The Therapeutic Effect of Intra-articular Normal Saline Injections for Knee Osteoarthritis

A Meta-analysis of Evidence Level 1 Studies

Bryan M. Saltzman,*† MD, Timothy Leroux,‡ MD, Maximilian A. Meyer,‡ BS, Bryce A. Basques,† MD, Jaskarndip Chahal,§ MD, FRCSC, MSc, Bernard R. Bach Jr,‡ MD, Adam B. Yanke,‡ MD, and Brian J. Cole,‡ MD, MBA
Investigation performed at the Rush University Medical Center, Chicago, Illinois, USA

Background: Intra-articular normal saline (IA-NS) injections have been utilized as a placebo in a number of randomized controlled trials pertaining to the management of knee osteoarthritis (OA); however, it is believed that these ''placebo'' injections may have a therapeutic effect that has not been quantified in the literature.

Purpose: To (1) quantify the effect of IA-NS injections on patient-reported outcomes (PROs) and (2) compare postinjection PROs to established minimal clinically important difference (MCID) criteria to demonstrate a potential therapeutic effect.

Study Design: Meta-analysis.

Methods: A review was conducted to identify all randomized, placebo-controlled trials on injection therapy for knee OA between 2006 and 2016. Patient demographics and PROs before the injection and at 3 and 6 months after the injection were collected for patients in the IA-NS injection group in each study. A random-effects model was used to compare preinjection scores and scores at each postinjection time point in a pairwise fashion.

Results: In total, there were 14 placebo cohorts in 13 studies that were analyzed after meeting inclusion criteria for this meta-analysis. This included 1076 patients (Kellgren-Lawrence grade 1-4), with a weighted mean age of 62.53 years and mean body mass index of 28.67 kg/m^2. There was only sufficient information to perform analyses of visual analog scale (VAS) pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) total scores. 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 preinjection values. Furthermore, improvements in both the VAS pain and WOMAC total scores at 6 months were clinically significant (MCID, 1.37 and 9, respectively).

Conclusion: The administration of an IA-NS placebo injection yields a statistically and clinically meaningful improvement in PROs up to 6 months after the injection in patients with knee OA. This observation supports the notion that the so-called placebo effect for IA-NS injections achieves a clinically meaningful response in patients with OA when provided during comparison studies to an active treatment group (ie, hyaluronic acid).

Keywords: saline; placebo; injection; knee; osteoarthritis; arthritis; arthrocentesis

Placebo-control groups play a critical role in the development of new therapies and in establishing a "null" baseline upon which a proposed intervention must demonstrate improvement to substantiate clinical use. Both meta-analyses and randomized controlled trials of medical therapies and psychotherapies have confirmed that for numerous pathological conditions, placebo treatment is superior to a lack of treatment[41] and, in some cases, can be as robust and as effective as the actual comparison treatment arm.[37] This response, commonly labeled the "placebo effect," stems from a complex interplay of sociopsychological factors, including the therapeutic ritual of receiving a perceived treatment, the interaction between patient and health care provider, the clinician's confidence in the treatment, the patient's personality effects, the method and frequency of substance administration, and the expectation for improvement by the patient.[1,10] The true biological and

The American Journal of Sports Medicine, Vol. XX, No. X
DOI: 10.1177/0363546516680607

disease-modifying effect of placebo varies based on the disease and organ system but largely remains unknown.

Knee osteoarthritis (OA) presents a major economic burden to society with patient-reported pain and reduction in the quality of life[10] and therefore is the focus of numerous ongoing clinical trials. Intra-articular normal saline (IA-NS) has been utilized as a placebo in a number of randomized controlled trials pertaining to the management of knee OA; however, it is believed that these "placebo" injections may have a therapeutic effect that has never been thoroughly quantified in the literature. This is of particular importance as often the interpretation of the results from placebo-controlled trials is affected by the magnitude of the response to a placebo arm. That is, the magnitude of the effect from a placebo will reduce the apparent effect size of the treatment arm when comparisons are made.[6] Beyond this, several recent injection trials for knee OA have compared novel therapies, such as biological agents or platelet-rich plasma (PRP), to existing standard-of-care treatments, such as corticosteroids (CS) or hyaluronic acid (HA), but have failed to include a true placebo arm as well.[8,13,36]

In the present study, we utilized data from existing evidence level 1 studies to (1) quantify the effect of IA-NS placebo injections on patient-reported outcomes (PROs) and (2) compare postinjection PROs to established minimal clinically important difference (MCID) criteria to demonstrate a potential therapeutic effect.

