week 12–13. The difference between knee and hip at week 12/13 was statistically significant ($P = 0.0003$).

Results for WOMAC pain subscale (range, 0–20)

For WOMAC, pain reduction was higher for knee than for hip, but their results were less striking. In hip trials, pain decreased by 1.7 (95%CI 0.6; 2.7), 2.1 (1.2; 3.0), 2.8 (1.5; 4.0) and 1.8 (1.0; 2.7). In knee trials the results were 2.0 (1.4; 2.5), 3.5 (2.7; 4.3), 3.5 (2.8; 4.2) and 2.4 (1.9; 2.9). The difference between knee and hip at week 12/13 was not statistically significant ($P = 0.22$).

Discussion

The major motivation of this meta-analysis was to detail the placebo response of knee and hip OA and to further elucidate its impact on the extent of results of placebo-controlled trials. For this purpose we analysed data of a representative population from coxib studies reported over an OA study duration relevant period (2 weeks to 3 months).

Our meta-analysis shows that the level of pain in the placebo groups is moderately decreased at 2–4 weeks in both knee and hip OA but further decrease up to 12 weeks occurs only in knee OA trials, especially for VAS.

The effect of NSAID or coxib treatment on reduction of pain has been documented to reach its maximum at 2 weeks, thereafter remaining stable up to 26 weeks[8,9]. In contrast the difference to placebo – needed to justify a clinically relevant benefit – is described to decrease over time with a best mean difference at 2.3 weeks for orally applied NSAIDs in knee OA patients[3]. For knee OA our meta-analysis confirms that this is caused by an increase in placebo effect that exceeds the minimal clinical important improvement (MCII)[10].

Several studies with both hip and knee OA patients documented more response to active treatment for knee than for hip OA with a difference of approx. 5 mm VAS after >6 weeks[13,4]. Generally, the placebo effect was found to be larger in knee than in hip OA patients[14].

In our analyses, the placebo group of hip OA patients shows a continuous course of pain intensity (12–14 mm; VAS) from 2 weeks on and the differences to knee OA reached 7 mm after 12 weeks related to the increase of placebo response/resolution of flare in knee OA patients.

As a result efficacy outcomes obtained after more than 4 weeks could be impacted and diminished as well by the difference between knee and hip as by the increasing placebo response in knee

