Intra-articular Injections for Pain Reduction in Knee Osteoarthritis: The Effectiveness of "Placebo" Normal Saline

By

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Background

Osteoarthritis (OA) is the most common form of arthritis, currently affecting an estimated 31 million Americans. Osteoarthritis is a degenerative disease of the joint spaces and is commonly thought of as a "wear and tear" disease. There are, in fact, more contributing processes as inflammatory factors have been shown to play a role in disease initiation and progression. Osteoarthritis is one of the most common causes of disability in the elderly, with pain, instability and loss of range of motion being the most common presenting symptoms in those affected. [1]

There are several processes that contribute to progression of disease to a state of osteoarthritis, and they are all influenced directly by associated risk factors. Age is the biggest factor that contributes to the "wear and tear" process that most people initially think about with OA. Changes in the extracellular and intracellular matrix include thinning of the articular cartilage with age, reduced hydration, and an accumulation of proteins containing advanced glycation end-products. These advanced glycation end-products cause cross-linking of collagen and result in the "brittleness" that sets people at higher risk for developing OA. [1,2]

Weight can also be a significant contributor to the progression of OA as well. Many years of carrying extra body weight can lead to increased burden on weight-bearing joints; more specifically, the knees and hips. Research has shown that this increased burden on joints can increase the rate of cartilage breakdown, the material that acts as a cushion between bones in joint spaces.[2]

Injury and overuse are also common causes of progression of OA. In the knees, for example, injury to ligaments in and around the joint space causes an increase in inflammatory

mediators within the joint space, which incite joint tissue destruction. The overuse of certain joints, such as those in the hands, leads to increased friction within the joint space on the cartilage and synovial fluid, which in turn dries out the space causing a similar inflammatory response. With each of these risk factors there is an increase in the likelihood of progression to OA. While the pathogenic process may vary, all incite increased degradation of joint tissue by means of perpetuating inflammatory mediators and proteases into the joint space.[2]

Current non-surgical treatment strategies for osteoarthritis target pain control, but none of these currently used modalities reverses the progression of disease. Lifestyle modifications are attempted first in the majority of the population, and include weight loss, exercise programs, stretching and heat/cold applications to affected joints. For those that need pharmacologic assistance, acetaminophen is the mainstay of treatment, with NSAIDS, COX2 inhibitors, and topical agents such as diclofenac or capsaicin used adjunctively. Intraarticular agents are the last line pharmacologically in those with pain uncontrolled with other treatment modalities. A final treatment option for those with hip or knee OA with pain inadequately managed by other means is surgical replacement of the affected joint.[3]

Of all non-surgical treatment modalities, intraarticular injections have been shown to be the most effective in reducing pain for those affected with moderate to severe OA. Clinical use of intra-articular injections dates back to the 1930s, with widespread and consistent use of the technique beginning in the 1950s when intra-articular injections of corticosteroids became common for treating patients with rheumatoid arthritis (RA). More recently, the use of intra-articular injections has expanded greatly with the approval of hyaluronic acid based injections as second line treatment for moderate to severe OA.[3] Other injectable formulas are also being

studied, including plasma rich protein (PRP) based solutions and morphine based solutions. One of the primary goals in the newer formulations is aimed at reducing side effects seen with more commonly used corticosteroid solutions. The biggest side effect studied in intra-articular corticosteroid based treatment is progression of cartilage degradation and subsequent joint space narrowing. Despite the fact that corticosteroid based injections offer only supportive analgesic outcomes without focusing on slowing, stopping or reversing the disease process, the steroid based injectable solutions remain the first line option for patients with osteoarthritis.[1,3]

More recently, studies have been conducted to evaluate many of these newer treatment modalities in comparison to the traditionally used steroid based injections. Intra-articular normal saline has been used in these more recent studies as a "placebo" medication, with intent to better blind study participants and eliminate bias for more reliable outcome data. However, many of these preliminary studies have shown outcomes indicating these "placebo" normal saline intra-articular injections may have a therapeutic effect that was not before seen or understood.[4] This raises the question: How effective are intraarticular saline injections at alleviating pain in those with osteoarthritis in comparison to traditionally used corticosteroid?