METHODS

A systematic review of the available literature was conducted according to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers separately completed the search on April 1, 2016 using the PubMed database on MEDLINE (April 1, 2006 to April 1, 2016) to provide a relevant, current sampling of studies over the most recent 10 years of literature publications. The electronic search algorithm utilized the following terms: "knee" AND "injection" AND "osteoarthritis." Articles eligible for inclusion were randomized, prospective, placebo-controlled trials of evidence level 1 that evaluated injection therapy for knee OA, in which the placebo was IA-NS. The initial exclusion process was through a review of article titles, abstracts, and study grade statements. If a question arose as to whether the article met the criteria for exclusion, the full-text article was reviewed. Articles were excluded for the following reasons: comparison studies without a placebo-controlled cohort, placebo being something other than IA-NS, nonoutcome studies (ie, incidence/predictive studies), reviews/systematic reviews, editorials, laboratory or biomechanical studies, letters to the editor, or studies evaluating the treatment of nonknee joints. Each study was reviewed by the same 2 independent reviewers, with any data collection conflicts resolved by means of mutual agreement. Basic information including article year of publication and journal of publication was first extracted.

Patient demographics that were detailed included the number of patients, mean age, sex, body mass index, and baseline Kellgren-Lawrence (KL) grade of OA. The type, volume, preparation, and administration protocol (frequency or injection) of the saline-based placebo utilized in each study placebo group were recorded. The following outcomes were documented for patients in the IA-NS group in each study before the injection and at 1, 3, and 6 months after the injection when available from the individual studies: visual analog scale (VAS) pain score both after walking and at rest; Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, stiffness, function, and total scores; International Knee Documentation Committee (IKDC) subjective score; Knee injury and Osteoarthritis Outcome Score (KOOS) pain, symptoms, activities of daily living, quality of life, sport, and total values; and Lequesne functional index value. The number of patient complications, patient requirements for operative management or proceeding to total knee arthroplasty in the study period, and satisfaction were documented as well when available.

Statistical Analysis

Descriptive statistics were calculated for all variables after normalizing for the cohort size, including means and SDs. A random-effects model was used to compare preinjection scores and scores at each postinjection time point where available (when more than 2 studies provided the reported score with mean and SD) in a pairwise fashion. An inverse variance approach was used, and mean differences (MDs) were reported from this model. The I^2 statistic was used to assess heterogeneity. Data were analyzed using RevMan 5.3 software (The Cochrane Collaboration). Additionally, preoperative and postoperative subjective outcomes were directly compared with reported MCIDs.[2] These MCIDs were determined by using currently available and defined standards in the published literature: An established MCID for the VAS pain score on a scale of 0 to 10 has been suggested as 1.37,[17] and an established MCID at 6 months after treatment for the WOMAC total score is 0.9 on a scale of 0 to 10 (or 9 on a 0-100 scale)[AQ: 1].[38] Statistical significance was set for all testing at $P < .05$.

*Address correspondence to Bryan M. Saltzman, MD, Department of Orthopedic Surgery, Rush University Medical Center, 1611 West Harrison Street, Suite 300, Chicago, IL 60612, USA (email: bryan.m.saltzman@gmail.com).

†Department of Orthopedic Surgery, Rush University Medical Center, Chicago, Illinois, USA.

‡Division of Sports Medicine, Department of Orthopedic Surgery, Rush University Medical Center, Chicago, Illinois, USA.

§Division of Sports Medicine, Department of Orthopedic Surgery, University of Toronto, Toronto, Ontario, Canada.

