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Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: a systematic review and meta-analysis of randomized trials

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Citation

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Review question(s)

To assess the clinical benefit of intra-articular saline in trials of intra-articular therapies in the treatment of patients with painful knee osteoarthritis (OA)

Searches

We will systematically search EMBASE (from 1974 to present) and MEDLINE (from 1946 to present), and we will include English language publications only. The search will be limited to randomized controlled trials (RCTs) using an RCT filter developed by the Health Information Research Unit (HiRU) at McMaster University. We will check reference lists of all primary studies and review articles for additional references. We will search for errata or retractions from included studies published in fulltext on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Types of study to be included

All randomized controlled trials (RCTs) that use intra-articular saline as the control group against any intra-articular viscosupplementation, platelet rich plasma, or corticosteroid comparator in adults with knee OA.

Condition or domain being studied

Osteoarthritis (OA) is a common, age-related disorder of synovial joints, pathologically characterized by areas of damaged articular cartilage. Besides the changes in bone structure, OA is associated with capsule thickening, weakness of the surrounding muscles, and joint instability. OA has been defined as “a heterogeneous group of conditions that lead to joint symptoms and signs, which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins.” As the disease advances, it becomes visible on radiographs with a narrowed joint space, the establishment of osteophytes, and possible changes in the subchondral bone. In patients with OA, pain is often induced by activity. Activities such as climbing stairs, getting out of a chair, and walking long distances can be painful in patients with knee OA. Although preventive measures are few and uncertain, first-line therapy includes weight loss in the obese and exercise to maintain fitness.

Participants/ population

All adults with symptomatic knee osteoarthritis diagnosed according to published ACR classification criteria, the algorithm developed by Altman or diagnosis based on clinical and/or radiographic measures.

Intervention(s), exposure(s)

Clinical trials that evaluate intra-articular interventions for knee OA often use intra-articular saline injection as a “placebo” (sham) intervention; however, the intra-articular saline injection has been shown to provide substantial pain relief in a number of trials. The pain relief observed with intra-articular saline has prompted some to question the efficacy of agents that have been compared to it in clinical studies, and others to question the validity of labelling intra-articular saline injection a “placebo.” Studies which compared viscosupplementation, platelet rich plasma, or corticosteroid to intra-articular saline injection as a placebo control in studies of agents employed for the treatment of OA will be included in this review.

Comparator(s)/ control

Any type of intra-articular viscosupplementation with hyaluronic acid or a derivative, platelet rich plasma injection, or corticosteroid injection used for the treatment of OA of the knee in humans.

Outcome(s)

Primary outcomes

Major outcomes will include pain intensity and the number of treatment-related adverse events (AEs). The pain parameter will represent the benefit outcome, as recommended for contemporary OA trials. The number of AEs will be the harm outcome. The minimum criterion for inclusion of the study requires adequate reporting of at least one of the primary end-points stated.

If data on more than 1 scale for pain or function are provided, we will refer to the previously developed hierarchy by Juhl et al and extract data on the scale that ranks highest according to this hierarchy.

Pain

1. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (Likert/100mm)

2. Pain during activity (visual analog scale [VAS])

3. Pain during walking (VAS)

4. Global knee pain (VAS)

5. Pain at rest (VAS)

6. Short Form 36 (SF-36, bodily pain [BP] subscale)

7. Health Assessment Questionnnaire (HAQ, pain subscale), Lequesne Algofunctional Index (pain subscale), Arthritis Impact Measurement Scale (AIMS, pain subscale), Knee-Specific Pain Scale (KSPS), McGill Pain Questionnaire (pain intensity), Arthritis-Self Efficacy Scale (ASES, pain subscale), Schmerzem pfindungs skala (SES)

8. Pain at night (VAS), pain during activity (Numerical Rating Scale [NRS]), pain on walking (NRS), number of painful days

If pain outcomes are reported at several time points, we will use data from the outcome assessment conducted between 1-3 months (range, 4–16 weeks) following completion of the intervention as the time point of primary interest. When data are available, we will also extract the effects at long-term follow-up, defined as 6 to 12 months from baseline (range, 4–12 months).

Treatment-related adverse events will be reported as either ‘serious’ or ‘non-serious’. Non-serious adverse events resulting from IA injection of saline that will be included for assessment include those that are procedure related: infection, hypersensitivity to local anesthesia, discomfort at injection site, and/or needle breakage or separation. Definition of a treatment-related serious adverse event (SAE): “An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.”

Secondary outcomes

None

Data extraction, (selection and coding)

Two review authors will independently screen titles and abstracts of all publications identified by the aforementioned search terms. References that are potentially eligible for inclusion, or for references where this determination cannot be made based on the title and abstract, will be coded as “retrieve,” references that clearly do not meet the criteria will be coded as “do not retrieve.” For the publications coded for retrieval, two reviewers will independently review the full-text study reports/publications independently and in duplicate. For each reference from the “retrieve” subset, the reviewers will identify studies for inclusion by coding them “include,” and those for exclusion by coding them “exclude.” Further, for those references that were identified for exclusion, the reviewers will document reasons for ineligibility. We will resolve any disagreement through discussion or, if required, we will consult a third reviewer. We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram. The Cohen’s ? (kappa) statistic will be calculated to evaluate agreement between the two reviewers for full text screening. Values within the range of 0.40 to 0.59 reflect fair agreement, between 0.6 to 0.74 to reflect good agreement, and 0.75 or more to reflect excellent agreement.