Methods

The following search databases were utilized: PubMed, CINHAL and the Cochrane Database of Systematic Reviews with keywords osteoarthritis, intraarticular injections, saline, corticosteroids and hyaluronic acid. An individual search was also conducted using reference lists through primary articles. Primary inclusion criteria consisted of randomized control trials, systematic reviews, retrospective cohort studies and meta analyses of randomized control trials

within the past 20 years. Exclusion criteria were observational studies, clinical review papers and abstracts. Search dates include: June 2018- August 2018.

Terms from PubMed Search

Osteoarthritis AND saline AND corticosteroids AND intraarticular injections

Osteoarthritis AND intraarticular injections

Osteoarthritis AND pain AND saline

Intraarticular injections AND corticosteroids AND saline

Mesh Terms:

("injections, intra-articular"[MeSH Terms] OR ("injections"[All Fields] AND "intra-articular"[All Fields]) OR "intra-articular injections"[All Fields] OR ("intraarticular"[All Fields] AND "injection"[All Fields]) OR "intraarticular injection"[All Fields]) AND ("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields]) AND ("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields] OR "saline"[All Fields]) AND ("2008/06/08"[PDat] : "2018/06/05"[PDat])

Primary articles were evaluated via the AMSTAR 2 risk of bias tool and the GRADE assessment tool for validity.

See table Table 1 and Checklist 1 in appendix for summary of results

Results:

Through the above search methods, one retrospective meta-analysis and one randomized control trial were found meeting all requirements as primary articles. A retrospective meta-analysis, *The Therapeutic Effect of Intra-articular Normal Saline Injections for Knee Osteoarthritis: A Meta-analysis of Evidence Level 1* conducted by BM Saltzman and a randomized control trial, *Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial* conducted by TE McAlindon are included in this review.

McAlindon et al[5] conducted a double blinded randomized control trial aimed to compare intraarticular (IA) injections of triamcinolone, 40mg every 3 months, to IA saline (0.9% sodium chloride) over a two-year period. Neither of the two injection options were mixed with local anesthetic and both were administered every 12 weeks for two years to their respective arms of the study. The primary outcomes to be assessed through the trial were cartilage loss, articular structure damage, pain and physical function. Inclusion criteria for candidates were age greater than 45 and a diagnosis of knee osteoarthritis as defined by the American College of Rheumatology classification criteria (come back to cite this). In total, 445 patients were deemed initially eligible, and further exclusion of 305 participants were made due to pain criteria, grade of cartilage degradation, effusion being absent, contraindications to MRI and other exclusionary medical conditions.

The study randomized the remaining 140 participants into two arms, one receiving triamcinolone and one receiving IA saline every three months for 2 years. Randomization was done via computer generated statistical randomization software, taking into consideration age and grade of cartilage loss (see Table 3). At each 3-month period the patients were assessed through physical examinations, subjective pain assessments, functionality scaled surveys and radiologic studies (x-ray and ultrasound every 3 months, and MRI at 0, 12 and 24 months). The WOMAC questionnaire was the pain scale chosen for this trial ranging from zero (no pain) to twenty (extreme pain).[5]

The initial results from the study did not show a significant different across the two treatment groups. −1.2 units (on WOMAC 0-20 pain assessment scale) in the triamcinolone vs −1.9 in the saline group; between-group mean difference: −0.64 (95% CI, −1.6 to 0.29) as illustrated in the table below (see Table 4).

Table 3: Participants Characteristics at Baseline

	Mean (SD)	
	Triamcinolone (n = 70)	Saline (n = 70)
Age, years	59.1 (8.3)	57.2 (7.6)
Women, No. (%)	37 (52.9)	38 (54.3)
White, No. (%)	47 (67.1)	42 (60.0)
BMI	30.8 (5.1)	31.7 (6.6)
Varus or Valgus Malalignment, No. (%)	53 (75.7)	55 (78.6)
Synovial Pouch depth, mm	4.2 (1.9)	4.5 (2.0)
KL Score, No. (%)		
• 2	29 (41.4)	29 (41.4)
• 3	41 (58.6)	41 (58.6)
Clinical		
• VAS Pain score	38.4 (22.2)	42.6 (22.1)
WOMAC Score		
• Pain	8.2 (3.0)	8.4 (3.0)
• Function	28.3 (10.8)	30.1 (9.5)
• Stiffness	3.7 (1.6)	4.0 (1.4)
20-m Walk, s	19.8 (6.7)	18.2 (3.8)
Chair Stand, s	18.3 (8.6)	17.2 (6.5)
Hemoglobin A1c Mean (SD), %	6.0 (0.8)	6.0 (0.6)
C-Reactive Protein, mean (SD), mg/L (log)	0.6 (1.2)	0.4 (1.1)

