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AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2018;■:■■■-■■■

META-ANALYSIS

Comparative Effectiveness of Injection Therapies in Rotator Cuff Tendinopathy: A Systematic Review, Pairwise and Network Meta-analysis of Randomized Controlled Trials

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Abstract

Objective: To compare the effectiveness of diverse injections in patients with rotator cuff tendinopathy using pairwise and network meta-analysis.

Data Sources: PubMed, EMBASE, Scopus, and Cochrane Library were searched for studies published up to September 31, 2017.

Study Selection: We included all published or unpublished randomized controlled trials (RCTs) comparing diverse injections including corticosteroid, nonsteroidal anti-inflammatory drugs, hyaluronic acid, botulinum toxin, platelet-rich plasma (PRP), and prolotherapy in patients with rotator cuff tendinopathy. Among the 1495 records screened, 18 studies were included in the meta-analysis.

Data Extraction: The quality of RCTs was assessed with Cochrane Risk of Bias Tool by 2 independent raters. The primary outcome was pain reduction, and the secondary outcome was functional improvement.

Data Synthesis: Standardized mean difference (SMD) was used for pairwise and network meta-analysis. In pairwise meta-analysis, corticosteroid was more effective only in the short term in both pain reduction and functional improvement. Network meta-analysis indicated that prolotherapy significantly reduced pain compared with placebo in the long term (over 24wk; SMD: 2.63; 95% confidence interval [CI], 1.88-3.38); meanwhile PRP significantly improved shoulder function compared with placebo in the long term (over 24wk; SMD: 0.44; 95% CI, 0.05-0.84).

Conclusions: For patients with rotator cuff tendinopathy, corticosteroid plays a role in the short term (3-6wk) but not in long-term (over 24wk) pain reduction and functional improvement. By contrast, PRP and prolotherapy may yield better outcomes in the long term (over 24wk). On account of heterogeneity, interpreting these results with caution is warranted.

Archives of Physical Medicine and Rehabilitation 2018;■:■■■-■■■

Rotator cuff tendinopathy, the most common cause of shoulder pain, is a chronic degenerative or overuse disorder in the absence of active inflammation.[1] Exercise therapy is widely used in rotator cuff tendinopathy, and the evidence for its effectiveness has been reported in many systematic reviews in these years.[2-4] Furthermore, Steuri et al suggested exercise as the first-choice therapy for patients with shoulder impingement symptoms.[5] As an adjunct therapy to exercise therapy, various injection options are available in clinical practice as symptomatic treatments.[6] However, few evidence-based guidelines provide recommendations for choosing among different injection substances in rotator cuff tendinopathy.

Since the last systematic review in 2010 by Coombes et al,[6] 13 prospective randomized controlled trials (RCTs) of injection therapies for rotator cuff tendinopathy have been performed. The medications used in these trials encompassed corticosteroid, nonsteroidal anti-inflammatory drugs (NSAIDs), hyaluronic acid (HA), botulinum toxin (BTX), platelet-rich plasma (PRP), and prolotherapy (injection of entheses with hypertonic dextrose).[7-19] Among these medications, corticosteroid is the most widely used, but it is a debatable substance due to the lack of inflammation in tendinopathy. Recent meta-analyses have suggested either unclear

Disclosures: none.

0003-9993/18/$36 - see front matter © 2018 by the American Congress of Rehabilitation Medicine
https://doi.org/10.1016/j.apmr.2018.06.028

or small transient effects of corticosteroid injections in rotator cuff tendinopathy.[6,20] On the other hand, PRP showed a marginal clinical superiority without reaching the significant level at a 6-month follow-up in the latest meta-analysis.[21] Other injection therapies, such as NSAIDs, HA, BTX, and prolotherapy, for rotator cuff tendinopathy were never studied in meta-analyses.

Understanding the comparative efficacy and toxicity of these medications is expected to help patients and physicians to formulate treatment strategies for rotator cuff tendinopathy. However, obtaining information about the relative effectiveness of these treatments from literature is difficult, partly because of few available head-to-head comparison studies and inability of traditional pairwise meta-analysis to integrate all evidence from several comparators. Consequently, in addition to pairwise meta-analysis, we performed network meta-analysis, which is an advanced method for comparisons of multiple treatments simultaneously. Network meta-analysis combines both direct and indirect evidence into the same statistical framework, so it can yield more robust results than traditional pairwise meta-analysis. For treatments that have not been directly compared in the literature, network meta-analysis uses indirect evidence to estimate the relative effects between these treatments.[22]

Therefore, to provide a guide for treatment decision making between patients and physicians, we aimed to compare the effectiveness of diverse injection therapies in patients with rotator cuff tendinopathy using both pairwise and network meta-analysis.

Methods

All methods for the systematic review and meta-analysis in this study were accomplished according to recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses.[22]

Study identification and search method

Our search was from the earliest records to September 31, 2017. We identified eligible trials by searching 4 electronic databases including PubMed, EMBASE, Scopus, The Cochrane Collaboration Central Register of Controlled Clinical Trials, and Cochrane Database of Systematic Reviews, as well as bibliographies of related trials. Relevant systematic reviews were manually searched for further references. The relevant gray literature was searched using ClinicalTrials.gov, OpenSIGLE (www.opengrey.eu), and the New York Academy of Medicine Grey Literature Report (www.greylit.org). The search was not limited to English language articles. Key terms were entered in all electronic database searches. (Detailed search strategies are listed in supplementary appendix S1, available online only at http://www.archives-pmr.org/).

List of abbreviations:

BTX	**botulinum toxin**
CI	**confidence interval**
HA	**hyaluronic acid**
NSAID	**nonsteroidal anti-inflammatory drug**
PRP	**platelet-rich plasma**
RCT	**randomized controlled trial**
SMD	**standardized mean difference**

Eligibility criteria

Types of studies

We included all published or unpublished RCTs. Studies with quasiexperimental trials, observational studies, case series, single-arm or animal studies were excluded.

Participants

Studies were included where adult participants were diagnosed with rotator cuff tendinopathy by either clinical or image evaluation. The definition of rotator cuff tendinopathy was based on a previous systematic review.[6,23] We excluded studies with participants of adhesive capsulitis, trauma, full-thickness tears, calcific rotator cuff disease, or rheumatological disease.

