Adjusting for the Intra-Articular Placebo Effect in Knee Osteoarthritis Therapies

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Background

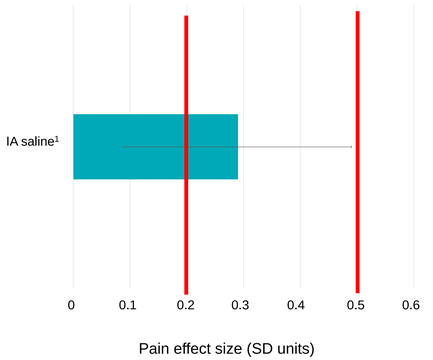
- Evidence suggests that intra-articular (IA) saline reduces knee osteoarthritis (OA)-related pain, prompting considerable debate about whether use of IA saline as a placebo (PBO), or a true null-effect comparator, in knee OA trials and meta-analyses is appropriate.[1,2]
- Minimal clinically important differences (MCIDs) provide thresholds to interpret the magnitude of a treatment's therapeutic effect that improves patient status in a clinically meaningful way.[3]
- **Study objectives**: (1) To assess the effect of IA saline against a range of MCID values to determine clinically meaningful improvements in pain outcomes and (2) to adjust treatment effect sizes of current knee OA therapies based on effects of IA saline on pain outcomes.

Methods

- A literature search identified recent high-quality meta-analyses of knee OA therapies (NSAIDs, acetaminophen, glucosamine, chondroitin, IA corticosteroids, and IA hyaluronic acid) assessing pain outcomes across different scales (e.g., WOMAC, VAS, NRS, Likert).
- IA therapies were adjusted for the treatment effect of IA saline derived from Bannuru et al. (2015), a previous network meta-analysis (Figure 1).[4]
- Values of 0.2 and 0.5 SD units were used as low and high threshold MCID cutoffs[5,6], the range of which includes the American Academy of Orthopaedic Surgeons's (AAOS) referenced MCID of 0.37 SD units for pain outcomes.[7]
- Oral NSAIDs were set as the baseline anchor for 'null response,' thus received no adjustment for PBO effect.
- 'Clinical significance' was defined using AAOS criteria: 1) clinically significant 2) possibly clinically significant 3) inconclusive and 4) not clinically significant.[7]
- To evaluate the robustness of the findings, adjustments for potential IA saline effects based on the lower and upper confidence limits were also performed in sensitivity analyses.

Results

Figure 1. IA saline effect compared with the MCID threshold range



[1]From Bannuru et al., 2015

Figure 2. Unadjusted pain effect estimates for pharmacologic knee OA therapies

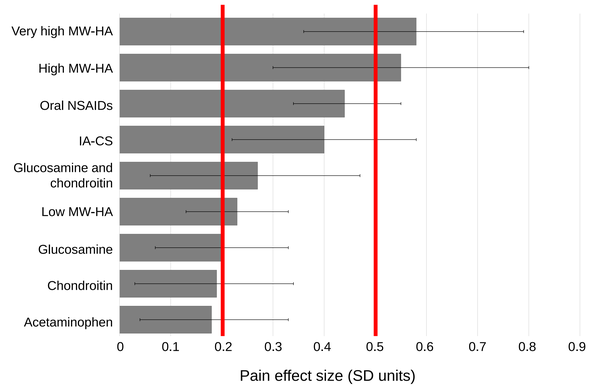
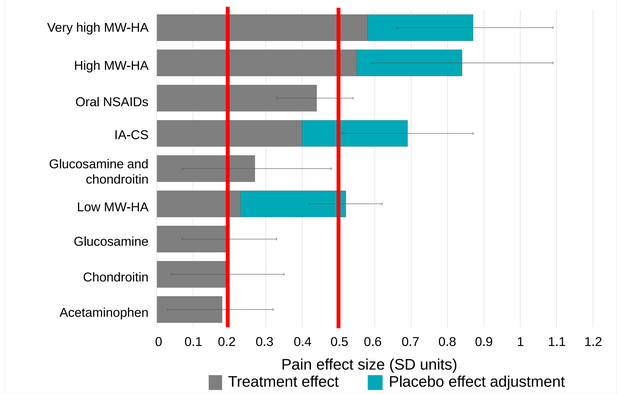


Figure 3. Pain effect estimates adjusted for IA saline effect



Red lines depict the range of plausible MCID cutoff values for clinical significance.

Intra-articular Saline

- IA saline effect size of 0.29 SD from Bannuru et al. (2015)[4] was considered 'possibly clinically significant' at the lower MCID cutoff of 0.2 SD (Figure 1).
- The upper CI of IA saline approached 0.5 SD; therefore, at all but the strictest MCID of 0.5 SD, IA saline was considered 'possibly clinically significant.'

Intra-articular therapies for knee OA

- Results from the literature data extraction and analysis showed that 3 unadjusted IA therapies (very high MW-HA, high MW-HA, and IA-CS) and oral NSAIDs would be considered 'possibly clinically significant' at the highest MCID cutoff of 0.5 SD (Figure 2).

Adjustment for IA saline treatment effect

- After adjusting for the effect of IA saline (an increase of 0.29 SD), IA therapies were considered 'clinically significant' even at the highest MCID cutoff of 0.5 (Figure 3).

Confidence Limits

- Clinical significance classifications did not change from unadjusted estimates after adjustment for lower confidence limit of IA saline (an increase of 0.09 SD).
- IA therapies (very high MW-HA, high MW-HA, and IA-CS) were 'clinically significant' according to AAOS criteria and surpassed the largest MCID threshold after adjustment for upper confidence limit of IA saline (an increase of 0.49 SD).

Conclusions

- The use of IA saline as a PBO comparator in randomized controlled trials of IA injectable therapies may be leading to underestimation of the true effects of these treatments.
- After adjusting for the IA saline effect, results demonstrated that IA-injectables may have 'clinically significant' treatment effects when compared with true null effects.
- Both the comparator and MCID cutoff may have an impact on the conclusions of clinical trials and meta-analyses of knee OA injectable therapies.

Limitations

- Patient populations differed with respect to disease severity, age, and comorbidities.
- Analytic approaches across studies may have differed.

Acknowledgements

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