Table 4: Treatment Effects on Symptoms and Function Outcomes

	Mean (95% CI) Triamcinolone (n=70)		Saline (n=70)		Between Group	
	Baseline	2-year change	Baseline	2-year change	Difference in Change	P value
WOMAC						
• Pain	7.5 (6.3 to 8.6)	-1.2 (-1.9 to -0.58)	8.2 (7.0 to 9.3)	-1.9 (-2.52 to -1.23)	-0.64 (-1.6 to 0.29)	.17
• Function	27.1 (23.1 to 31)	-4.1 (-7.4 to -0.83)	29.2 (25.3 to 33.1)	-5.1 (-8.1 to -2.19)	-1.01 (-4.9 to 2.9)	.59
• Stiffness	3.5 (3.0 to 4.1)	-0.59 (-1.1 to -0.06)	3.8 (3.3 to 4.3)	-0.53 (-1.0 to -0.01)	-0.06 (-0.43 to 0.56)	.79
VAS Pain Score	30.8 (22.9 to 38.7)	-2.7 (-11.9 to 6.6)	35.4 (27.6 to 43.2)	-7.6 (-15.4 to 0.16)	-5 (-13.9 to 3.9	.26
Function Tests:						
• 20-m Walk	20.6 (19.0 to 22.2)	-0.29 (-1.03 to 0.44	19.2 (17.7 to 20.8)	0.14 (-0.58 to 0.86)	0.43 (-0.62 to 1.5)	.41
• Chair Stand	22.1 (19.0 to 25.2	-1.1 (-3.5 to 1.2)	21.2 (18.1 to 24.2	-1.2 (-3.6 to 1.1)	-0.11 (-2.8 to 2.6)	.94
Acetaminophen use:						.43
• None	5	-2	9	-6	-4	
• % (95% CI)	7.1 (1.1 to 13.1)	-2.8 (-10.5 to 4.9)	12.9 (5.0 to 20.8)	8.6 (-17.8 to 0.6)	-5.8 (-17.8 to 6.2)	

The final conclusion discussed from this trial by the authors stated that IA saline was non-inferior to triamcinolone in regards to analgesic effects over the two year period and was thus, in that regard, showing no increased benefit of using corticosteroids over saline for treatment.[5]

In evaluating bias within this article there was little evidence for performance bias in that the participants, the providers administering the medication and providing evaluation, and those collecting and compiling the analysis were all blinded. There is little concern for detection bias given the analysist gathering and compiling the information were blinded as well. Attrition bias was addressed by the authors, both in their setup of the trial and afterwards: Eleven patients discontinued therapy from the triamcinolone arm before the two-year mark, while ten discontinued from the IA saline arm before the end of the designated study timeframe. Pre-trial

setup was determined to use 140 participants with an assumed 20% drop out from each group. with 7.1% drop out from IA saline arm and 7.8% drop out from triamcinolone arm showing no significant difference in dropout rate between the two arms of the study. Reporting bias was also addressed by the authors, to which they stated known limitations to the study. These limitations included pain not being measured subjectively within the first 4-weeks after injections, during which time benefits were perceived to be observed most, as well as patients being permitted to continue other medications during this trial, with possibility of altering analgesic effects. All results were reported. A summary table for risk of bias is listed above (see Table 1)

Saltzman et al[4] conducted a meta-analysis of level 1 studies that looked at the placebo-controlled trials of injection therapy for knee OA between 2006 and 2016. The primary outcomes measured by the authors were subjective pain scores assessed the Visual Analog Scale (VAS) for pain and the WOMAC pain assessment. Two independent reviewers separately completed search for relevant publications, with randomized, prospective and placebo-controlled trials of evidence level 1 that evaluated injection therapy for knee OA and with placebo of IA normal saline. Any collection conflicts were resolved by mutual agreement. From these criteria, 14 placebo cohorts in 13 studies were analyzed that met inclusion for the meta-analysis. The 14 placebo cohorts included 1076 placebo control patients.