Interventions

Allocated groups in studies treated with at least 2 arms of injection therapies (including corticosteroid, NSAIDs, HA, BTX, PRP, prolotherapy, placebo) were eligible for inclusion. The number or guidance method of injection had no restriction.

Outcomes

The primary outcome was pain reduction. The secondary outcome was functional improvement of the shoulder, evaluated by the function or disability scale. All validated measures of shoulder function and pain were feasible. The postinterventional follow-up time points were allocated into 3 groups: 3-6 weeks (short term), 12 weeks (medium term), and over 24 weeks (long term).

Data extraction

Eligibility of all related studies was assessed and reviewed for inclusion by the first and second authors independently. We used interrater reliability with the kappa statistic for strength of interrater agreement. Disagreements were resolved by a consensus-based discussion with the corresponding author. Number of patients, age, symptom duration, injection interval, dosage, guidance method and injection location, cointerventions, follow-up, and adverse effects were obtained from included trials. Mean, SD, and number of participants were extracted for outcome measurements. If the data were not extractable or expressed in other form instead of mean and SD, we contacted the corresponding author to request the information by e-mail. If the corresponding author did not reply, we contacted the author again 3 weeks later and repeated the above request for 2 further times.

Risk of bias assessment

The quality of RCTs was evaluated with Cochrane Risk of Bias Tool, as described in the Cochrane Handbook for Systematic Reviews of Interventions.[24] There are 7 items in the 5 major domains of bias (selection bias, performance bias, detection bias, attrition bias, reporting bias) in addition to a generalized category of other biases. All items were assessed by 2 authors independently. Risk of bias for each outcome within a study (across domains) and each outcome across the studies were rated as *low risk*, *unclear risk*, or *high risk* of bias.[24] We used interrater reliability (the κ statistic) to evaluate the strength for the risk of bias assessments. The disputes

were discussed with the corresponding author. Any discrepancies were resolved through consensus.

Data synthesis and analysis

The outcome change was used to reveal the effectiveness of each injection, calculated as the difference between baseline and post-injection outcome: $outcome_{baseline} - outcome_{postinjection}$. Because of the differences between outcome scales or questionnaire measures, we adopted the standardized mean difference (SMD) for sufficient comparability of outcome change between 2 different injection therapies. For instance, the SMD of corticosteroid versus placebo was presented as ($outcome\ change_{corticosteroid} - outcome\ change_{placebo}$)/pooled $SD_{between\text{-}injections}$.[24,25] Formulation of pooled $SD_{between\text{-}injections}$ is described in supplementary appendix S1. The positive value of the SMD indicated that the effect of corticosteroid was more beneficial than that of the placebo.[24,25]

We used the random-effects model to pool the SMD with 95% confidence interval (CI) in pairwise meta-analysis. The heterogeneity was synthesized by I^2 and Cochran's Q methods. I^2 over 50% was recognized as significant heterogeneity.[24] Publication bias, defined as the tendency for positive trials to be published and for negative and null trials to be unpublished, was assessed with funnel plot and Egger's test.[26] Sensitivity analysis was executed by excluding low-quality studies.

Frequentist approach to random-effects network meta-analysis was used and implemented in the statistical software package Stata.[27] The restricted maximum likelihood method was used for model estimation. The comparison of model fit was performed using the likelihood ratio test, such as the comparison between random- and fixed-effects models. When the likelihood ratio test is statistically significant, the model with greater parameters is preferred to the model with fewer ones.

The geometry of the network was shaped by the studies underlying each comparison, and it reflects rational choices for treatment comparison.[22] As a result, using the geometry of network allows us to explore comparator preference bias, such as how long a treatment has been available, the perceived effectiveness and safety of a treatment, and which treatment has been considered the standard or reference therapy.

We used network meta-regression to examine the relation of age and symptom duration to reduction in pain and functional recovery of the shoulder. We further evaluated the potential inconsistency within the network meta-analyses, including inconsistency between direct and indirect evidence for each treatment contrast across the entire network, inconsistency between direct and indirect evidence within a closed loop, and the inconsistency between studies with different sets of treatments for each treatment contrast. The Wald test was then used to evaluate the overall inconsistency within the network meta-analysis.[28,29]

Analysis was performed using Stata 14.0[a] and Review Manager 5.3.[b] All *P* values were 2-sided, and the significance level was set at 5% except for the testing of between-study heterogeneity.

Results

Characteristics of included studies

We identified 1495 studies from electronic databases, and 811 citations were screened by title and abstract after the removal of duplicates. A total of 32 full-text articles were evaluated for eligibility (fig 1). We excluded 3 non-RCTs,[30-32] 2 studies comparing corticosteroid and hyaluronidase with corticosteroid,[33,34] 3 RCTs with other etiologies (posttraumatic impingement, rotator cuff calcific tendinosis, chronic subacromial bursitis)[35-37] and 1 RCT with duplicated data published by the same author[38] after full manuscript review. All eligible articles were written in English, although the search was not limited to English language.

Twenty-three RCTs were included in qualitative synthesis (table 1).[7-19,39-48] In 5 studies, the presented data were not extractable, either with median and interquartile range or missing.[41,44,45,47,48] We contacted the corresponding authors, and the author of 1 trial replied with available summarized data.[16] Finally, 18 of the RCTs in qualitative synthesis were included in the final meta-analysis.[7-19,39,40,42,43,46] The comparison between various injection therapies and placebo in the pairwise meta-analysis consisted of 13 studies with 734 patients; the same comparison in the network meta-analysis consisted of 18 studies with 996 patients (see table 1).

