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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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ABSTRACT

Objectives: Hyaluronic acid and corticosteroids are common intra-articular (IA) therapies widely used for the management of mild to moderate knee osteoarthritis (OA). Many trials evaluating the efficacy of IA administered therapies commonly use IA saline injections as a placebo comparator arm. Using a systematic review and meta-analysis, our objective was to assess the clinical benefit associated with use of IA saline in trials of IA therapies in the treatment of patients with painful knee OA.

Methods: MEDLINE and Embase databases were searched for articles published up to and including August 14th, 2014. Two reviewers assessed the eligibility of potential reports and the risk of bias of included trials. We analyzed short (≤ 3 months) and long-term (6–12 months) pain reduction of the saline arm of included trials using standardized mean differences (SMDs; estimated assuming a null effect in a comparator group) that were combined and weighted using a random effects model. Treatment-related adverse events (AEs) were tabulated and presented using descriptive statistics.

Results: From 40 randomized controlled trials (RCTs) eligible for inclusion only 38 provided sufficient data to be included in the meta-analysis. Based on data with moderate inconsistency IA saline was found to significantly improve short-term knee pain in 32 studies involving 1705 patients (SMD $= -0.68$; 95% CI: -0.78 to -0.57; $P < 0.001$; $I^2 = 50\%$). Long-term knee pain was significantly decreased following IA injection with saline in 19 studies involving 1445 patients (SMD $= -0.61$; 95% CI: -0.76 to -0.45; $P < 0.001$) with a substantial degree of inconsistency ($I^2 = 74\%$). Overall, 29 of the included trials reported on adverse events, none of which found any serious treatment-related AEs following IA injection with saline.

Conclusions: Pain relief observed with IA saline should prompt health care providers to consider the additional effectiveness of current IA treatments that use saline comparators in clinical studies, and challenges of identifying IA saline injection as a "placebo."

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Background

Osteoarthritis (OA) is a common condition affecting the adult population and is characterized by joint pain and dysfunction [1,2]. It is estimated that over 9-million adults in the United States suffer from symptomatic knee osteoarthritis, with roughly 1 in 3 adults over the age of 60 having evidence of radiographic knee OA [3,4]. OA also remains a leading contributor to global disability, and as measured in 2010, both hip and knee OA collectively account for over 17 million years lived with disability [5].

Non-surgical treatments are integral to the management of patients suffering from knee OA [6]. To that end, many trials have evaluated the efficacy of intra-articular (IA) treatments. There has been controversy on the value of IA treatments since it was introduced by Waugh in 1938 [7] and popularized by the use of hydrocortisone by Hollander et al. in 1951 [8]. Indeed, in one of the first clinical trials, IA lactic acid + Novocain, Novocain alone, hydrocortisone, saline, and needle stick alone were all equally effective 6 months after treatment [9]. Despite the controversies over their benefit, the need for non-surgical therapy for OA exists and current therapies have included hyaluronic acid [viscosupplementation (HA), crystalline forms of corticosteroids [10,11] and more recently, platelet-rich plasma (PRP) [12]]. Although such trials commonly use IA saline injections as a placebo comparator arm, there has been growing recognition that the administration of IA saline may not be without effect [2,13]. The potential therapeutic effect of single puncture and saline injection was first proposed in 1952 by Desmarais [14]. In a systematic review of 198 trials, it was concluded that pain, stiffness, and functional deficits associated with knee OA, could be effectively managed by placebo therapy using IA saline, as a large effect size was reported following this treatment [13]. It must be noted, however, this conclusion was drawn from a clinically heterogeneous sample, with a broad range of placebo therapies compared to various active treatments.

Given the central role of saline injections as a common placebo intervention in studies of IA treatment for knee OA, a study to determine the empirical evidence for a potential therapeutic effect of saline remains warranted, as designating saline as placebo treatment may be undermining the true effectiveness of current IA treatments. The objective of this study was to perform a systematic review and meta-analysis to assess the effect of IA saline on reducing pain associated with knee OA across randomized trials using saline as a control arm against three different IA therapies—corticosteroid, HA, and PRP.

Methods

This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [11]. Study selection, assessment of eligibility criteria, data extraction, and statistical analysis were performed, based on a predefined protocol (PROSPERO 2015: CRD42015014487). The findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Literature search

MEDLINE and Embase databases were systematically searched for articles published up to and including August 14th, 2014. MeSH and EMTREE headings were used in various combinations and supplemented with free text. A search strategy was initially conducted to capture studies using IA-HA, and a second search strategy was used to capture studies of corticosteroid or PRP injection (Appendix 1). An RCT filter developed by the Health Information Research Unit (HiRU) at McMaster University was applied to the search [16]. No language or publication date restrictions were applied. Manual review of reference lists of key articles that fulfilled our eligibility criteria, and also use of the "related articles" feature in PubMed were conducted to identify additional studies.