The authors stated that the studies were setup in similar fashion, setting a control and test group which were blinded to the treatment being provided. Each of the studies also evaluated patients every three months, at which time another treatment of the respective injection was given. Based on the studies available, there was only sufficient evidence for VAS

pain and WOMAC total scores at 3 and 6 months, which came from 4 of the 13 studies. These values were compared to changes seen in similar pain scores from corticosteroid injections, along with comparison to minimal clinically important difference (MCID) criteria, which was pre-established to evaluate post-injection outcomes based on likely placebo effect.

At 3 months after the IA-NS placebo injection, there was a significant improvement in VAS pain scores (mean difference [MD], 12.10 [95% CI, 3.27 to 20.93]; $P = .007$), whereas improvement in the WOMAC total scores approached but did not reach statistical significance (MD, 19.75 [95% CI, –0.50 to 40.09]; $P = .06$). At 6 months, both VAS pain scores (MD, 16.62 [95% CI, 12.13-21.10]; $P < .00001$) and WOMAC total scores (MD, 11.34 [95% CI, 7.03-15.65]; $P < .00001$) were significantly improved in comparison to pre-injection values. Furthermore, improvements in both the VAS pain and WOMAC total scores at 6 months were clinically significant (MCID, 1.37 and 9, respectively).[4]

Calculated change in the VAS pain score (Δ = 16.62 of 100) at 6 months after the injection exceeds the published MCID of 13.7, suggesting that IA-NS placebo injections provide a statistically and clinically meaningful improvement in knee pain for OA. The calculated change in the WOMAC total score (Δ = 11.34) at 6 months after the placebo injection was greater than the published MCID of 9, implying that the placebo intervention resulted in a clinically significant improvement as well. Comparing to the corticosteroid injections in similar trials, CS injections demonstrated to improve VAS pain from 71.5 to 65.6 (Δ = 5.9 of 100) in three months (similar WOMAC scores were not provided). Extrapolated, this would show a superiority of IA normal saline above IA corticosteroids for analgesic effects.[4]

Outcome Variable	Calculated Mean Improvement	MCID	Meets MCID?
VAS pain score at 6 months	16.62 of 100	13.70 of 100	Yes
WOMAC total score at 6 months	11.34	9.00	Yes

*Table 3: 6 month outcomes for pain reduction scores, *MCID, minimal clinically important difference; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index*

Bias was addressed by the authors within their collective study. The most prominent issues discussed were the variability of different trials in terms of evaluative and comparative results with differing study setups, inclusion criteria for patients, degree of disease being studied, follow up time and outcome measurements. Volume of the injections in various trials were also different, and could have affected the outcomes. The heterogeneity in scores reported among studies, the lack of objective findings reported and lack of comparison in the given studies to a "no treatment" group increases bias without a placebo blinded control group and adds additional limitations which lowers the overall validity of the compiled findings. Allocation concealment was not mentioned within the review. All results were reported. A summary of the risk of bias can be found in the table listed above (see Table 2).

Discussion:

After reviewing these papers, there is clinically significant analgesic effect of IA saline, with the different reviews showing variance in comparison to traditionally used corticosteroid injections for knee OA.

There are serious limitations and high bias risk with the Saltzman et al report, though interesting discussion of the placebo effect is addressed in terms of interpreting data collected.

This meta-analysis was the first to address on a systematic level the comparative effects of normal saline injections as a possible treatment as opposed to a control placebo. Taking this into account, limited data and comparison models were available to effectively compare these two treatment options at a level of high validity.

In regard to the McAlindon et al report, this was the first of its kind in terms of trialing primary outcomes towards the therapeutic effects of normal saline in comparison to corticosteroids. A great deal of effort was made in the set up and follow through of this trial to address any concerns of bias and present outcomes in the most reliable unbiased way. This report showed variance of clinically indistinguishable analgesic affect, or straight superiority of normal saline in this regard depending on the follow up time evaluated through the two years of the trial. One area not addressed was the placebo effect, which was thoroughly addressed in Saltzman et al report. Despite this, there is low risk of bias, and any perceived biases were properly managed through the set-up of the trial as well as through follow up and self-reported variances to the original plan.

Other outcomes not taken into consideration during this review, which could play a role in the choice of therapy for knee OA are functional outcomes, progression of joint space narrowing, degradation of cartilage and progression to further stages of OA. With this in mind, analgesia is not deemed the only primary outcome to consider in treatment of those with OA.