The mean age of participants in each study from the 23 RCTs ranged from 39.1 to 61.3 years. The symptom duration varied across studies, ranging from 0.8 to 110 months. The sample size of each arm in the studies ranged from 12 to 55 patients. The inclusion criteria were diverse regarding the diagnosed physical examinations or radiography methods. MRI was used for diagnosis in 5 studies[9,10,16,17,39] and ultrasound in 2 RCTs.[18,19] The outcomes were extracted at baseline and different follow-up time points in most of the studies. Regarding guidance methods of injections, 16 studies used landmark guidance, 6 trials used ultrasound guidance,[7,12,14-16,19] and 1 RCT used arthroscopy guidance.[9] As to the location of injection, 19 RCTs performed subacromial injection, 2 supraspinatus tendon injection,[15,41] 1 periarticular injection,[47] and 1 painful enthuses.[18] The main medication and excipients of every injection therapy and frequency of interventions are summarized in table 1.

Risk of bias assessment

The risk of bias summary and graph are presented in supplemental figs S1 and S2(available online only at http://www.archives-pmr.org/) where risk of bias for both outcomes (pain and function) within a study was identical. Interrater reliability was substantial with value of kappa 0.706 (95% CI, 0.538-0.874). A total of 13 included studies generated low risk of bias in random sequence, and only 9 trials used a suitable method in allocation concealment (see supplemental fig S1). With reference to the blinding of participants and personnel, 5 studies[10,15,17,19,39] were rated as high risk because blood drawing was necessary in PRP[15,17] and blinding the patients was difficult. Most of the studies (n=17) presented a successful method of outcome assessor blinding. Fourteen trials reported adequate description for incomplete results, earning a low risk of attrition bias (see supplemental fig S1). Only 2 RCTs were unclear in presenting reporting bias.[12,17]

Risk of bias for primary outcome (pain reduction) across the studies was rated as low or unclear risk of bias according to most information from studies, and risk of bias for secondary outcome (functional improvement) across the studies was rated as low or unclear risk of bias as well.

Results of pairwise and network meta-analysis

The forest plots of pairwise meta-analysis between active treatments (botulinum, HA, NSAID, PRP, corticosteroid) and placebo

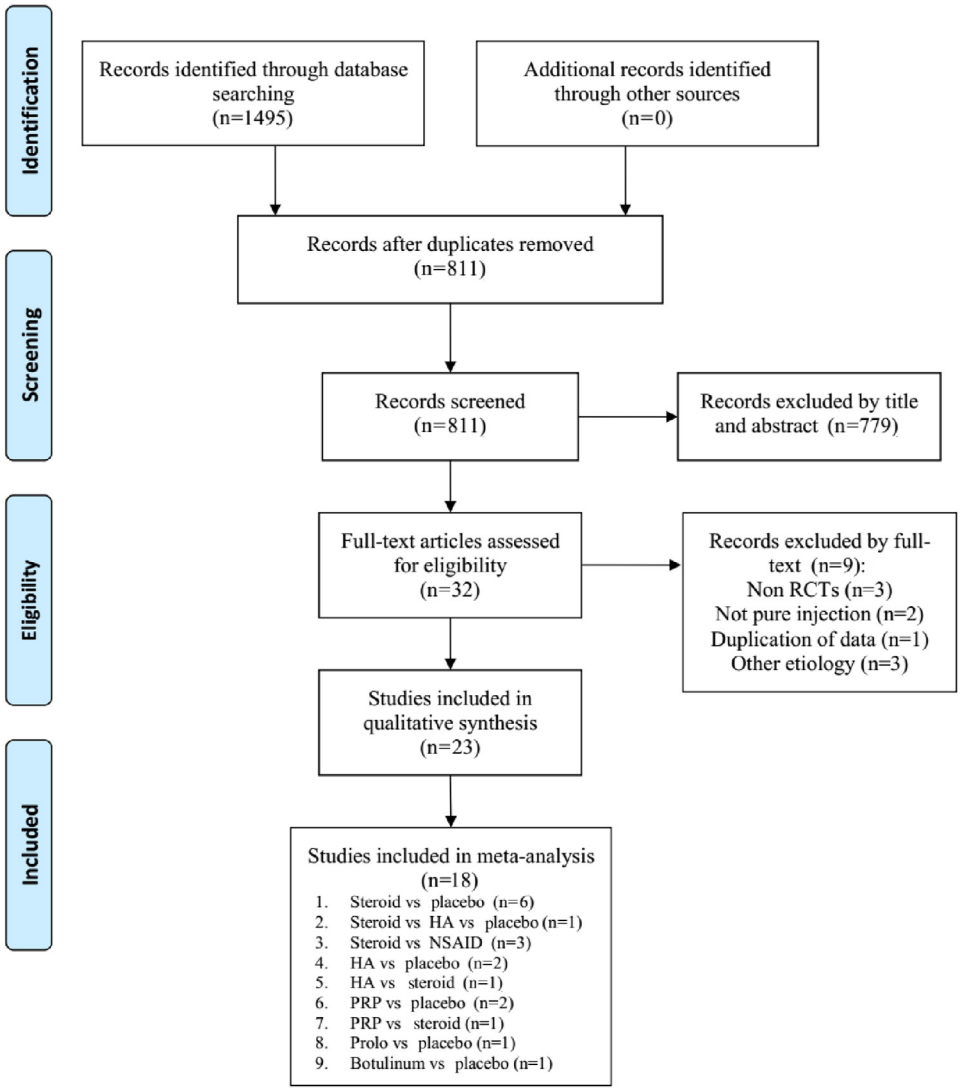

Fig 1 A flow diagram of study inclusions. Abbreviations: Prolo, prolotherapy; PT, physiotherapy.

are presented in supplemental figs S3-S8 (available online only at http://www.archives-pmr.org/). In network meta-analysis, supplemental fig S9 (available online only at http://www.archives-pmr.org/) revealed the network graph. The forest plot of network meta-analysis is shown in fig 2; tables 2 and 3 and supplemental tables S1-S4 (available online only at http://www.archives-pmr.org/) are league tables of pairwise and network meta-analyses.

Primary outcome (pain reduction)

In the extraction of primary outcome data, we used the score of overall pain. If resting pain, activity pain, and night pain were only available, we adopted activity pain to represent the real clinical condition.[39] In the pairwise meta-analysis, the effectiveness of corticosteroid was better than that of the placebo only in the short term (3-6wk; SMD: 0.51; 95% CI, 0.01-1.01) (see supplemental fig S3); the effectiveness of prolotherapy was better than that of the placebo only in the long term (over 24wk; SMD: 2.63; 95% CI, 1.88-3.38) (see supplemental fig S5).

