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

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FRI0542

Background

- Knee osteoarthritis (OA) is characterized by pain and loss of function and disability, and treatment focuses on symptom relief.[1]
- In trials evaluating the efficacy of IA-administered therapies in knee OA, IA saline injections are widely used as a placebo (PBO) control arm;[2-4] however, there is increasing evidence that IA saline may have active analgesic effects,[5,6] making it an inappropriate "null effect" comparator in these trials.
- This analysis is an update of the previously published systematic review by Altman et al., which showed significant reductions from baseline in pain relief due to IA saline in both the short (≤3 months) and long (6-12 months) terms in knee OA randomized controlled trials (RCTs).[6]
- The objective of this analysis was to assess the clinical benefit associated with use of IA saline as PBO in knee OA trials in order to assess the potential impact its use may have on observable treatment effects of active IA therapies under study.

Methods

- MEDLINE and Embase databases were searched for RCTs with the key words and MeSH terms "knee OA" and "injections, intra-articular" published through Oct. 12, 2017.
- RCTs comparing IA saline with IA treatment (corticosteroid, hyaluronic acid [HA], or platelet-rich plasma [PRP]) in adult patients with symptomatic knee OA were eligible.
- The primary efficacy outcomes were short- (≤3 months) and long- (6-12 months) term pain reduction from baseline evaluated using any pain questionnaire. Treatment-related adverse events were summarized descriptively.
- Results for short- and long-term pain were summarized using standardized mean differences (SMDs), calculated as mean change from baseline using the standard deviation (SD) for IA saline compared with an imputed comparison group with an assumed average null change from baseline.[7]
- A meta-analysis to combine SMDs was performed with random effects models and the inverse variance method.[8] Heterogeneity was quantified with the I^2 index.[7,9]

Results

Figure 1. Study flow diagram

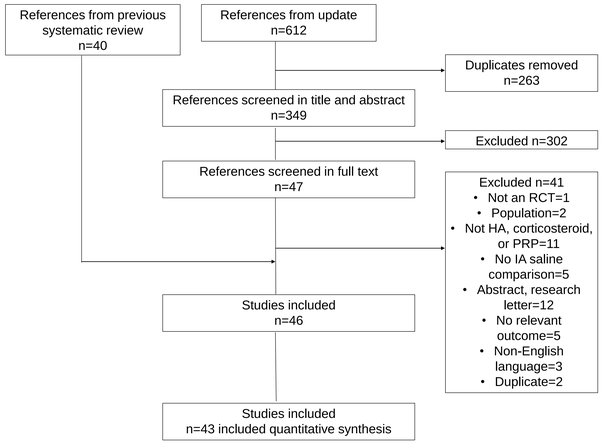


Figure 1. 172 articles underwent full screening, 46 were eligible, and 43 RCTs were entered into the meta-analysis. Enrolled patients had a mean age of 46.6 to 72.9 years.

Summary

- Pain scales utilized in included studies were: WOMAC (n=18), KOOS (n=1), or VAS (n=24).
- Of 21 studies reporting Kellgren-Lawrence grades, a median of 40% of subjects were KL-2 and 43% were KL-3.
- Thirty-six studies (n=1908) reported short-term (≤3 months) and 25 studies (n=1758) reported long-term (6-12 months) pain outcomes.
- Overall, patients receiving IA saline showed significant improvements in knee pain from baseline in both the short (SMD, -0.72 [-0.85,-0.59]; I^2=72%) and long (SMD, -0.68 [-0.84,-0.51]; I^2=81%) terms (Figures 2 and 3, respectively).
- RCTs of IA corticosteroid and IA viscosupplementation favored IA saline.
- 33 of the included trials reported on adverse events (AEs), none of which reported any serious treatment-related AEs following IA saline injection.

Figure 2. Standardized mean differences of short-term (≤3 months) pain changes from baseline

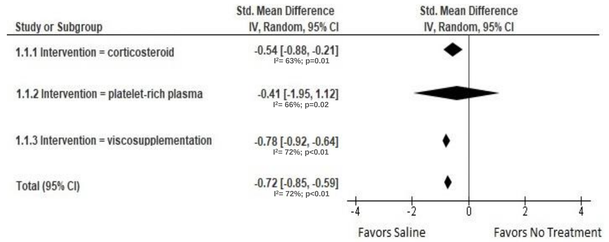
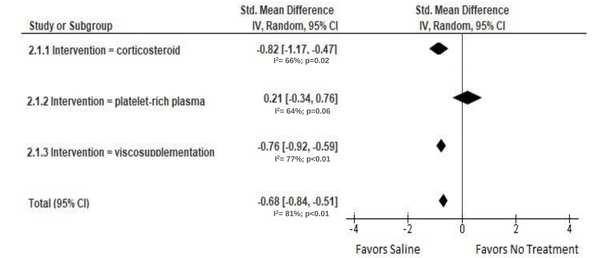


Figure 3. Standardized mean differences of long-term (6-12 months) pain changes from baseline



Discussion

- This systematic review and meta-analysis suggested that IA saline may provide a therapeutic benefit to patients with knee OA in both the short (≤3 months) and long (6-12 months) terms, suggesting that the effect of IA saline may persist up to 12 months.
- Findings support the need to take into account the added efficacy of IA saline when interpreting study results and consideration of the length of RCTs and the appropriateness of using IA saline injection as a PBO in future RCTs.
- Therefore, future studies should consider adjusting treatment effect sizes of current knee OA therapies for effects of IA saline on pain outcomes, given that IA saline may not be a true null-effect comparator (**Poster SAT0565**).
- This review is limited by poor methodological quality of the original trials along with the need to transform different pain scales to the index scale, which assumed that scores could be linearly transformed without losing scale increments.
- High heterogeneity was seen in the long-term pain analysis, and subgroup analysis failed to explain this.
- There were only 2 PRP RCTs available for analysis, both with less than 100 patients. This makes estimates imprecise with wide CIs; there were not enough data to make a reasonable conclusion from these studies.
- The "null effect" in the 'no treatment' group may be considered an idealistic scenario when in reality, changes in pain due to progression or PBO effect are likely to occur.

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Acknowledgements

The authors would like to acknowledge Mark Philipps, PhD candidate, McMaster University, Ontario, CA, and ORTHOEVIDENCE™ for performing this analysis and Aladdin H. Shadyab, PhD for his assistance with the preparation of this work.

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