Intra-Articular Injections for Analgesia in Knee Osteoarthritis: "Placebo" Normal Saline vs Corticosteroids

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Background

Knee Osteoarthritis

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.[2]

Risk Factors for developing Knee OA:
- Female Gender
- Age
- Obesity
- Previous Knee Injury and Overuse

Clinical Manifestations:
- Chronic Progressive Knee Pain
- Joint Swelling
- Crepitation with Range of Motion

Diagnosis:
- Positive History
- Aspirate Fluid Examination
- Imaging: X-ray showing:
  - Joint space narrowing
  - Osteophyte formation

Current Treatment Modalities:
- Lifestyle changes:
  - Weight loss
  - Lower Extremity Strengthening
  - Weight-Bearing Exercise Programs/Classes
- Acetaminophen/NSAIDS
- Intra-articular Injections
  - Corticosteroids
  - Hyaluronic Acid
- Surgery
  - Total Knee Replacement

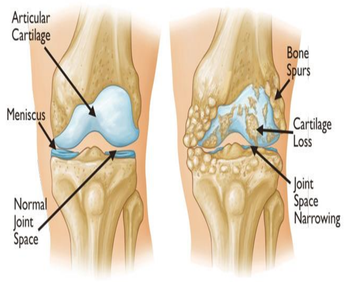


Figure 1. Osteoarthritis Pathophysiology[1]

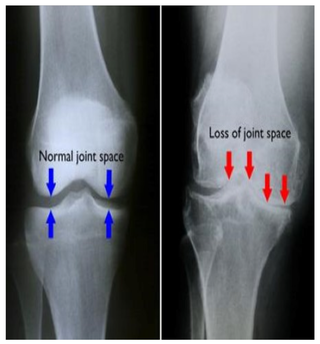


Figure 2. Knee OA Clinical Manifestations[1]

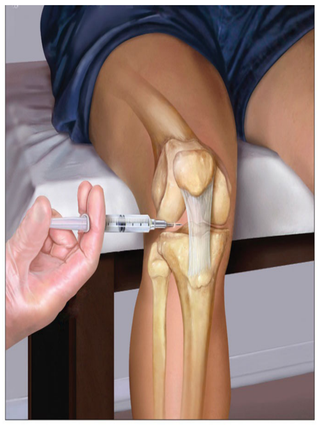


Figure 3. Intra-articular Injections[1]

Role of Intra-Articular Injections

Intraarticular injections have been shown to be the most effective non-surgical treatment modality in reducing pain for those affected with moderate to severe knee osteoarthritis. 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. 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.[3]

Normal Saline Intra-Articular Injections

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]

Methods

Databases utilized:
- PubMed, CINHAL and the Cochrane Database of Systematic Reviews

Keywords:
- osteoarthritis, intraarticular injections, saline, corticosteroids and hyaluronic acid

**An individual search was also conducted using reference lists through primary articles*

Primary Inclusion Criteria:
- randomized control trials, systematic reviews, retrospective cohort studies and meta analyses of randomized control trials within the past 20 years including primary

Primary Exclusion criteria:
- observational studies, clinical review papers and abstracts.

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

Search dates include: June 2018- August 2018.

Primary articles were evaluated via Cochrane risk of bias tool and the GRADE assessment tool for validity

Table 1: GRADE Risk of Bias, McAlidon et al

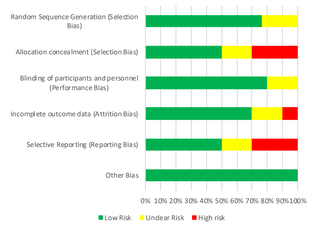
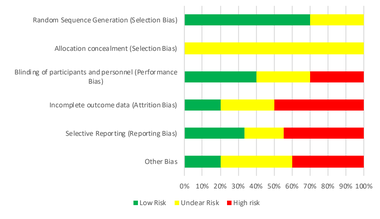


Table 2: Cochrane Risk of Bias, Saltzman et al



Results

The Therapeutic Effect of Intra-articular Normal Saline Injections for Knee Osteoarthritis: A Meta-analysis of Evidence Level 1

Saltzman et al

Retrospective meta-analysis of level 1 studies looking at the placebo-controlled trials of injection therapy for knee OA between 2006 and 2016. Primary outcomes measured were subjective pain scores assessed via Visual Analog Scale (VAS) for pain and the WOMAC pain assessment.

14 placebo cohorts in 13 studies analyzed included 1076 placebo control patients.

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 pain scores from trials with corticosteroid injections, taking into account a likely **placebo effect**.

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.[5]

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)	

Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial

McAlidon et al

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)

Double blinded randomized control trial investigating intraarticular (IA) injections of triamcinolone, 40mg every 3 months, to IA saline (0.9% sodium chloride) over a two-year period.

Primary outcomes were cartilage loss, articular structure damage, pain and physical function. Inclusion criteria: 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).

140 participants separated into two arms: triamcinolone and IA saline groups every three months for 2 years. Characteristics of each group can be seen in Table 3.

Initial results 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).

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.[6]

Discussion

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.

McAlindon et al report, 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.

Conclusions

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.

References

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