With reference to the network meta-analysis, the difference between active treatments (HA, NSAID, PRP, corticosteroid) and placebo was not significant in the short and medium term (see fig 2). However, prolotherapy significantly reduced pain than placebo in the long term (SMD: 2.63) (see fig 2). Publication bias was detected with statistically significant Egger's test in the short term in pain reduction (supplemental fig S10, available online only at http://www.archives-pmr.org/).

Secondary outcome (functional improvement)

Regarding the secondary outcome, we selected the constant score in 1 trial[17] and Disabilities of the Arm, Shoulder and Hand Score in the other,[40] in which more than 1 validated shoulder function scale was available. In the pairwise meta-analysis, corticosteroid was beneficial than placebo only in the short term (3-6wk; SMD: 0.33; 95% CI, 0.00-0.67) (see supplemental fig S6). PRP showed superiority to placebo in functional improvement at long-term follow-up (over 24wk; SMD: 0.54; 95% CI, 0.06−1.02) (see supplemental fig S8).

Table 1 Summary: the characteristics of included studies

Reference	Study/LOE	Interventions	Inclusion Criteria	Number	Age	Symptom Duration (mo)	Injection/ Interval	Rx Dose/Guidance Method and Injection Location	Cointerventions	Outcome Measure	Follow-up wk	Adverse Effect
Withrington et al, 1985[41]	RCT/level 1	Corticosteroid vs placebo	Clinically diagnosed supraspinatus tendonitis	12/13	61.3/55.3	4.1/4.6	1/NA	Steroid: 80-mg methylprednisolone, 2 mL of 2 % lignocaine, total 4 mL Placebo: 4 mL of 0.9% saline/method: landmark guided; supraspinatus tendon	No formal PT. No NSAID or Paramol.	VAS	2, 8	No mention
Petri et al, 1987[42]	RCT/level 1	Corticosteroid vs placebo	Shoulder pain with at least 2 of painful abduction, painful arc, tenderness over supraspinatus tendon	25/25	No mention	3.9	1/NA	Steroid: 40-mg triamcinolone (1 mL), 3 mL of 1% lidocaine, placebo tablets Placebo: 4 mL of 1% lidocaines, placebo tablets/method: landmark guided; subacromial	1. ROM exercise, heat and cold	Pain score, limitation of function, ROM	4	Mild
Adebajo et al, 1990[43]	RCT/level 1	Corticosteroid vs placebo	Acute RC tendinitis of, pain with resisted movement, normal passive ROM	20/20	53	2.2/2.1	1/NA	Steroid: 80-mg triamcinolone, 2 mL of 0·5% lidocaine, placebo tablets Placebo: 3 mL of 0.5% lidocaine, placebo tablets/method: landmark guided; subacromial	1. Pendular or wall climb exercises	VAS	4	No mention
Vecchio et al, 1993[44]	RCT/level 1	Corticosteroid vs placebo	Clinical diagnosed acute RC tendinitis, pain with resisted movement, normal passive ROM	28/27	56/56.5	1.3/1	1/NA	Steroid: 40-mg methylprednisolone (1 mL), 1 mL of 1% lidocaine Placebo: 1 mL of 1% lidocaine/method: landmark guided; subacromial	Pendular and wall climb exercises	VAS	2, 4, 12	No mention
Blair et al, 1996[45]	RCT/level 1	Corticosteroid vs placebo	Clinically diagnosed subacromial impingement syndrome	19/21	56/57	8	1/NA	Steroid: 80-mg triamcinolone (2 mL), 4 mL of 1% lidocaine Placebo: 6 mL of 1% lidocaine/method: landmark guided; subacromial	PT (passive, assisted, active, or Theraband strength exercise)	Pain score (0-4), ROM	12-55	No complication

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Table 1 (*continued*)

Reference	Study/LOE	Interventions	Inclusion Criteria	Number	Age	Symptom Duration (mo)	Injection/ Interval	Rx Dose/Guidance Method and Injection Location	Cointerventions	Outcome Measure	Follow-up wk	Adverse Effect
Akgün et al, 2004[39]	RCT/level 1	Corticosteroid vs placebo	Clinically diagnosed subacromial impingement syndrome, MRI diagnosis (stage 2), injection test	16/16	48.5/47.5	19/11.8	2/10 days	Steroid: 40-mg methylprednisolone, 10 mL of 1% lidocaine Placebo: 10mL of 1% lidocaine/method: landmark guided; subacromial	1. Pendular or strength or stretch exercises 2. 500-mg naproxen	VAS, constant score, ROM	4, 12	No complication
Alvarez et al, 2005[40]	RCT/level 1	Corticosteroid vs placebo	Chronic tendinosis or partial cuff tear	30/28	50/46	45.6/30	1/NA	Steroid: 6-mg betamethasone (1 mL), 4 mL of 2% xylocaine Placebo: 5mL of 2% xylocaine/method: landmark guided; subacromial	No mention	VAS, DASH, ASES, WORC, ROM	2, 6, 12, 24	No mention
Álvarez-Nemegyei et al, 2008[46]	RCT/level 1	Corticosteroid vs placebo	Subacromial impingement syndrome (RC tendinitis), positive Neer's injection test	27/29	53/52	2/0.8	1/NA	Steroid: 80-mg methylprednisolone (2 mL), 1 mL of 1% lidocaine Placebo: 3 mL of 1% lidocaine/method: landmark guided; subacromial	Standard PT and NSAID	VAS, SDQ, ROM	4, 8, 12, 24	Mild
Hong et al, 2011[7]	RCT/level 1	Corticosteroid vs placebo	Clinically diagnosed impingement syndrome or RC lesions	27/27	50.8/51	8.9/8.6	1/NA	Steroid: 4 mL of 40-mg of triamcinolone Placebo: 4 mL of 1% lidocaine/method: ultrasound guided; subacromial	Exercise program, no additional medications	VAS, SDQ, ROM	2, 4, 8	Mild
Karthikeyan et al, 2010[48]	RCT/level 1	Corticosteroid vs NSAID	Clinically diagnosed subacromial impingement syndrome	26/30	60/58	8/10	1/NA	Steroid: 40-mg methylprednisolone, 5 mL of 1% lignocaine NSAID: 20-mg tenoxicam, 5 mL of 1% lignocaine/ method: landmark guided; subacromial	Standardized outpatient physiotherapy	Constant score, DASH, OSS	2, 4, 6	No complication