We will use a data collection form for study characteristics and outcome data that has been piloted. One review author will extract study characteristics from included studies. A second review author will spot-check study characteristics for accuracy against the trial report. We will extract the following study characteristics: patient characteristics (average age, gender, mean duration of symptoms); trial design, including the frequency and duration of treatment, trial size, dosage of intra-articular saline (mL), use of lidocaine and location where used (skin, injection track, joint space); duration of follow-up (outcome assessment); type of pain-related outcome extracted, treatment-related serious and non-serious AEs; the comparator treatment; type and source of financial support; and publication status from trial reports. We will extract the number of observations in the saline group, the reported mean change from baseline, and the corresponding standard deviation. When necessary, we will approximate means and measures of dispersion from figures in the reports. For crossover trials, we will extract data from the first period only because of possible carryover effects. Whenever possible, we will extract results from the ITT population. If effect sizes (ES) cannot be calculated, we will contact the authors for additional data.

Risk of bias (quality) assessment

Two review authors will independently assess risk of bias for each included study using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials. We will resolve any disagreements by discussion or by involving another author. We will assess the risk of bias according to the following risk of bias parameters:

1. Random sequence generation

2. Allocation concealment

3. Blinding of participants

4. Blinding of personnel

5. Incomplete outcome data

6. Selective outcome reporting

We will grade each potential source of bias as high, low, or unclear (risk of bias) and provide a quote from the study report together with a justification for our judgment in the “Risk of bias” table. We will summarize the risk of bias judgments across different studies for each of the critical domains (ie, Selection bias, Performance bias, Detection bias, Attrition bias, Reporting bias). When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome. We will present the figures generated by the risk of bias tool to provide summary assessments of the risk of bias. A weighted ? statistic will be computed to evaluate inter-observer agreement between the two reviewers for the risk of bias assessment.

Strategy for data synthesis

Whenever possible, we will use results from the ITT population and subsequent analysis. Anticipating that different scales are used to measure the same conceptual outcome (ie, pain), standardized mean differences (SMDs) will be calculated with corresponding 95% confidence intervals (CIs). Using only data from the intra-articular saline arm of

the RCTs, we will calculate a modified SMD for each study. Unlike a typical meta-analysis, we will not be able to estimate the net benefit from being allocated to the “placebo/control group;” however, we will assume that a matched group who did not receive any clinical support will on average have a null change from baseline values. As a consequence we will compute the SMD on the basis of the central change estimate (e.g., a mean change from baseline) and the corresponding dispersion (e.g., SD) in the reported intra-articular saline group and simulate a “null effect” for contrast with the same dispersion measure applied. The ES for benefit will be signed so that negative values (SMD <0) indicate a benefit of intra-articular saline treatment. To ease interpretation, the combined SMD will be converted back to a typical scale (eg, 0–100 mm VAS) by multiplying the summarized SMD by a typical among-person standard deviation. We anticipate most trials to have only a few AEs, so the odds ratios (ORs) and 95% CIs will be calculated with the use of the Peto method. Trials in which patients had no AEs following intra-articular saline were excluded from the safety analysis. For the artificial (simulated) comparator group, we will apply a null event rate throughout. From the pooled Peto’s OR, we will estimate the number needed to treat in order to harm a patient (NNTH), with 95% CI on the basis of the combined OR value, applying an external event rate as a proxy for baseline risk (1%).

Two-tailed tests of significance for treatment effects will be performed and a p value of less than 0.05 will be considered statistically significant. We will conduct meta-analyses with Review Manager version 5.2 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark).

Analysis of subgroups or subsets

We will evaluate the statistical heterogeneity using Cochran’s Q-test. We will apply the I-squared metric as an interpretable measure of the amount of inconsistency (I-squared) across studies in a meta-analysis. The I-squared takes values from 0% to 100%, and often cut offs are used to claim whether an important inconsistency exists or not. We will explore heterogeneity by performing subgroup analyses to assess the impact of risk of bias on our primary analyses. Trials at low risk for selection bias or detection bias may show smaller effect sizes than trials with unclear or high risk for bias when assessing long-term pain.

Dissemination plans

The beneficial effect of placebo interventions has been well established and has even been perceived as ethically permissible among internists and rheumatologists, especially in the absence of an appropriate pharmaceutical intervention. This study will evaluate the role of intra-articular saline in the treatment of patients with knee OA. This intervention has served as the control or placebo arm in clinical trials that evaluate intra-articular treatments, but may provide physiological benefit beyond that of a placebo. In addition, the role of intra-articular saline as an analgesic will be carefully scrutinized for both benefit and potential harm in patients with knee OA. Systematic evidence-based literature reviews are considered the cornerstone upon which guideline-generating panels build their recommendations for interventions in the treatment of painful knee OA, and we aim to shed light on the effect of intra-articular saline and to clarify its role in OA clinical trials. Professor Roy D. Altman will draft a paper describing the systematic review, and the study will be disseminated by conference presentation and peer-review publication.

Contact details for further information

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01 November 2014

Anticipated completion date
30 November 2015

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This study is funded by Ferring Pharmaceuticals Inc.

Conflicts of interest
Anke Fierlinger and Faizan Niazi are paid employees of Ferring Pharmaceuticals Inc.

Roy Altman is a consultant for Cytori, DuPuy, Ferring, Flexion, Iroko, Novartis, Oletec, Pfizer, Q Med, Rotta, Strategic Science & Technologies, and Teva.

Mohit Bhandari is a consultant for Ferring, Smith and Nephew, Stryker, Amgen, Zimmer, Moximed, Bioventus, Merck, Eli Lilly, Sanofi, Conmed. He has grants/grants pending from Stryker, Zimmer, Amgen, Smith and Nephew, DePuy, Eli Lilly, Bioventus

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Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No

Risk of bias (quality) assessment	No	No
Data analysis	No	No