One or more of the authors has declared the following potential conflict of interest or source of funding: B.R.B. receives research support from Arthrex Inc, Conmed Linvatec, DJ Orthopaedics, Ossur, Smith & Nephew, and Tornier. A.B.Y. receives research support from Arthrex Inc and NuTech. B.J.C. receives research support from Aesculap/B. Braun, Arthrex Inc, Cytori, National Institutes of Health, Medipost, and Zimmer; is a paid consultant for Arthrex Inc, Regentis, and Zimmer; receives financial or material support from Athletico, Ossur, Smith & Nephew, and Tornier; receives royalties from Arthrex Inc and DJ Orthopaedics; and holds stock or stock options in Arthrex Inc, Carticept, and Regentis.

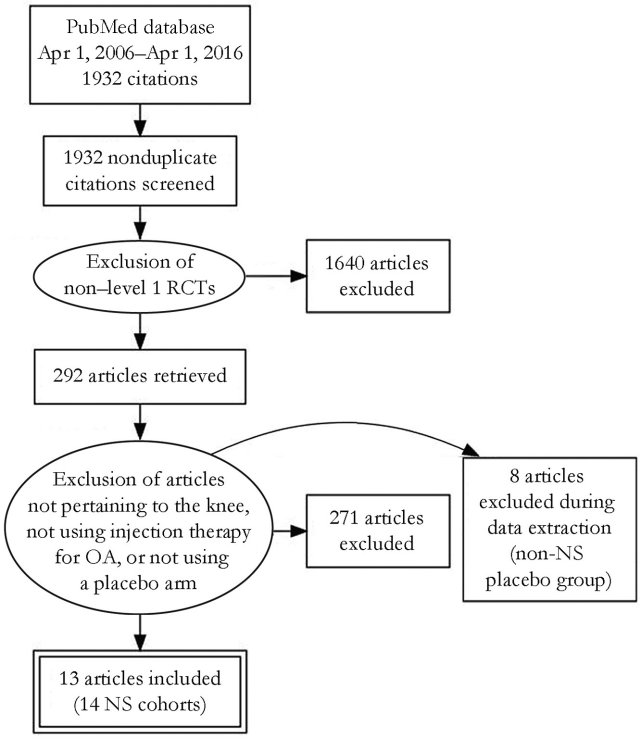

Figure 1. Flowchart of study inclusion according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. NS, normal saline; OA, osteoarthritis; RCT, randomized controlled trial.

RESULTS

After applying the aforementioned inclusion and exclusion criteria, a total of 14 placebo cohorts in 13 studies were appropriate for analysis (Figure 1). No additional studies were added after the reference lists from these 13 studies were reviewed to determine if additional articles existed that were appropriate for inclusion. All articles were evidence level 1. The most common trial arm for comparison to the IA-NS placebo-control group of interest was HA (7/14; 50.0%), with PRP (2/14; 14.3%), CS (1/14; 7.1%), low–molecular weight human albumin (1/14; 7.1%), interleukin-1 antagonist (1/14; 7.1%), transforming growth factor–β1 (1/14; 7.1%), and clodronate (1/14; 7.1%) providing the additional trial arms. Five cohorts (35.7%) included patients with KL grade 1 OA, 13 (92.9%) included patients with KL grade 2 OA, 13 (92.9%) included patients with KL grade 3 OA, and 7 (50.0%) included patients with KL grade 4 OA; 1 article reported patient inclusion by Ahlbäck grades (including grades 1-3).

The 14 placebo cohorts included 1076 placebo-control patients, with a weighted mean age of 62.53 years and mean body mass index of 28.67 kg/m^2; 36% were male. Based on the studies available, there was only sufficient information to perform analyses of VAS pain and WOMAC total scores at 3 and 6 months, which came from only 4 of the 13 studies; there were not enough documented data among the studies to determine overall changes in the VAS score after walking or at rest, the WOMAC stiffness or function score, the IKDC subjective score, KOOS subscores, or the Lequesne functional index value at any postinjection time point (Table 1). At 3 months after the IA-NS placebo injection, significant improvement was seen in the VAS pain score (3 studies included, n = 210 patients; MD, 12.10 [95% CI, 3.27-20.93]; P = .007). The WOMAC total score at 3 months after the injection improved considerably (2 studies included, 180 patients; MD, 19.75 [95% CI, –0.50 to 40.09]; P = .06) but did not reach statistical significance. At 6 months after the IA-NS placebo injection, VAS pain scores (2 studies included, 180 patients; MD, 16.62 [95% CI, 12.13-21.10]; $P < .00001$) and WOMAC total scores (2 studies included, 180 patients; MD, 11.34 [95% CI, 7.03-15.65]; $P < .00001$) were significantly improved in comparison to preinjection values (Figure 2). None of these patients required total knee arthroplasty during the study period. In 1 study,[5] there were 2 local postinjection reactions causing withdrawal from the study. In the remaining studies, there were no recorded serious adverse events.