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Table 1 (*continued*)

Reference	Study/LOE	Interventions	Inclusion Criteria	Number	Age	Symptom Duration (mo)	Injection/ Interval	Rx Dose/Guidance Method and Injection Location	Cointerventions	Outcome Measure	Follow-up wk	Adverse Effect
Min et al, 2013[8]	RCT/level 1	Corticosteroid vs NSAID	Clinically diagnosed subacromial impingement syndrome; shoulder pain with passive and/or active abduction	15/17	39.6/39.1	>1	1/NA	Steroid: 40-mg triamcinolone, 6 mL of 1% lidocaine with epinephrine NSAID: 60-mg ketorolac, 6 mL of 1% lidocaine with epinephrine/method: landmark guided; subacromial	No mention	VAS, UCLA shoulder rating scale, ROM	4	Mild
Çift et al, 2015[9]	RCT/level 1	Corticosteroid vs NSAID	Clinically diagnosed shoulder impingement syndrome or MRI-diagnosed RC tendinitis	20/20	46.5/45.3	No mention	Steroid: 1/ NA; NSAID: 3/1W	Steroid: methylprednisolone (Depo-Medrol) NSAID: tenoxicam (Oksamen)/method: arthroscopy guided; subacromial	Home-based exercise program	VAS, DASH, ROM	6, 52	Mild
Aksakal et al, 2017[10]	RCT/level 1	Corticosteroid vs NSAID	Clinically and MRI-diagnosed subacromial impingement syndrome	35/35	53/53	0.8	1/NA	Steroid: 1 mL of betamethasone (9.06 mg) NSAID: 2 mL of (8 mg) lornoxicam/method: landmark guided; subacromial	No mention	Constant score, UCLA questionnaires	2, 4, 6	No complication
Itzkowitch et al, 1996[47]	RCT/level 1	NSAID vs placebo	Clinically diagnosed RC tendinitis without radiograph pathology	40/40	56.3/60	>3	4/1 wk	NSAID: tenoxicam 20 mg 2 mL Placebo: 2-mL excipient/ method: landmark guided; periarticular	Analgesic, NSAIDs, PT were prohibited	VAS, clinical global impression	Day 1, 1 wk, 2 wk, 3 wk, 4 wk	Mild
Chou et al, 2010[11]	RCT/level 1	Hyaluronic acid vs placebo	Clinically and imaging-diagnosed RC pathology without a complete tear	25/26	51.2/52.4	12.5/11.7	5/1 wk	Hyaluronic acid: ARTZ dispo, 25 mg Placebo: 0.9% normal saline 2.5 mL/method: landmark guided; subacromial	No mention	VAS, constant score	1-6, 12	No complication

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Table 1 (*continued*)

Reference	Study/LOE	Interventions	Inclusion Criteria	Number	Age	Symptom Duration (mo)	Injection/ Interval	Rx Dose/Guidance Method and Injection Location	Cointerventions	Outcome Measure	Follow-up wk	Adverse Effect
Kim et al, 2012[12]	RCT/level 1	Hyaluronic acid vs corticosteroid	Subacromial impingement syndrome without a RC tear	38/42	55.9/54.1	>3	HA: 3/1 wk; steroid: 1/NA	Hyaluronic acid: Hyruan plus: 300,000,000 dalton molecular weight, 20 mg, 2 mL Steroid: dexamethasone 5 mg 1 mL, lidocaine 2% 4 mL, 5 mL of saline/ method: ultrasound guided; subacromial	PT: RC strengthening exercise	VAS, ASES, ROM	3, 6, 12	No severe complication
Penning et al, 2012[13]	RCT/level 1	Hyaluronic acid vs corticosteroid vs placebo	Clinically diagnosed shoulder impingement syndrome	51/53/55	53/52/54	>1.5	3/3W	Hyaluronic acid: 2 mL of hyaluronic acid (Ostenil), 8 mL of lidocaine 1% Steroid: 20-mg triamcinolone (2 mL), 8 mL of lidocaine 1% Placebo: 8 mL of lidocaine 1%, 2 mL of NaCl 0.9%/ method: landmark guided; subacromial	No associated treatment allowed	VAS, constant score	3, 6, 12, 26	Mild
Moghtaderi et al, 2013[14]	RCT/level 1	Hyaluronic acid vs placebo	Clinically and ultrasound diagnosed RC pathology without a complete tear	20/20	No mention	>6	3/1W	Hyaluronic acid: Fermathron 20 mg, 2 mL Placebo: 0.9% normal saline 2 mL/method: ultrasound guided; subacromial	No mention	VAS, constant score	1-3, 12	No complication
Rha et al, 2013[15]	RCT/level 1	PRP vs placebo	Supraspinatus tendon lesion (tendinosis or a partial tear)	20/19	52.2/53.9	9.6/9.2	2/4W	PRP: Prosys 3 mL Placebo: dry needling/ method: ultrasound guided; supraspinatous tendon	Self-exercise rehabilitation program	VAS, SPADI, ROM	2, 4, 6, 12, 24	No complication
Kesikburun et al, 2013[16]	RCT/level 1	PRP vs placebo	RC tendinosis or partial tear diagnosed by MRI	20/20	45.5/51.4	8.5/10	1/NA	PRP: 5 mL (GPS III Platelet Separation System) Placebo: 5 mL of saline/ method: ultrasound guided; subacromial	Exercise program (supervised by PT), then home program	VAS, SPADI, WORC, ROM	3, 6, 12, 24, 48	No complication
Shams et al, 2016[17]	RCT/level 1	PRP vs corticosteroid	Painful partial RC tears diagnosed by MRI	20/20	52/50	>3	1/NA	PRP: MyCells Autologous Platelet System Steroid: 40-mg triamcinolone/method: landmark guided; subacromial	Home exercises without PT	VAS, constant score, ASES, SST	6, 12, 24	No mention

