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

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**Background:** Currently, there is a large debate regarding the appropriateness of intra-articular (IA)-saline injection as a “placebo” comparator in knee osteoarthritis (OA) trials and meta-analyses. There is substantial evidence to suggest that the injection of saline into the joint is not without treatment effect.

**Objective:** This study aimed to assess the current literature’s estimates of the IA-saline treatment effect against a range of appropriate minimal clinically important difference (MCID) values to identify if IA-saline provides a therapeutic effect that is not indicative of a null-effect.

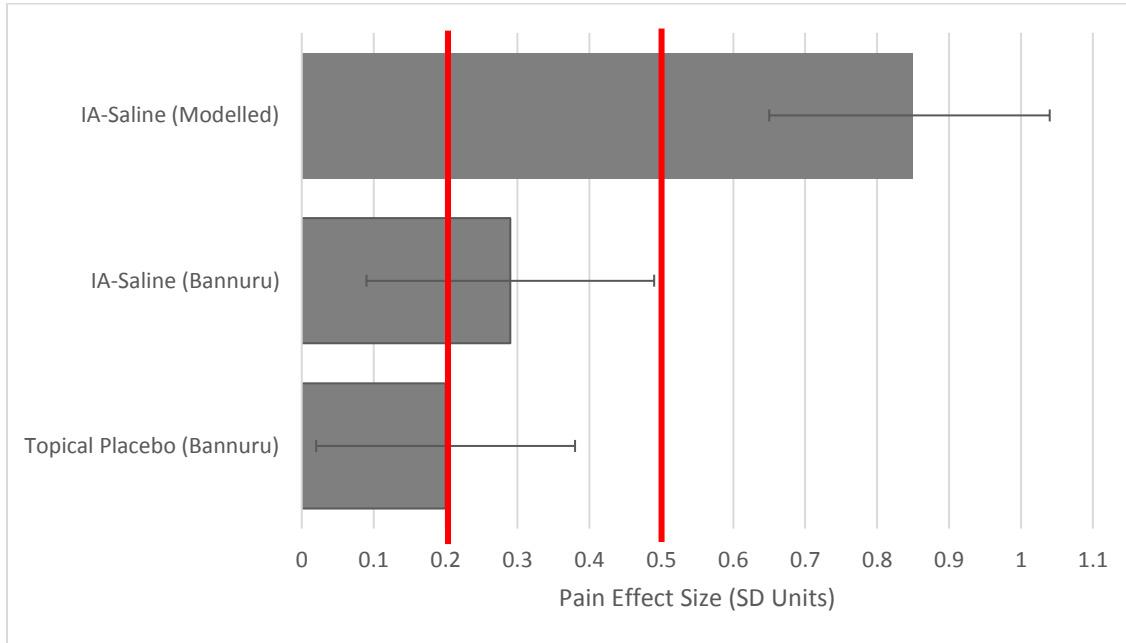
**Methods:** The treatment effect estimates of IA-saline and topical placebo for knee OA pain, relative to oral placebo, were derived from a published network meta-analysis (Bannuru et al, 2015) and compared across a range of plausible MCID values. Effect estimates of pharmacologic knee OA treatments were also extracted from recent high-quality meta analyses, and the effect of IA-saline or topical placebo was used as an adjustment for meta-analyses that used IA-saline or topical placebo as a comparator, respectively. This was done to estimate the therapeutic effect of these treatment options when compared to a truly null treatment option, as IA-saline has been shown to not be a null-effect intervention. The unadjusted and adjusted treatment effect values were compared across an MCID value range of 0.2 to 0.5 standard deviation units representing an effect size range. This range was used to determine if the adjustment for the effect of IA-saline would affect the potential clinical interpretation of the previously published meta-analysis results.

**Results:** IA-saline provides a therapeutic benefit that is potentially clinically meaningful to patients based on a range of MCID values (Fig. 1). Across the same range of MCID values, the effects of high molecular weight IA-hyaluronic acid products and IA-corticosteroid treatments were not conclusively clinically significant. However, when reassessing these treatments while accounting for the treatment effect of IA saline, they were found to have a clinically significant effect at the strictest MCID value (Fig. 2).

**Conclusion:** The use of IA-saline as a placebo treatment within RCTs of IA injectable therapies is inappropriately underestimating the true effect of these treatments. When the potential therapeutic effect that IA-saline demonstrates is accounted for, these IA therapies show a considerably larger therapeutic effect.

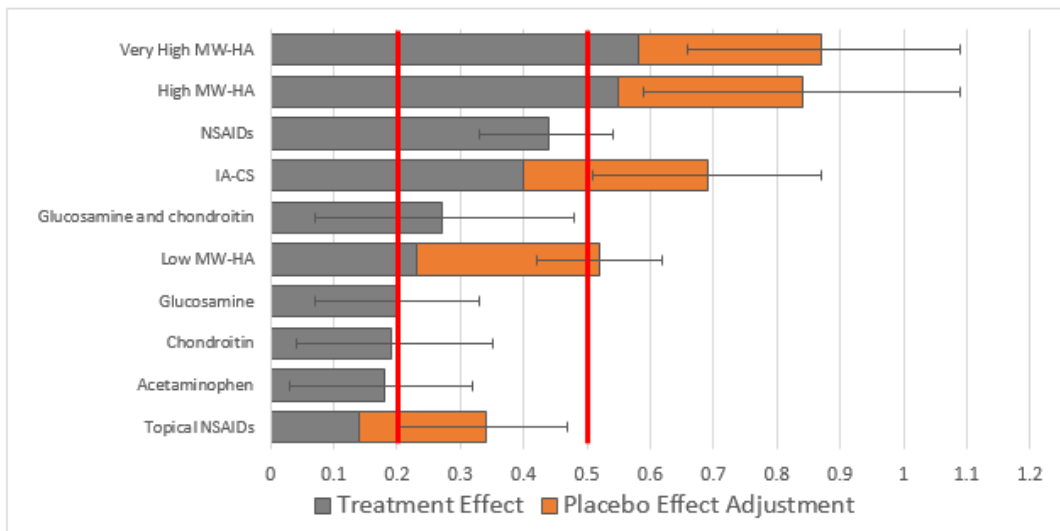
**Reference:** Bannuru RR et al. *Ann Intern Med* 2015;163:365-72.

**Figure 1: Effects of topical placebo and IA-saline in comparison to the MCID threshold range**



Red lines depict the range of plausible MCID cutoff values for clinical significance. Estimates from Bannuru et al (2015) are relative to the oral placebo effect, whereas the Modelled estimate is in relation to an effect of zero.

**Figure 2: Pain effect estimates adjusted for placebo effect estimate**



Red lines depict the range of plausible MCID cutoff values for clinical significance. Topical placebo adjustment corresponded to an increase of 0.2 SD units, while IA-saline adjustment corresponded to a 0.29SD unit increase.