Our calculated change in the VAS pain score (Δ = 16.40 of 100[AQ: 3] 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 = 11.35[AQ: 4] 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 (Table 2). At 3 months after the intervention, MCID criteria did not exist for these outcome variables and so could not be compared.

There was no homogeneous reporting of patient satisfaction among the included studies. However, those studies that reported some marker of patient satisfaction at the postinjection time points demonstrated notable patient improvements with the placebo injection (Table 3).

DISCUSSION

Our results suggest that the administration of an IA-NS placebo injection yields a statistically and clinically meaningful improvement in PROs at 6 months after the injection in patients with knee OA (KL grades 1-4). Furthermore, the findings quantify the therapeutic response of the "placebo effect" with IA-NS administration, providing a standard minimum improvement value that future trial therapies should surpass before clinical application. The grouped effects are impressive considering that certain studies have reported effect sizes of 0.2 to 0.3 for some conventional pharmacological therapies (ie, oral analgesics and nonsteroidal anti-inflammatory drugs) [AQ: 5].[28] As the results of treatments are often reported in comparison to the placebo as a specific treatment effect, our data suggest that investigators should focus not only on these comparative effects but also the overall treatment effects in isolation.[41] Additionally, there should be consideration for a placebo-control arm as well as a "no-treatment arm" for randomized controlled trials to distinguish these effects.[1]

TABLE 1
PROs in the Included Studies[a]

Study (Year)	IKDC Subjective	VAS			WOMAC				KOOS				LFI
		Pain	Rest	After Walking	Total	Pain	Stiffness	Function	Total	Pain	Symptoms	Sport	
Lee et al[23] (2015)	XY	XY			XY				XY				
Rossini et al[34] (2015)		X				X							X
Yavuz et al[39] (2012)		X*											X*
Bar-Or et al[7] (2014)					X	X	X	X					
Patel et al[30] (2013)		XY			XY	XY	XY	XY					
Baltzer et al[5] (2009)		X*Y*			X*Y*	X*Y*	X*Y*	X*Y*					
Auw Yang et al[4] (2008)		X*Y*			X*Y*					XY	XY	XY	
Huang et al[20] (2011)				Y*		Y		Y					
Navarro-Sarabia et al[29] (2011)				X									
Jorgensen et al[21] (2010)				XY									XY
Lundsgaard et al[24] (2008)				X									
Petrella et al[31] (2008)			X	X									
Petrella and Petrella[32] (2006)													

[a]An "X" denotes that the PRO was provided at 3 months after the injection; a "Y" denotes that the PRO was provided at 6 months after the injection. An asterisk (*) indicates that the SD was provided along with the mean score in the included study for both the preoperative and postoperative time points, thus allowing for statistical comparisons to be made[AQ: 2]. IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; LFI, Lequesne functional index; PRO, patient-reported outcome; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