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Table 1 (*continued*)

Reference	Study/LOE	Interventions	Inclusion Criteria	Number	Age	Symptom Duration (mo)	Injection/ Interval	Rx Dose/Guidance Method and Injection Location	Cointerventions	Outcome Measure	Follow-up wk	Adverse Effect
Bertrand et al, 2016[18]	RCT/level 1	Prolotherapy vs placebo	RC tendinopathy, ultrasound-confirmed supraspinatus tendinosis/ partial tear	27/27	53.8/49	61/101	3/4W	Prolotherapy: 25% dextrose/0.1% lidocaine/saline onto painful entheses Placebo: 0.1% lidocaine/ saline superficial to painful enthuses/ method: landmark guided; painful enthuses	Programmed PT	VAS, USPRS	12, 36	No complication
Lee et al, 2011[19]	RCT/level 1	Botulinum vs steroid	Clinically diagnosed shoulder impingement syndrome or subacromial bursitis	31/30	57.9/55.8	8.2	1/NA	Botulinum: Myobloc 2500 U (0.5 mL), 0.5% lidocaine 2 mL Steroid: triamcinolone 40 mg, lidocaine 2 mL/ method: ultrasound guided; subacromial	No PT or prescribed medication	NRS, DASH, active ROM	4, 12	Mild

Abbreviations: ASES, American Shoulder and Elbow Surgeons Shoulder Score; DASH, Disabilities of the Arm, Shoulder and Hand Score; LOE, level of evidence; MRI, magnetic resonance imaging; NRS, numeric rating scale; OSS, Oxford Shoulder Score; PT, physiotherapy; RC, rotator cuff; ROM, range of motion; Rx, treatment; SDQ, Shoulder Disability Questionnaire; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; UCLA, University of California Los Angeles; USPRS, Ultrasound Shoulder Pathology Rating Scale; VAS, visual analog scale; WORC, Western Ontario Rotator Cuff Index.

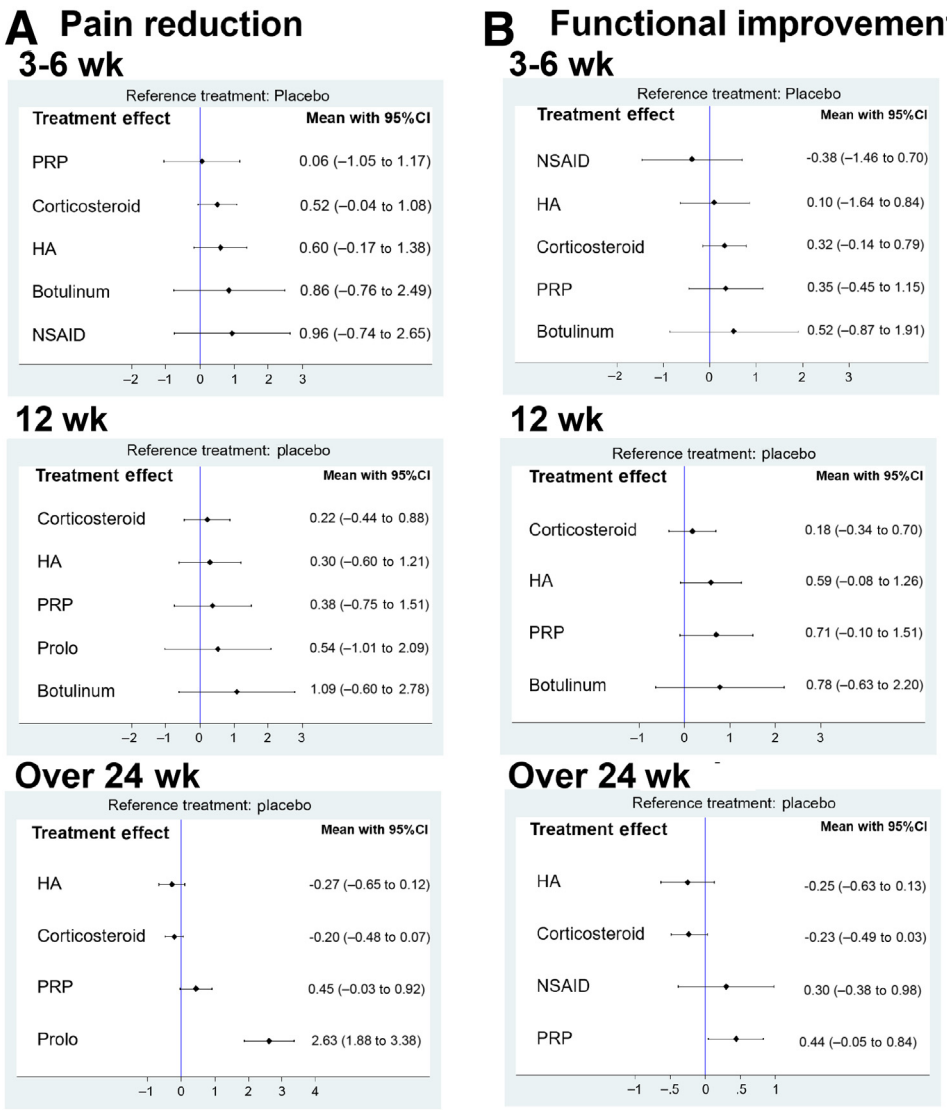

Fig 2 A forest plot of network meta-analysis: comparison between injection therapies in functional improvement (A) and pain reduction (B) at 3-6 weeks (short term), 12 weeks (medium term), and over 24 weeks (long term). Abbreviation: Prolo, prolotherapy.

In network meta-analysis, PRP significantly recovered the function of the shoulder compared with placebo in the long term (over 24wk; SMD: 0.44; 95% CI, 0.05-0.84) (see fig 2). Egger's test for publication bias was not statistically significant (supplemental fig S11, available online only at http://www.archives-pmr.org/).