Study selection

Randomized controlled trials (RCTs) were included if they compared IA saline to an IA comparator (i.e., corticosteroid, HA, or PRP) in adults with symptomatic knee OA. No eligibility criteria were made regarding publication date, presence or absence of co-interventions, or length of follow-up. Studies selected were limited to English language. Two reviewers (T.D. and M.B.) independently, in duplicate, screened titles and abstracts of identified citations from the electronic search. Disagreements during abstract screening were carried forward for full text review. The full texts of potentially eligible reports were independently evaluated in duplicate, and disagreements were resolved through a consensus process to determine final eligibility.

Data extraction and risk of bias assessment

One reviewer extracted study characteristics from included studies using a piloted electronic data extraction form. The second reviewer subsequently spot-checked the data for accuracy against the trial report. Authors of included studies were contacted if important data were unclear or not reported. Data were extracted from graphical representations when required using a graph digitizing software (GraphClick, Arizona Software, Switzerland).

The primary effectiveness outcome of the study included both short (≤ 3 months) and long-term (6–12 months) pain reduction. The time points were extracted from individual trials that were closest to the pre-specified follow-up endpoints of this study. Various scales were used to measure pain across eligible studies [17]; Thus, if data on more than one scale for pain were provided in the available article, the previously developed hierarchy by Juhl et al. [18] was utilized.

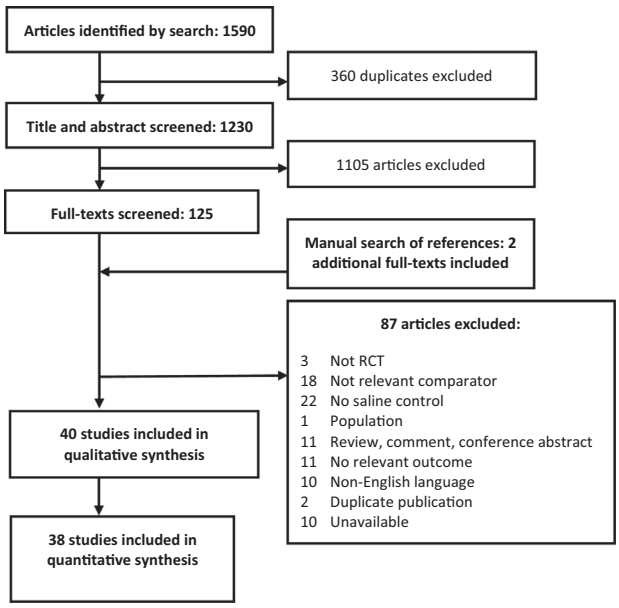

Fig. 1. Study flow diagram.

Treatment-related adverse events (TRAEs) were captured as the safety outcome for this study and were coded as either "serious" or "non-serious." Non-serious AEs resulting from IA injection of saline included those that are procedure and treatment related—local superficial infection/flare-ups, hypersensitivity to local anesthesia, effusions at the injected knee, discomfort at injection site, needle breakage or separation, and any other local adverse events reported by the authors of individual trials. A serious adverse event (SAE) was defined as an "adverse event or suspected adverse reaction that, in the view of either the investigator or the sponsor, 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 [1] (e.g., post-IA injection septic arthritis)."

For the assessment of methodological quality, both reviewers independently assessed the risk of bias of included studies using the Cochrane Risk of Bias tool [19]. The Cochrane Risk of Bias (RoB) tool separates judgments about risk of bias from inadequate reporting of methodology. The Cochrane RoB-tool evaluates the following items: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Studies were scored as having high, low, or unclear risk of bias for each component of the tool. The reviewers resolved discrepancies for each item through discussion until consensus was reached.