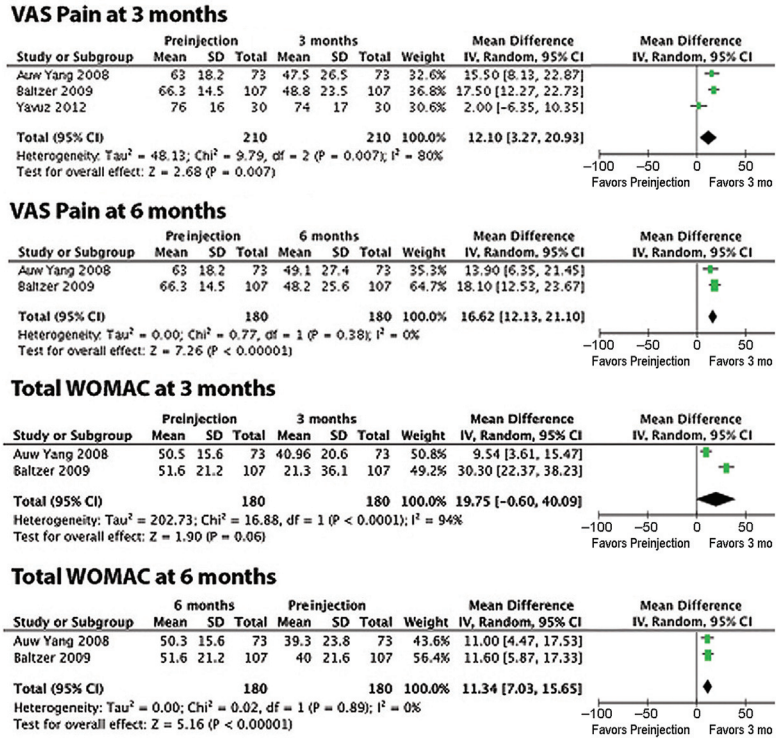

Figure 2. Random-effects model comparing preinjection to postinjection time points at 3 months and 6 months for visual analog scale (VAS) pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) total scores.

Our findings for the efficacy of placebo injections are similar to those proposed in prior publications for other intra-articular options for knee OA. For example, PRP was demonstrated by Gobbi et al[15] to improve the VAS pain score from 4.2 to 2.8 (Δ = 1.4) and from 4.3 to 3.2 (Δ = 1.1) of 10 at 12 months after treatment for 1- and

TABLE 2
Improvement in Outcome Variables and Comparison to the MCID in the Literature[a]

Outcome Variable	Calculated Weighted Mean Improvement	MCID	Meets MCID?
VAS pain score at 6 mo	Δ16.40 of 100	Δ13.70 of 100	Yes
WOMAC total score at 6 mo	Δ11.35	Δ9.00	Yes

[a]MCID, minimal clinically important difference; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

TABLE 3
Markers of Patient Satisfaction at Time Points After the Placebo Injection

Study (Year)	Patient Satisfaction After Injection
Patel et al[30] (2013)	4.3% fully satisfied and 6.5% partially satisfied at final follow-up
Baltzer et al[5] (2009)	Patient global assessment of satisfaction: 36% satisfied or better at 3 mo and 42% satisfied or better at 6 mo after injection
Huang et al[20] (2011)	Patient's assessment of effectiveness: 45% reported "slightly improved" or better
Petrella et al[31] (2008)	Patient global assessment was, on average, 2 of 5 at 1 mo and 1 of 5 at 3 mo

2-cycle preparations, respectively. A CS injection was demonstrated by Askari et al[3] to improve the VAS pain score from 7.15 to 5.69 (Δ = 1.46) and 6.56 (Δ = 0.59) of 10 at 1 and 3 months after the injection, respectively. The same authors[3] demonstrated HA to improve the VAS pain score from 7.52 to 6.63 (Δ = 0.89) and 6.70 (Δ = 0.82) of 10 at 1 and 3 months after the injection, respectively. If these literature references are extrapolated, they demonstrate comparability, even superiority, of the findings for the placebo from this study in terms of the VAS pain score at 3 months (Δ = 12.10) and 6 months (Δ = 16.40[AQ: 6]) after the injection.

