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## **Potential Nociceptive Pain Relief of Intra-Articular Saline Control in Clinical Trials of Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Trials**

Ismail Simsek, Timothy Phalen, Angela Bedenbaugh, and Jeyanesh R. S. Tambiah

Samumed, LLC, San Diego, CA

**Background:** Hyaluronic acid, corticosteroids, and platelet-rich plasma are widely used intra-articular (IA) therapies for the management of mild to moderate knee osteoarthritis (OA). Many trials evaluating the efficacy of IA-administered therapies commonly use IA saline injections as a placebo comparator arm. A previously published systematic review (Altman et al., 2016) showed significant reductions in pain relief with IA saline in both the short- (3 months) and long-term (6-12 months).

**Objectives:** The aim of this updated systematic review and meta-analysis was to assess the clinical benefit and harm associated with use of IA saline in trials of IA therapies for patients with painful knee OA.

**Methods:** We searched MEDLINE and Embase databases for randomized controlled trials (RCTs) published up to and including October 12th, 2017. Two reviewers independently assessed the eligibility of potential reports and the risk of bias of included trials. We analyzed short ( $\leq 3$  months) and long-term (6-12 months) pain reduction from baseline of the saline arm of included trials using standardized mean differences (SMDs; estimated assuming a null-effect in a comparator group) that were weighted and pooled using a random-effects model. Pain scores were transformed to a 100-point scale when necessary. We summarized and presented treatment-related adverse events (AEs) descriptively.

**Results:** We included 46 RCTs, of which 44 provided sufficient data to be included in the meta-analysis for benefit. IA saline significantly improved short-term knee pain from baseline vs. a null effect for a comparator group across 36 studies involving 1,908 patients (SMD -0.85, 95% CI -1.05 to -0.66;  $I^2 = 87\%$ ). There was also significant reduction in long-term knee pain following IA injection with saline across 25 studies involving 1,758 patients (SMD -0.78, 95% CI -1.02 to -0.55) with a substantial degree of heterogeneity ( $I^2 = 90\%$ ). Thirty-three of the included trials reported on adverse events, none of which found any serious treatment-related AEs following IA injection with saline.

**Conclusions:** The pain relief observed with IA saline should prompt one to consider the added effectiveness of current IA treatments that use saline comparators in clinical studies, and challenges of classifying IA saline injection a “placebo.”