Table 1
Characteristics of included studies

Study	No. of patients	Mean age, years	Female sex, %	Placebo/control intervention	Comparator	No. of injections	No. of treatment cycles	Duration of follow-up, weeks	
								Short-term	Long-term
Altman et al. [26]	174	63.3	64	3 mL 0.9% saline	HA	1	1	13	26
Altman et al. [27]	295	60.8	63	2 mL PBS	HA	3	1	–	26
Arden et al. [28]	110	60.9	46	3 mL PBS	HA	1	1	6	–
Baltzer et al. [29]	107	60.3	64	Saline	HA	3	1	13	26
Chao et al. [30]	39	63.2	12.4	1 mL 0.9% NaCl	Cortico	1	1	12	–
Chevalier et al. [31]	129	62.5	68	PBS	HA	1	1	12	26
Creamer et al. [32]	12	72.2	100	2 mL saline	HA	5	1	9	–
Cubukcu et al. [33]	10	57.6	100	2 mL saline	HA	3	1	8	–
Day et al. [34]	124	62	61	Saline	HA	5	1	18	–
DeCaria et al. [35]	15	72.9	NR	1.2 mL 0.001 mg/mL inert HA	HA	3	1	3[a]	6
Dieppe et al. [36]	12	65	8.1	1 mL saline	Cortico	1	1	1	–
Diracoglu et al. [37]	21	56.2	93	0.9% saline	HA	3	1	4	–
Dixon et al. [38]	33	68.5	54	2 mL 0.2 mg sodium hyaluronate	HA	11	1	15	48
Dougados et al. [39]	55	69	65	2 mL placebo	HA	4	1	4	49
Gaffney et al. [40]	42	68	8.6	1 mL 0.9% saline	Cortico	1	1	6	–
Henderson et al.[b] [41]	20	60	75	2 mL buffered saline	HA	5	1	5	–
Henderson et al., 1994b[b] [41]	26	67	69	2 mL buffered saline	HA	5	1	5	–
Huang et al. [42]	100	64.2	78	2 mL saline	HA	5	1	–	25
Huskisson et al. [43]	50	64.8	58	2 mL saline	HA	5	1	4	6
Karlsson et al. [44]	66	71	61	3 mL PBS	HA	3	1	12	26
Kotevoglu et al. [45]	NR	60.1	88.9	2 mL saline	HA	3	1	–	6
Lohmander et al. [46]	120	58	67	2.5 PBS	HA	5	1	13	20
Lundsgaard et al. [47]	84	69.6	52.4	2 mL physiological saline	HA	4	1	12	26
Navarro-Sarabia et al.[c] [48]	152	63.9	83.7	2.5 mL saline	HA	5	4	–	–
Patel et al. [12]	26	53.7	8.17	8 mL normal saline	PRP	1	1	3	12
Petrella et al.[d] [50]	NR	62.6	42.9	2 mL isotonic NaCl solution	HA	3	1	4	–
Petrella et al., 2002b[d] [50]	NR	66.3	42.3	2 mL isotonic NaCl solution + NSAIDs	HA	3	1	4	–
Petrella et al. [51]	53	62.4	46.3	2 mL saline	HA	3	1	6	–
Petrella et al. [49]	50	71	60	Saline	HA	3	1	16	–
Pham et al. [52]	85	64.9	61.2	2.5 mL saline	HA	3	3	–	12
Puhl et al. [53]	107	60.8	55	0.25 mg sodium hyaluronate in 2.5 mL PBS	HA	5	1	–	–
Ravaud et al., 1999 [54]	28	63	11	1.5 mL 0.9% NaCl	Cortico	1	1	–	24
Raynauld et al. [55]	34	63.3	9	1 mL saline	Cortico	8	1	–	12
Scale et al. [56]	40	58.6	50	2 mL buffered saline	HA	2	1	12	–
Sezgin et al. [57]	19	59.4	68.4	2 mL 0.9% NaCl	HA	3	1	3	–
Smith et al. [58]	38	66.3	11.8	1 mL saline	Cortico	1	1	12	24
Stein et al. [59]	17	66.6	5.2	Saline solution	Cortico	1	1	6 days	–
Strand et al. [60]	128	60.3	60.2	PBS	HA	1	1	13	–
Tamir et al., 2001 [61]	24	70	71	2 mL PBS	HA	5	1	–	–
Wobig et al. [62]	60	62	74	2 mL PBS	HA	3	1	12	26
Wu et al. [63]	54	NR	NR	2.5 mL PBS	HA	5	1	–	–
Yavuz et al. [64]	30	60	6.1	1 mL 0.09% NaCl	Cortico	1	1	12	–

Note: Cortico = corticosteroid; HA = hyaluronic acid; NaCl = sodium chloride; NR = Not reported; PBS = phosphate buffered saline; PRP = platelet-rich plasma.

[a] months.

[b] For the purposes of statistical analysis, the authors stratified patients into two groups, I and II, on the basis of severity of radiological changes seen on radiographs taken before recruitment; Henderson et al. [41] = Group I (Kellgren and Lawrence (K–L) grade I or II); Henderson et al., 1994b = Group II (K–L grade III or IV).

[c] Number of patients = number allocated, not the number randomized; mean age is for the initial whole study sample.

[d] Same trial; two arms separated arms reported with respect to placebo/control intervention.