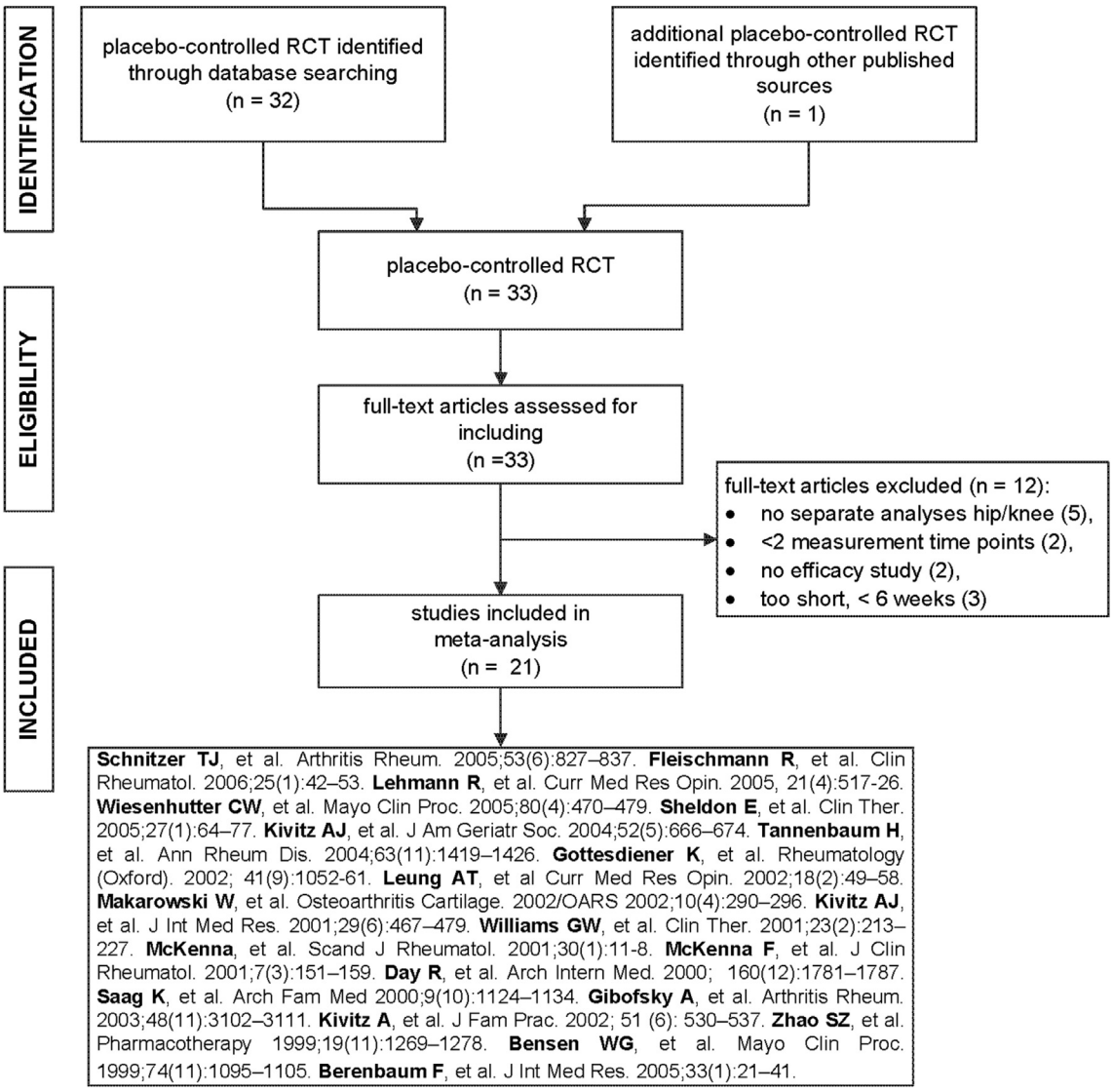

Fig. 1. Selection of articles that evaluate symptomatic efficacy of the coxibs in OA in placebo randomized controlled trials.

OA. The Committee for Medicinal Products for Human Use (CHMP) guideline requires demonstration of maintenance of effect at 3 months[11], however to reach a clinically relevant difference to placebo of >10 mm on a 100 mm VAS (regarded as minimum perceptible clinical improvement)[12] seems to be challenging.

As a consequence placebo response at measurement time points between 2 weeks and 4 weeks could have least impact on results. Present pain levels show appropriate magnitude and placebo response between knee and hip OA is comparable. A comparison to placebo could reach most magnitude and differences could thus most sensitively at best quantitatively be detected. This time frame seems appropriate to be used for primary endpoint in studies assessing NSAID-like treatment with a rapid onset of action. Pain reduction for knee and hip OA should be evaluated separately at least at measurement time points later than 4 weeks.

This study has strengths but also limitations. The selection of randomized placebo-controlled coxib trials provides a favourable database of studies with acceptable methodological quality, comparable design and treatment. The population provided clinically relevant samples with exacerbations of pain at begin of the study leading to similarity/comparability within the course of symptoms. These conditions ensure a clean comparison among different time points. However, the number of available studies with hip OA patients is limited and single studies may have therefore a substantial influence on the results. In particular, the result of meta-regression analysis of the difference between knee and hip after week 12/13

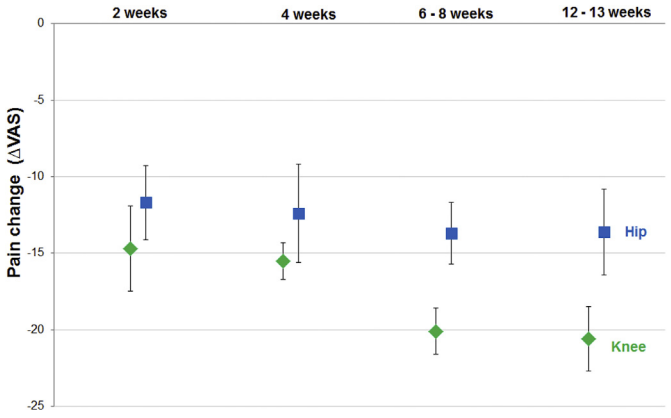

Fig. 2. Pain change (ΔVAS) of the pain intensity in patients with knee OA and hip OA.