Ranking—cumulative probability

Based on the simulation of ranking probability (supplemental fig S12, available online only at http://www.archives-pmr.org/), the best treatment choice could not be decided based on pain reduction in the short and medium term. Nevertheless, prolotherapy seemed to be the best treatment according to ranking probability in the long term, where the probability was 100%.

In functional improvement, PRP was ranked as first therapeutic option in the long term, where the probabilities of the best treatment were 66.9% (see supplemental fig S12).

Inconsistency analysis

Loop and design inconsistency were not detected in our model of network meta-analysis (supplemental table S5, available online only at http://www.archives-pmr.org/).

Meta-regression

We performed meta-regression to examine the effect of symptom duration and age of patients on study effect size (see supplemental table S5). In the domain of pain reduction, there was no association between symptom duration and effect size or age of patients and effect size (see supplemental table S5). Regarding the average symptom duration of patients, it significantly affected the differences in shoulder functional improvement between NSAID and placebo in the short term (3-6wk) (see supplemental table S5).

Table 2 Result of pairwise and network meta-analysis for pain reduction at short term (3-6wk)

Comparison Between Two Injections	Pairwise Meta-analysis	Network Meta-analysis
Corticosteroid vs		
PRP	ND	0.46 (−0.78, 1.70)
NSAID	−0.44 (−1.14, 0.27)	−0.44 (−2.04, 1.16)
HA	0.02 (−1.34, 1.38)	−0.09 (−0.89, 0.72)
Botulinum	−0.34 (−0.86, 0.18)	−0.34 (−1.87, 1.18)
placebo	0.51 (0.01, 1.01)*	0.52 (−0.04, 1.08)
PRP vs		
NSAID	ND	−0.89 (−2.92, 1.13)
HA	ND	−0.54 (−1.89, 0.81)
Botulinum	ND	−0.80 (−2.77, 1.17)
Placebo	0.06 (−0.45, 0.57)	0.06 (−1.05, 1.17)
NSAID vs		
HA	ND	0.35 (−1.44, 2.14)
Botulinum	ND	0.09 (−2.12, 2.30)
Placebo	ND	0.96 (−0.74, 2.65)
HA vs		
Botulinum	ND	−0.26 (−1.99, 1.47)
Placebo	0.49 (−0.66,1.65)	0.60 (−0.17, 1.38)
Botulinum vs		
Placebo	ND	0.86 (−0.76, 2.49)

NOTE. The data were presented as SMD, with 95% CI. In A intervention vs B intervention, positive SMD means better efficacy of A intervention; negative SMD means better efficacy of B intervention.
Abbreviations: PRP, Platelet-Rich Plasma; NSAID, Nonsteroidal Anti-Inflammatory Drugs; HA, Hyaluronic Acid.
* $P<.05$.

Table 3 Result of pairwise and network meta-analysis for pain reduction at long term (over 24wk)

Comparison Between Two Injections	Pairwise Meta-analysis	Network Meta-analysis
Corticosteroid vs		
PRP	ND	−0.65 (−1.20, −0.10)*
Prolotherapy	ND	−2.83 (−3.63, −2.03)*
HA	0.1 (−0.32, 0.51)	0.06 (−0.32, 0.45)
Placebo	−0.2 (−0.48, 0.07)	−0.20 (−0.48, 0.07)
PRP vs		
Prolotherapy	ND	−2.18 (−3.07, −1.29)*
HA	ND	0.71 (0.10, 1.32)*
Placebo	0.45 (−0.03, 0.92)	0.45 (−0.03, 0.92)
Prolotherapy vs		
HA	ND	2.89 (2.05, 3.73)*
Placebo	2.63 (1.88, 3.38)*	2.63 (1.88, 3.38)*
HA vs		
Placebo	−0.23 (−0.64, 0.18)	−0.27 (−0.65, 0.12)

NOTE. The data were presented as SMD, with 95% CI. In A intervention vs B intervention, positive SMD means better efficacy of A intervention; negative SMD means better efficacy of B intervention.
Abbreviations: PRP, Platelet-Rich Plasma; HA, Hyaluronic Acid.
* $P<.05$.

Discussion

Our principle findings revealed that regarding pain reduction, corticosteroid injection was better in the short term, whereas prolotherapy provided more pain reduction in the long term. Regarding functional improvement, corticosteroid injection may be more effective in the short term, whereas PRP yielded more functional improvement in the long term (fig 3). For patients with rotator cuff tendinopathy, corticosteroid plays a role in the short term but not in long-term pain reduction and functional improvement. By contrast, PRP and prolotherapy may yield better outcomes in the long term (see fig 3).

This study indicated the short-term effectiveness of corticosteroid in the pairwise meta-analysis, which is in agreement with previous evidence.[6,20] Rotator cuff tendinopathy is considered as a chronic overuse disease where inflammation is not characterized pathologically. Nevertheless, in vitro studies showed that corticosteroid still provided therapeutic effect to the tendon and the surrounding connective tissues by inhibiting collagen, extracellular matrix molecules, and granulation tissue production, in addition to inflammatory suppression.[49] Such positive therapeutic effect of corticosteroids may exist only in the short term, because 1 systematic review revealed the long-term harmful effects of glucocorticoid on tendon cells in vitro, reducing cell viability, proliferation, and the mechanical properties of tendon.[50] Corticosteroid injection was not recommended for lateral epicondylalgia in the intermediate term (6mo).[51] The other concern of corticosteroid use was the adverse effect, such as increasing probability of tendon rupture. Although tendon and fascial ruptures were some reported complications of injected corticosteroids, current medical literature does not provide precise estimates for complication rate.[52] In our review, no event of tendon rupture occurred. Of the included 23 trials, only 8 RCTs reported minor transient complications, such as facial flushing, dizziness with vasovagal reaction, pain, and skin pigmentation.

In our study, PRP showed effectiveness in functional improvement in the long term. Several in vitro studies of human samples documented the beneficial anabolic effects of certain growth factors from PRP to promote tendon matrix repair.[53] Meanwhile, numerous evidence elucidated the potency of PRP in lateral epicondylalgia and plantar fasciopathy.[51,54] As to the rotator cuff disease, PRP was still debated for the adjunct use of rotator cuff repair surgery, reporting no clear improvement.[55,56] In our meta-regression analysis, older patients didn't receive more benefits from PRP injections. Previous study correspondingly showed that age did not influence platelet count or growth factor concentrations in the PRP.[57] The current meta-analysis showed positive evidence to support the clinical utility of PRP in the long term in patients with rotator cuff tendinopathy.