Data synthesis

Standardized mean differences (SMDs) were used to summarize results for short- and long-term pain. Only data from the IA saline arm of the RCTs were used; thereby, calculating a modified SMD for each study. As a result, unlike a typical meta-analysis, the net benefit from being allocated to the "placebo/control group" could not be estimated. However, it was assumed that a matched group was available—who did not receive any clinical support—this was imputed as having an average null-change from baseline. This assumption of null effect in the group that did not receive any treatment is confirmed in a previous analysis, that demonstrated a negligible effect size in knee OA patients who did not receive any treatment for their condition [13]. Thus, we computed the SMD as a mean change from baseline and the corresponding standard deviation (SD) and simulated a "null effect" for contrast with the same dispersion (i.e., SD) measure as the observed IA saline arm. The SMDs were combined using the inverse variance method combining based on a random effects model [20]. When mean change scores were not presented explicitly, the mean changes from baseline values were obtained by subtracting the final mean from the baseline mean [19]. When there was not enough information available to calculate SDs for the change scores or when SDs were not reported from individual studies, they were estimated from standard errors, *P* values, CIs, or ranges where possible, or they were estimated from similar included studies [19,21,22].

Heterogeneity was quantified using the *Q*-test for heterogeneity and inconsistency was interpreted based on I^2 index [19,23]. According to the protocol a priori hypotheses were developed to explain potentially high heterogeneity in the treatment effect according to the following trial characteristics: presence or absence of blinding of patients and outcome assessors, one versus two or more number of treatment cycles, and one or two versus three versus four or more injections.

Inter-observer agreement was evaluated for reviewer's assessments of study eligibility with the Cohen κ (kappa) coefficient and inter-observer agreement for the risk of bias assessment with the weighted κ coefficient [24,25]; all of the coefficients were calculated using SPSS software (version 21.0; SPSS Inc.). All tests of significance were 2-tailed, and *P* values of < 0.05 were considered significant. Inconsistent and variable reporting of TRAEs and SAEs did not lend for a pooled analysis, and thus, were tabulated and presented using descriptive statistics.

Results

Included studies and study characteristics

Of 1590 potentially eligible studies identified, 125 were reviewed in full. Two additional full text articles were reviewed following a hand search of reference lists, increasing the total reviewed articles to 127. Overall, 40 RCTs were included [12,26–64], of which 31 trials compared IA saline to IA-HA, while 8 trials compared IA saline to IA corticosteroid and only 1 trial compared IA saline against IA PRP. 38 of the included trials were entered into the meta-analysis (Fig. 1 and Table 1).

All eligible trials included patients with knee OA as defined by the American College of Rheumatology criteria, confirmed by the radiographic Kellgren–Lawrence score, Ahlbäck classification, Larsen score, or other knee OA diagnostic criteria. Of the 13 trials [26–28,31,41–43,47,48,52,57,60,61] reporting Kellgren–Lawrence grades of radiographic severity [65]; grade 2 was found in a median of 39% of participants, and grade 3 in a median of 47.8% participants. Of the included studies, the mean age of participants 63.7 (SD = 4.52), and the mean percentage of women ranged from 64% (SD = 17%). The longest duration of follow-up in the trials ranged from 6 days to 52 weeks. Overall, 31 trials [12,26–29,31–35,38,41–49,51–55,57–62] permitted the use of

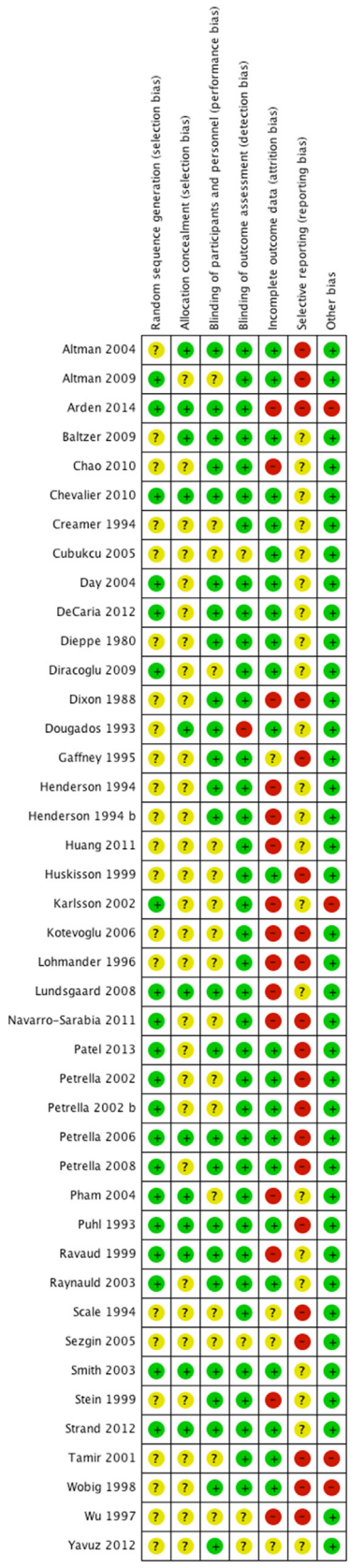

Fig. 2. Risk of bias assessment of included randomized controlled trials.

concomitant therapies throughout the study period, three trials did not allow co-interventions [50,56,63], and in six studies it was not reported [30,36,37,39,40,64].