Improvements in the WOMAC total score in the literature for PRP and HA have demonstrated relative comparability as well. Raeissadat et al[33] reported an improvement in the WOMAC total score in their cohort with PRP use at 1 year after the injection (from 39.50 to 18.44; Δ = 21.11)[AQ: 7]. These authors found substantially less improvement in the WOMAC total score with their HA cohort (from 28.69 to 27.46; Δ = 1.22), however. Meheux et al[25] systematically reviewed the literature and reported improvements in the WOMAC score with PRP from 52.36 to 28.50 (Δ = 23.86) at 12 weeks and 22.80 (Δ = 29.56) at 26 to 52 weeks. With HA, the WOMAC score improved from 52.05 to 43.40 (Δ = 8.65) at 12 to 26 weeks and 38.10 (Δ = 13.95) at 26 to 52 weeks. Overall, this PRO finds similarity as well to the findings for the placebo from this study in terms of the WOMAC total score at 3 months (Δ = 19.75) and 6 months (Δ = 11.34) after the injection.

Current evidence suggests that the therapeutic benefits from placebo treatments are a consequence of symptomatic alterations but without true changes to the pathophysiology of the disease at hand. This is supported by the observation of the placebo response for continuous subjective measures of disease activity and not when objective (physical examination or laboratory values) measures are incorporated.[19,22,26] However, our data may suggest a true biological effect of IA-NS in its use for OA of the knee. Specifically, our findings demonstrate that an intra-articular placebo injection with normal saline achieves both a statistically and clinically meaningful effect in subjective pain and knee function. Given these clinically noticeable improvements after IA-NS placebo injections, our findings ultimately call into question the use of IA-NS injections as a null control group for comparison to investigative trial arms, as saline may in itself provide a biological disease-modifying effect. One hypothesis for this mechanism of action is the dilution of inflammatory mediators within the knee, providing relief of perceived pain and subjective stiffness. As described previously, the power of the complex interplay of psychological factors behind the "placebo effect" cannot be ignored as possible means for this improvement as well. Regardless of the mechanism, such drastic improvements in pain and function warrant investigation of IA-NS as a potential treatment option for knee OA. However, determining an adequate control to IA-NS would also remain challenging. Presumably, a sham group with a simple needle stick into the joint would remedy some concerns for the potential biological therapeutic effect of IA-NS.

The placebo response in the recent literature has been best reported for symptomatic improvement of patient pain and distress, which are 2 important targets of symptoms in OA.[1] Recently published data have suggested that statistically significant predictors of the magnitude of the placebo response in OA-related pain have included an invasive route of delivery (such as by injection or even in one case sham arthroscopic surgery),[12,27,35] higher baseline pain,[1] greater frequency of administration,[40] and higher treatment effect sizes.[1] These effects are a consequence of complex neurobiological mechanisms of the brain and their activation through various neurotransmitters.[14] The credibility of the placebo effect has been enhanced with the identification of patient-specific genetic codings that are beginning to point out patients who are more likely to respond to a placebo.[16]

Prior analyses on the topic of intra-articular placebo use in knee OA have come short of defining an absolute effect size of the placebo and comparing it to MCIDs to suggest

a clinically significant benefit. Bannuru et al[6] performed a network meta-analysis on OA trials to evaluate the effects of alternative (intra-articular, topical, oral) placebo types on pain outcomes in knee OA. They determined that this effect was not influenced by a patient's perceived likelihood for being assigned randomly to the active treatment arm. They additionally found an improvement with placebo administration in other subjective outcomes including stiffness, self-reported function, and physician's global assessment; however, it lacked improvement in most objective outcomes (quadriceps strength, knee swelling and range of motion, radiographic joint space narrowing). Their conclusions suggested that all placebos are not equal and that some can substantially alter estimates of the relative efficacies of active treatments, although the purpose of their study was not to determine an absolute placebo effect size as is provided in our study results.

Zhang et al[40] systematically reviewed the literature involving 16,364 patients receiving a placebo for OA to examine the placebo effect in its treatment and found it considerably effective. The reported effect size was 0.51 (95% CI, 0.46-0.55) in comparison to the effect size of nearly zero in patients who received absolutely no treatment. Conaghan et al[9] additionally reported the differences in placebo interventions for knee OA. These authors compared the effects of oral and topical placebos in 699 patients and found an effect size of 0.27 (95% CI, –0.01 to 0.55) favoring the topical placebo. Hrobjartsson and Getzsche[18] performed a systematic review of 130 trials comparing treatment arms to placebo-control cohorts. They reported that the placebo cohorts had small benefits in studies with continuous subjective outcomes and for the treatment of pain. A benefit from the placebo effect has been found as well with the treatment of systemic and nonsystemic juvenile idiopathic arthritis.[11]