Conclusion:

The administration of IA placebo saline yields a statistically and meaningful improvement in regard to analgesic effect and has shown to be non-inferior to corticosteroids over three months to two years in time. Due to the small population of comparative studies

available, more data needs to be collected to confirm this outcome. Additionally, further trials are necessary to compare IA saline to other treatment modalities, such as hyaluronate, PRP and morphine based intra-articular solutions. Secondary outcomes also need to be further investigated including progression of disease through cartilage degradation, joint space narrowing and overall functionality.

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Appendix

Checklist 1: AMSTAR 2 Review of Meta-Analysis: Therapeutic Effect of Intra-articular Normal Saline Injections for Knee OA

1. Did the research questions and inclusion criteria for the review include the components of PICO?
   For Yes:
   Population: Yes
   Intervention: Yes
   Comparator group: No
   Outcome: No
   Optional (recommended): Timeframe for follow-up: Yes
   Author's assessment: **Yes**

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
   For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:
   Review question(s): Yes
   Search strategy: Yes
   Inclusion/exclusion criteria: Yes
   Risk of bias assessment: No
   Author's assessment: **No**

3. Did the review authors explain their selection of the study designs for inclusion in the review?
   For Yes, the review should satisfy ONE of the following:
   Explanation for including only RCTs: Yes
   OR Explanation for including only NRSI: No
   OR Explanation for including both RCTs and NRSI: No
   Author's assessment: **Yes**

4. Did the review authors use a comprehensive literature search strategy?
   For Partial Yes (all the following):
   Searched at least 2 databases (relevant to research question): Yes
   Provided key word and/or search strategy: Yes
   Justified publication restrictions (e.g. language): Yes
   Author's assessment: **Partial Yes**

5. Did the review authors perform study *selection* in duplicate?
   For Yes, either ONE of the following:
   At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include: Yes

OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer: No
Author's assessment: **Yes**

6. Did the review authors perform data *extraction* in duplicate?
   For Yes, either ONE of the following:
   At least two reviewers achieved consensus on which data to extract from included studies: Yes
   OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer: No
   Author's assessment: **Yes**

7. Did the review authors provide a list of excluded studies and justify the exclusions?
   For Partial Yes:
   Provided a list of all potentially relevant studies that were read in full-text form but excluded from the review: Yes
   Author's assessment: **Partial Yes**

8. Did the review authors describe the included studies in adequate detail?
   For Partial Yes (ALL the following):
   Described populations: Yes
   Described interventions: Yes
   Described comparators: Yes
   Described outcomes: Yes
   Described research designs: Yes
   Author's assessment: **Yes**

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? *Complete the assessment for RCTs, non-randomized studies, or both, depending on what types of studies are included in your chosen systematic review.*
   For Yes, must also have assessed RoB from:
   Allocation sequence that was not truly random: No
   AND Selection of the reported result from among multiple measurements or analyses of a specified outcome: Yes
   Author's assessment: **No**

   No NRSI conducted
   Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?
    For Yes
    Must have reported on the sources of funding for individual studies included in the review.

Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies: Yes
Author's assessment: **Yes**

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
    RCTs For Yes:
    The authors justified combining the data in a meta-analysis: Yes
    AND they used an appropriate weighted technique to combine study results and adjusted for: Yes heterogeneity if present.
    AND investigated the causes of any heterogeneity: Yes
    Author's assessment: **Yes**

    No meta-analysis conducted For NRSI
    Includes only RCTs

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
    For Yes:
    Included only low risk of bias RCTs: No
    OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect: No
    Author's assessment: **No**

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
    For Yes:
    Included only low risk of bias RCTs: No
    OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results: No
    Author's assessment: **No**

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
    For Yes:
    There was no significant heterogeneity in the results: No
    OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review: No
    Author's assessment: **Yes**

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
    For Yes:

Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias: No
Your assessment: **No**

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?
For Yes:
The authors reported no competing interests: no
OR the authors described funding sources and how they managed potential conflicts of interest: Yes
Author's assessment: **Yes**

Therapeutic Effect of Intra-articular Normal Saline Injections for Knee OA
Author's Assessment via AMSTAR 2: **Critically Low Quality Review**

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