All trials were found to have a high (n = 28 [12,26–28,30,38–54,56,57,59,61–63]) or uncertain (n = 12 [29,31–37,55,58,60,64]) risk of bias (Fig. 2). Inter-observer agreement for the overall risk of bias assessment was satisfactory (κ = 0.79, 95% CI: 0.65–0.94). Random sequence generation was adequate in 20 trials, allocation concealment was ensured in 12 trials, 25 trials were judged to have adequately blinded participants, and 37 blinded outcome assessors (Fig. 2). In all, 13 studies [28,31–33,35,36,49,51,52,54,55,58,60] analyzed all patients according to the intention-to-treat principle.

Pain

As illustrated in Fig. 3, there was a significant improvement in short-term knee pain ($\leq$3 months) following IA injection with saline across 32 studies [12,26,28–41,43,44,46,47,49–51,56–60,62,64] involving 1705 patients (SMD = −0.68; 95% CI: −0.78 to −0.57; P < 0.001) with moderate heterogeneity (I^2 = 50%). In addition, there was a significant reduction in long-term knee pain (6–12 months) following IA injection with saline across 19 studies [12,26,27,29,31,35,38,39,42–47,52,54,55,58,62] involving 1445 patients (SMD = −0.61, 95% CI: −0.76 to −0.45, P < 0.001) with substantial amount of heterogeneity (I^2 = 74%; Fig. 4).

Pooled estimates for both short- and long-term pain varied when sensitivity analyses were performed according to blinding of outcome assessors, and number of injections; however, there was considerable overlap of CIs between strata and P values for interaction were all negative.

Adverse events

The incidence of serious and non-serious treatment-related AEs has been summarized in Table 2. Overall, 29 of the included trials [12,26–29,31,32,34,35,37–39,41–44,47,48,53–56,58–64] reported on adverse events, none of which found any serious TRAEs following IA injection with saline.

Discussion

Empirical evidence shows that IA saline injections, often used as a “placebo” or “sham” intervention in clinical trials evaluating IA interventions for knee OA, provide a statistically significant effect of saline on both short- ($\leq$3 months) and long-term (6–12 months) pain relief.

This review has limitations. A major limitation is the poor methodological quality of a majority of the included trials. SMDs were used to summarize pooled data, as various measurement scales were reported between included studies; however, given