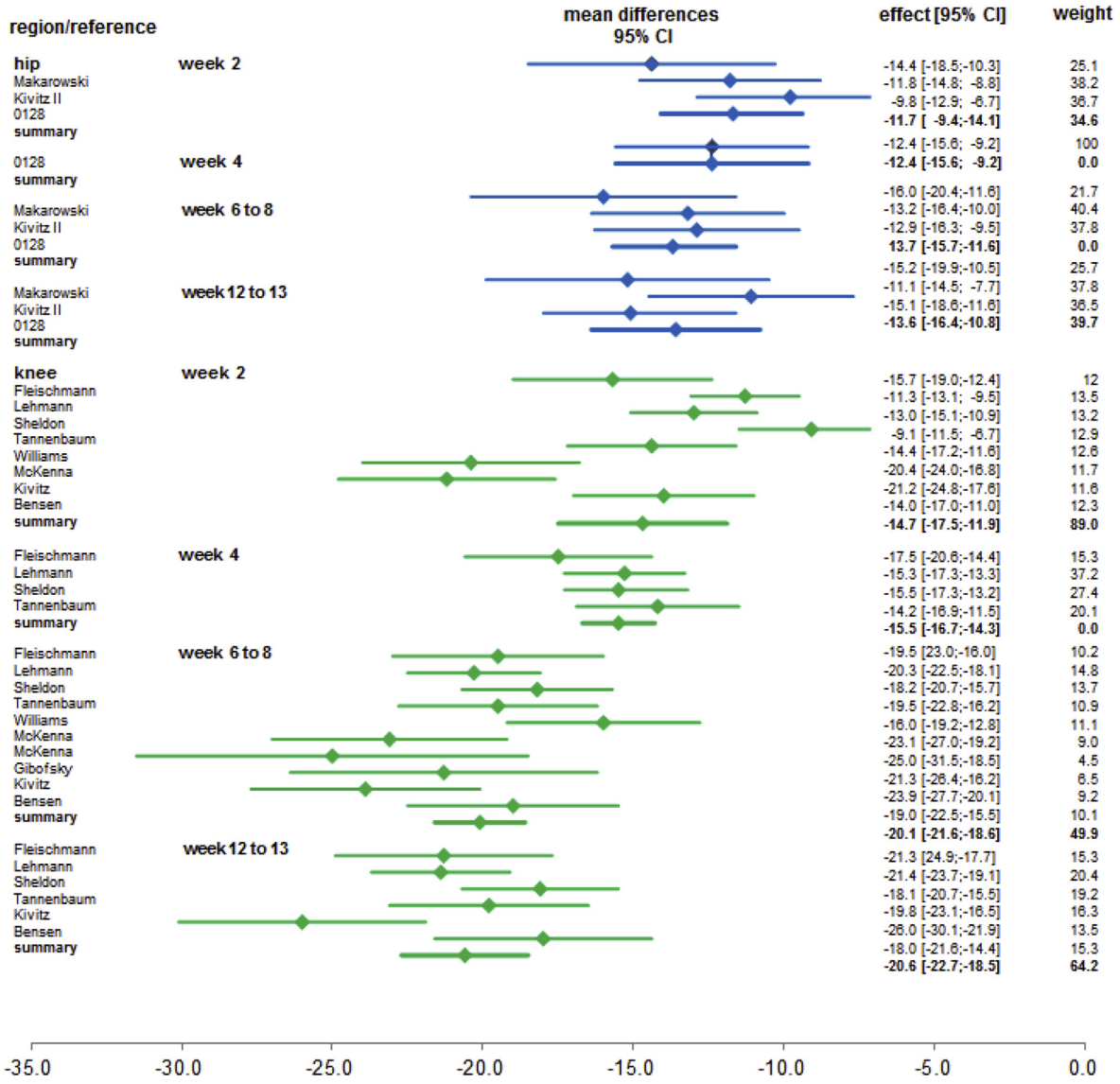

Fig. 3. Forest plot, change from baseline of pain VAS in patients with knee OA and hip OA.

based on a small number of studies should be interpreted with care. Pain intensity was not assessed in each study at the same time points thus pooled estimates at the different time points are to some extent based on data from different studies.

Conclusion

Placebo response on pain intensity is different for knee and hip OA with clinically relevant impact on the outcome of trials assessing treatment with a rapid onset of pain reduction. Pain as primary endpoint should be assessed at 2–4 weeks.

Author contributions

SNR performed the conception of the study, the acquisition of data. SNR and MB performed analyses and interpretation of data. All authors (SRN, MB, JD) contributed to the design of the study and have critically analysed and approved the final manuscript.

Conflict of interest

All authors declared having no conflict of interest.

Competing interests

The authors received no funding in the preparation of this manuscript and do not have any conflict of interest that is directly relevant to its contents.

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