Our study does have inherent limitations. First, the chronicity of the pathogenesis of OA and the often-fluctuating course of symptoms can make the placebo effect difficult to estimate. Benefits over the course of the treatment follow-up may affect PROs and can include the natural variation in disease severity, spontaneous improvements, or general regression toward the mean.[1] The selected trials presented somewhat different study designs and included patients with differing KL grades; the relatively low percentage of overall patients being evaluated in the referenced studies who have grade 4 changes may also not reflect the most common patients receiving injections in some orthopaedic practices. While the studies indicated that patients were discouraged from utilizing coincident analgesic medications to prevent confounding results, it is always possible in such settings that the original data would be influenced if these recommendations were not followed. The exact volume and injection frequency differ for placebo injections among the trials as well. In addition, there is tremendous variability in the MCID for the WOMAC score from prior publications; we have selected our comparison MCID based on previous studies with similar methodology published in high-impact journals. Other studies[2] have provided an MCID for the WOMAC total score of as high as 11.5 at 6 months after treatment; even so, the calculated change in the WOMAC total score with our analysis (Δ = 11.35) still nears this mark and suggests clinical relevance[AQ: 8]. Additionally, only a small number of the studies generated from our overall search were appropriate to include in the final meta-analysis. Finally, the heterogeneity in the PRO scores reported among the studies, the lack of objective findings reported (physical examination, radiographic evaluation) from the included studies, and the lack of comparison to "no treatment" groups additionally limit our reporting of the intra-articular placebo effect generated on knee OA.

CONCLUSION

The administration of an IA-NS placebo injection yields a statistically and clinically meaningful improvement in PROs at 6 months after the injection in patients with knee OA. This observation supports the notion that the so-called placebo effect for IA-NS achieves a clinically meaningful response in patients with OA and must be considered when reviewing comparative trials investigating injectable therapeutics for the treatment of knee OA.

REFERENCES

1. Abhishek A, Doherty M. Mechanisms of the placebo response in pain in osteoarthritis. *Osteoarthritis Cartilage*. 2013;21:1229-1235.
2. American Orthopaedic Society for Sports Medicine Outcomes Task Force. Summary of clinical outcome measures for sports-related knee injuries. 2012.[AQ: 9]
3. Askari A, Gholami T, Naghizadeh MM, Farjam M, Kouhpayeh SA, Shahabfard Z. Hyaluronic acid compared with corticosteroid injections for the treatment of osteoarthritis of the knee: a randomized control trial. *SpringerPlus*. 2016;5:442.
4. Auw Yang KG, Raljmakers NJ, van Arkel ER, et al. Autologous interleukin-1 receptor antagonist improves function and symptoms and in osteoarthritis when compared to placebo in a prospective randomized controlled trial. *Osteoarthritis Cartilage*. 2008;16(4):498-505.
5. Baltzer AW, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. *Osteoarthritis Cartilage*. 2009;17(2):152-160.
6. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and implications of alternative placebo treatments. *Ann Intern Med*. 2015;163:365-372.
7. Bar-Or D, Salottolo KM, Loose H, et al. A randomized clinical trial to evaluate two doses of an intra-articular injection of LMWF-5A in adults with pain due to osteoarthritis of the knee. *PLoS One*. 2014;9(2):e87910.
8. Bodick N, Lufkin J, Willwerth C, et al. An intra-articular extended-release formulation of triamcinolone acetonide prolongs and amplifies analgesic effect in patients with osteoarthritis of the knee: a randomized clinical trial. *J Bone Joint Surg Am*. 2015;97(11):877-888.
9. Conaghan PG, Dickson J, Bolten W, Cevc G, Rother M. A multicenter randomized placebo- and active-controlled trial comparing the efficacy and safety of topical ketoprofen in Transfersome gel (IDEA-033) with ketoprofen-free vehicle (TDT 064) and oral celecoxib for knee pain associated with osteoarthritis. *Rheumatology (Oxford)*. 2013;52:1303-1312.
10. De Campos GC. Placebo effect in osteoarthritis: why not use it to our advantage? *World J Orthop*. 2015;6(5):416-420.
11. Demirkaya E, Lanni S, Bovis F, et al. A meta-analysis to estimate the placebo effect in juvenile idiopathic arthritis in randomized controlled trials. *Arthritis Rheumatol*. 2016;68(6):1540-1550.
12. Doherty M, Dieppe P. The ''placebo'' response in osteoarthritis and its implications for clinical practice. *Osteoarthritis Cartilage*. 2009;17:1255-1262.

13. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med*. 2015;43(7):1575-1582.
14. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet*. 2010;375:686-695.
15. Gobbi A, Lad D, Karnatzikos G. The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2015;23:2170-2177.
16. Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. *Trends Mol Med*. 2015;21:285-294.
17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain. *Arthritis Care Res (Hoboken)*. 2011;63(S11):S240-S252.
18. Hrobjartsson A, Getzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med*. 2001;344:1594-1602.
19. Hrobjartsson A, Getzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*. 2010;(1):CD003974.
20. Huang TL, Chang CC, Lee CH, Chen SC, Lai CH, Tsai CL. Intra-articular injections of sodium hyaluronate (Hyalgan®) in osteoarthritis of the knee: a randomized, controlled, double-blind, multicenter trial in the Asian population. *BMC Musculoskelet Disord*. 2011;12:221.
21. Jorgensen A, Stengaard-Pedersen K, Simonsen O, et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicenter, randomized, placebo-controlled, double-blind study of 337 patients followed for 1 year. *Ann Rheum Dis*. 2010;69(6):1097-1102.
22. Kaptchuk TJ, Miller FG. Placebo effects in medicine. *N Engl J Med*. 2015;373:1-2.
23. Lee MC, Ha CW, Elmallah RK, et al. A placebo-controlled randomized trial to assess the effect of TGF-B1-expressing chondrocytes in patients with arthritis of the knee. *Bone Joint J*. 2015;97(7):924-932.
24. Lundsgaard C, Dufour N, Fallentin E, Winkel P, Gluud C. Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial. *Scand J Rheumatol*. 2008;37(2):142-150.
25. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. *Arthroscopy*. 2016;32(3):495-505.
26. Miller FG, Rosenstein DL. The nature and power of the placebo effect. *J Clin Epidemiol*. 2006;59:331-335.
27. Morison RA, Woodmansey A, Young AJ. Placebo responses in an arthritis trial. *Ann Rheum Dis*. 1961;20:179-185.
28. National Collaborating Centre for Chronic Conditions. *Osteoarthritis: National Clinical Guideline for Care and Management in Adults*. London: Royal College of Physicians; 2008.
29. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicenter, randomized placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. *Ann Rheum Dis*. 2011;70(11):1957-1962.
30. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;41(20):356-364.
31. Petrella RJ, Cogliano A, Decaria J. Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Clin Rheumatol*. 2008;27(8):975-981.
32. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol*. 2006;33(5):951-956.
33. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord*. 2015;8:1-8.
34. Rossini M, Adami S, Fracassi E, et al. Effects of intra-articular clodronate in the treatment of knee osteoarthritis: results of a double-blind, randomized placebo-controlled trial. *Rheumatol Int*. 2015;35(2):255-263.
35. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med*. 2013;369:2515-2524.
36. Vega A, Martin-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation*. 2015;99(8):1681-1690.
37. Wampold BE, Minami T, Tierney SC, Baskin TW, Bhati KS. The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *J Clin Psychol*. 2005;61:835-854.
38. Wandel S, Juni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*. 2010;341:c4675.
39. Yavuz U, Sokucu S, Albayrak A, Ozturk K. Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. *Rheumatol Int*. 2012;32(11):3391-3396.
40. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomized controlled trials. *Ann Rheum Dis*. 2008;67:1716-1723.
41. Zhang W, Zou K, Doherty M. Placebos for knee OA: reaffirmation of ''needle is better than pill''. *Ann Intern Med*. 2015;163:392-393.