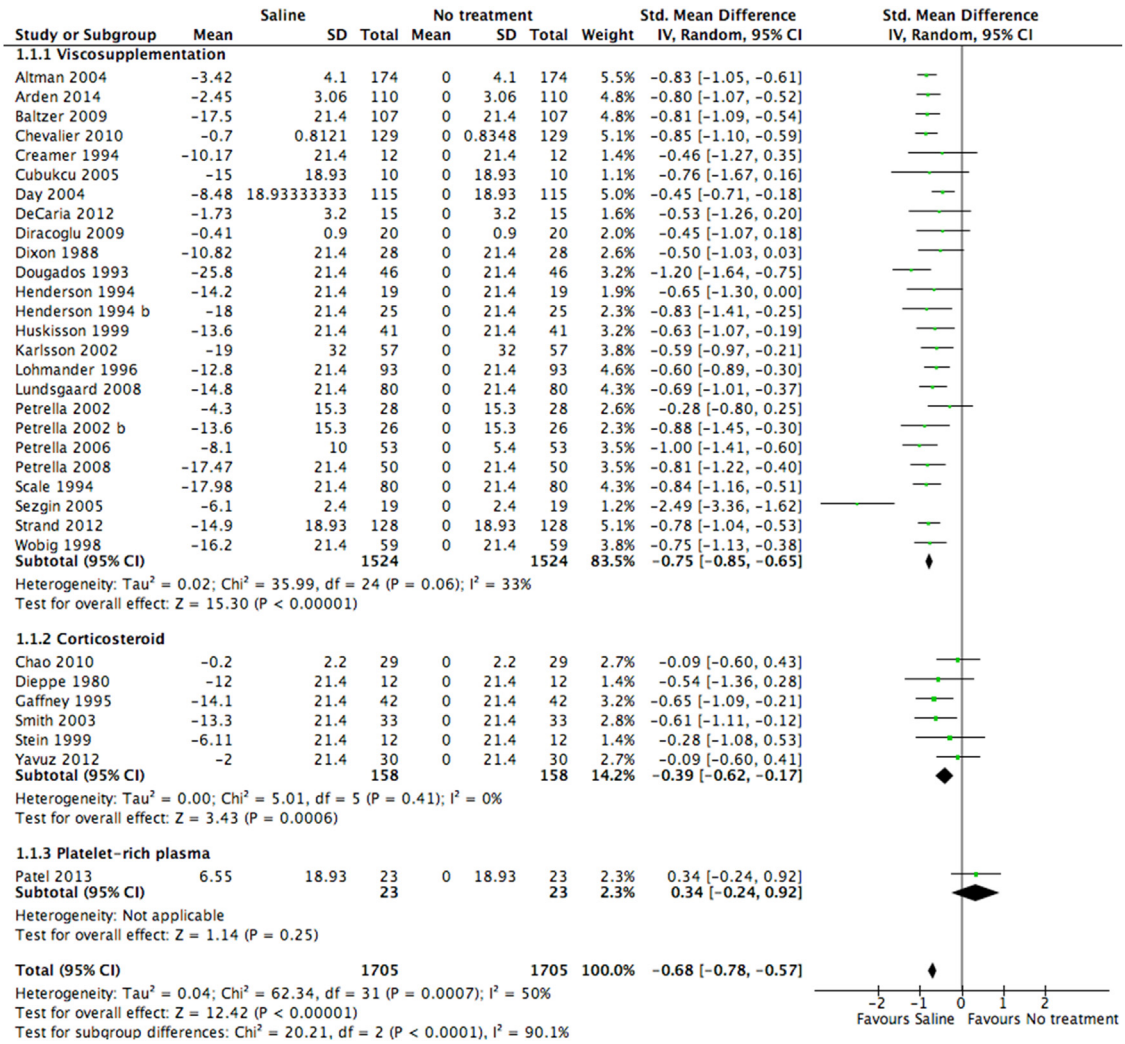

Fig. 3. Standardized mean differences, short-term pain ($\leq$3 months) from baseline

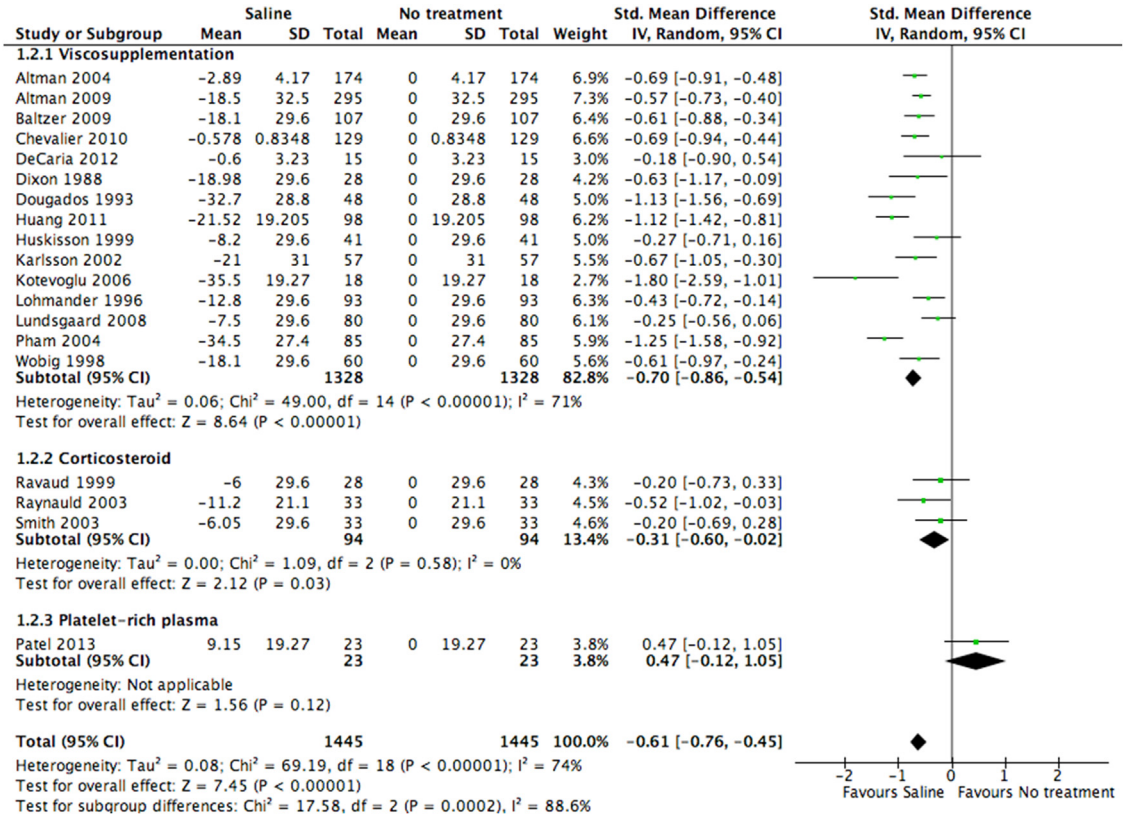

Fig. 4. Standardized mean differences, long-term pain (6–12 months) from baseline

their disease-specific similarities, it is believed this method was appropriate and justified. Studies entered into the meta-analysis included a mixture of change from baseline and final value scores for short- and long-term pain. It is inappropriate to combine final value and change scores using SMDs, since the difference in SD reflects no differences in measurement scale, but rather differences in the reliability of measurements; thus, only change from baseline values for both outcomes were entered [19]. Where data were only reported as absolute values, computed change scores as described previously in the methods for data synthesis were included. For some studies this required transforming the original scale (e.g., 5 point WOMAC Likert scale) to a 100-mm visual analog scale (VAS) to allow for imputation of SDs obtained from other included studies [66], which may be an extreme assumption given that their SDs may not be transformable on the same scale; however, centering our analysis around a single measure would have limited the number of studies available for a pooled analysis. Another practical issue with this method of data synthesis is that baseline and final measurements may have been reported for different numbers of participants due to loss to follow-up. Of the 29 studies entered into the meta-analysis, we were unable to determine the percentage of patients completing follow-up assessments in seven trials [40,45,50,56,57,62,64], and four trials [30,46,54,59] reported a loss to follow-up rate of more than 20%, which may have introduced attrition bias in our estimates. Despite sensitivity testing with a priori hypotheses, we could not explain the high heterogeneity seen in the pooled analysis for long-term pain. We can speculate that this heterogeneity is possibly due to differences in study methodology and execution, variability in patient populations, placebo effect, or a combination of these factors; however this is unclear and not confirmable.

An additional limitation stems from the potential placebo effect from expected improvement within patients treated with intra-articular saline for knee OA. Although this may be a contributing factor to the differences in pain outcomes between no treatment and IA saline, there is a plausible mechanism and sufficient evidence to suggest that beneficial effects of IA saline are not solely due to a placebo effect. We acknowledge that there is a potential for therapeutic effect to be seen within the group receiving no treatment, however we can justify our assumption that this effect would be negligible based on the 0.03, 95% (CI: −0.13 to 0.18) effect size of a "no treatment" group reported within a previous meta-analysis [13].

Implications for practice and research

Therapeutic interventions without active biologics, including irrigation or lavage of a joint with sodium chloride, Ringer, or Ringer and lactate, as well as exploratory arthroscopic procedures involving thorough rinsing of the joint have shown to be effective in alleviating pain in osteoarthritic or trauma patients with painful joints [67–69]. However, the physiological mechanisms contributing to the antinociceptive effects are poorly understood and there is no scientific or biological basis to account for these beneficial effects. It has been postulated that extensive rinsing through fluid lavage removes active pain-signaling or pain-mediating molecules present in the IA joint space, and this technique may also extract proteoglycans and aggrecans from the superficial cartilage matrix compartment, thereby transiently promoting the adhesion of repair cells, which may induce an anti-inflammatory response [70]. Despite controversy between study results of available literature, overall, joint lavage, whether performed by the closed-needle-hole technique or through arthroscopic intervention does appear to be effective for brief periods of time [67,71–73]. IA injection differs from joint lavage, as the fluid used in IA injection is not removed from the joint. The aforementioned mediators and markers removed using lavage thus remain within the joint following IA injection. Aspiration of the joint prior to IA injection

Table 2
Treatment-related adverse events

Study	*N* randomized	*N* analyzed	Serious		Non-serious	
			Number of patients	Number of events	Number of patients	Number of events
Altman et al. [26]	174	174	0	0	15	NR
Altman et al. [27]	295	295	0	0	32	48
Arden et al. [28]	110	110	0	0	6	6
Baltzer et al. [29]	107	107	0	0	30	NR
Chevalier et al. [31]	129	130	0	0	4	NR
Creamer et al. [32]	12	12	NR	NR	NR	7
Day et al. [34]	124	115	0	0	NR	13
DeCaria et al. [35]	15	15	0	0	0	0
Diracoglu et al. [37]	21	20	0	0	0	0
Dixon et al. [38]	33	NA	0	0	0	0
Dougados et al. [39]	55	48	0	0	0	0
Henderson et al. [41]	46	44	0	0	10	NR
Huang et al. [42]	100	98	0	0	0	0
Huskisson et al. [43]	50	41	0	0	0	0
Karlsson et al. [44]	66	66	0	0	0	0
Lundsgaard et al. [47]	84	80	0	0	0	0
Navarro-Sarabia et al. [48]	NA	153	0	0	11	14
Patel et al. [12]	26	23	0	0	0	0
Puhl et al. [53]	107	107	0	0	5	NR
Ravaud et al., 1999 [54]	28	28	0	0	5	0
Raynauld et al. [55]	34	33	0	0	0	0
Scale et al. [56]	40	NA	0	0	0	0
Smith et al. [58]	38	33	0	0	0	0
Stein et al. [59]	17	12	0	0	0	0
Strand et al. [60]	128	128	0	0	33	58
Tamir et al., 2001 [61]	24	20	0	0	11	NR
Wobig et al. [62]	60	NA	0	0	2	NR
Wu et al. [63]	54	51	0	0	0	0
Yavuz et al. [64]	30	30	0	0	0	0

NA, not applicable.

may lead to the removal of these markers prior to introducing the saline into the joint, hypothetically providing a similar effect to lavage.

Detailed and thorough reporting of safety information was not a commonality within the included studies. Safety data should not be overlooked with respect to HA treatment, and future studies should ensure that thorough and accurate safety outcomes are reported.

A recent network meta-analysis assessing the effectiveness of pharmacologic interventions for knee osteoarthritis demonstrated that IA therapies were the most effective treatments for knee OA [74]. When compared with oral placebo, IA placebo was more effective in alleviating pain [effect size = 0.29 (95% credible interval: 0.04–0.54)], an observation that a traditional meta-analysis does not aim to address [74]. This network meta-analysis also showed that none of the oral NSAIDs were significantly superior to IA placebo [74], further strengthening the support for the potential physiological role of IA saline. This finding raises important questions about the extent to which this therapeutic effect is attributable to a true placebo response versus physiologic effects after directly injecting a fluid into the knee joint [74], and about the potential for IA fluids to influence nociceptive response and have pathophysiologic benefits [74,75], especially if any fluid was aspirated from the knee joint [76–78].

Conclusions

IA saline injection, though often used as a “placebo” treatment in clinical trials for knee OA has demonstrated the potential to provide substantial pain relief in a number of studies. Pain relief observed with IA saline should prompt health care providers to consider the additional effectiveness of current IA treatments that use saline comparators in clinical studies, and challenges of identifying IA saline injection as a “placebo.”

Appendix 1

Search strategy for MEDLINE (adapted for EMBASE)

1 osteoarthritis/
2 osteoarthritis.mp.
3 knee Joint/
4 knee Joint.mp.
5 1 or 2
6 3 or 4
7 5 and 6
8 osteoarthritis, knee/
9 7 or 8
10 exp Injections, Intra-Articular/
11 viscosupplements/
12 viscosupplement$.mp.
13 hyaluronic Acid/
14 hyaluronic Acid.mp.
15 hyaluron$.mp.
16 hylan.mp.
17 healonid.mp.
18 hyalgan.mp.
19 hylectin.mp.
20 hyalflex.mp.
21 hylartil.mp.
22 replasyn.mp.
23 suplasyn.mp.
24 polyreumin.mp.
25 nrd 101.mp.

26 artz$.mp.
27 slm 10.mp.
28 neovisc.mp.
29 orthovisc.mp.
30 adant.mp.
31 etapharm.mp.
32 or/10-31
33 9 and 32
34 randomized controlled trial.pt.
35 randomized.mp.
36 placebo.mp.
37 or/34-36
38 33 and 37
39 limit 38 to animals
40 limit 39 to human
41 39 not 40
42 38 not 41

Search strategy for MEDLINE (adapted for EMBASE)—Corticosteroid and PRP

1 osteoarthritis/
2 osteoarthritis.mp.
3 knee joint/
4 knee.mp.
5 1 or 2
6 3 or 4
7 5 and 6
8 osteoarthritis, knee/
9 7 or 8
10 corticosteroid$.mp.
11 glucocorticoid$.mp.
12 hydroxycorticosteroid$.mp.
13 exp adrenal cortex hormones/
14 corticoid$.mp.
15 ketosteroid$.mp.
16 androstenedione.mp.
17 methylprednisolone acetate.mp.
18 triamcinolone acetate.mp.
19 betamethasone acetate.mp.
20 triamcinolone hexacetonide.mp.
21 dexamethasone.mp.
22 platelet-rich plasma/
23 platelet-rich plasma.mp.
24 platelet rich plasma.mp.
25 platelet transfusion/
26 platelet transfusion.mp.
27 PRP.mp.
28 blood transfusion, autologous/
29 plasma rich.mp.
30 autologous conditioned plasma.mp.
31 autologous blood.mp.
32 or/10-31
33 9 and 32
34 randomized controlled trial.pt.
35 randomized.mp.
36 placebo.mp.
37 or/34-36
38 33 and 37
39 limit 38 to animals
40 limit 39 to humans
41 39 not 40
42 38 not 41

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