Prolotherapy ranked first in the aspect of pain reduction at long-term follow-up in our network meta-analysis. Hypertonic dextrose, which is inexpensive, readily available, and reported to be safe, is the most commonly used prolotherapy solution.[58] Both inflammatory and noninflammatory pathways for stimulating tissue healing have been demonstrated by basic science studies.[59] The clinical use of prolotherapy is effective in lower limb tendinopathy and fasciopathy.[59] The current meta-analysis also showed promising effects for rotator cuff tendinopathy in the long term. However, only 1 paper with a large effect size is included in our study. More studies are necessary to confirm its role in rotator cuff tendinopathy.

In our meta-analysis, injections of BTX, HA, and NSAID were all ineffective for treatment of rotator cuff tendinopathy. As for BTX, animal models have demonstrated the direct analgesic effects by inhibiting neurotransmitters, such as glutamate and

	Pain reduction	Functional improvement
Short term	Corticosteroid (pairwise)	Corticosteroid (pairwise)
Medium term	?	?
Long term	Prolotherapy (pairwise + network)	PRP (pairwise + network)

Fig 3 Summary of evidence: recommendations for best therapeutic injection at short, medium, and long term according to pain reduction and functional improvement. The method (pairwise or network meta-analysis) in parentheses represented statistical significance of the injection with this method.

substance P.[60,61] A recent meta-analysis have also supported the use of BTX for shoulder pain, but most studies recruited patients with hemiplegic shoulder pain.[62] Different etiologies and limited number of studies may contribute to the lack of positive effects of BTX injection in our study. As for HA, many studies supported the beneficial effects of intra-articular HA injection for osteoarthritis of the knee[63] and shoulder.[64,65] However, most of the reported mechanisms of action, such as the promotion of chondrocyte HA synthesis and reduction of matrix metalloproteinases, are specific to the condition of osteoarthritis.[66] The clinical application of subacromial HA injection for rotator cuff tendinopathy was still inconclusive in the current meta-analysis. As for NSAID, the results of our study were in concordance with other RCTs that showed an inferiority to corticosteroid injections for rotator cuff tendinopathy.[10,48] Making correct diagnosis is important for the treatment selected to be effective.

Implications for future research

This meta-analysis revealed short-term efficacy of corticosteroid and long-term efficacy of PRP or prolotherapy. There is a paucity of clinical study exploring combination regimens to cover both short and long term. Consequently, high-quality RCTs are needed to investigate different combination regimens of injection therapies for treating rotator cuff tendinopathy.

Limitations

This meta-analysis has several limitations. Firstly, there is heterogeneity in diagnosis criteria among different trials. Many of the trials used clinical diagnosis for rotator cuff tendinopathy without image confirmations. Complete tear or partial tear may not be easily identified through physical examinations. As well, the cause of rotator cuff tendinopathy included internal factors (eg, degenerative or overuse disorder) and external factors (eg, impingement syndrome); some RCTs described patients as having *impingement syndrome* but others as having *rotator cuff tendinopathy*. Furthermore, diagnosis criteria varied (*clinical or image diagnosis*, *clinical and image diagnosis*, or *clinical diagnosis*). So, these RCTs were unable to be categorized accurately for subgroup analysis stratified by clinically diagnosed and image-diagnosed subgroups. Nevertheless, it may be part of the rotator cuff *spectrum* or rotator cuff *syndrome*. Second, although the original trials were all randomized, the meta-regression analysis is across trials and does not have the benefit of randomization. The relation described by a meta-regression is an observational association across trials. A causal interpretation of symptom duration and patient age with treatment outcomes could not be drawn from this study. Third, the guidance methods to approach the subacromial space may have an effect on the outcomes. Among the 18 included trials, ultrasound guidance was adopted in 6 studies, arthroscopy guidance in 1 study, and landmark guidance in the remaining studies. However, the number of RCTs in each comparison of interventions (eg, PRP vs placebo) was too small to perform subgroup analysis stratified by different guidance methods. Fourth, there were differences in doses, media preparation, and regimen within each group of injectants (see table 1). Limited study numbers hindered us from performing subgroup analysis as well. Last, only 1 trial qualified for each of the BTX and prolotherapy groups. The 3 trials regarding PRP injections were also suboptimal for yielding powerful conclusions.

From the clinician's perspective, heterogeneity reflects the rotator cuff pathology, duration of symptoms, age, previous and concurrent treatment. In our method part, we performed meta-regression and examined the relation of age and symptom duration to reduction in pain and functional recovery of the shoulder. However, the results of meta-regression (no relation of age or symptom duration to outcomes) were insignificant to produce a conclusion of over- or underestimation of the benefits of injections. Regarding sex, previous or concurrent treatment (rehabilitation, medications, surgery), as well as injection therapy dose and regimen, most of the included trials did not provide sufficient information for us to analyze the effects of these factors. Furthermore, an insufficient number of studies prevented a more detailed subgroup meta-analysis. More studies are needed to confirm the positive long-term effects of regenerative therapies for rotator cuff tendinopathy implied by our meta-analysis.

Conclusion

The current meta-analysis showed that, for patients with rotator cuff tendinopathy, corticosteroid plays a role in the short-term (3-6wk) but not in long-term (over 24wk) pain reduction and functional improvement. By contrast, PRP and prolotherapy may yield better outcomes in the long term (over 24wk). On account of heterogeneity, interpreting these results with caution is warranted.

Suppliers

a. Stata 14.0; StataCorp LP.
b. Review Manager (RevMan) 5.3; Cochrane Collaboration.

Keywords

Injections; Meta-analysis; Rehabilitation; Rotator cuff

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Acknowledgment

We appreciate great effort of all investigators who conducted the trials and were included in our meta-analysis.

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Supplemental Appendix S1 Methods

Identification of Trials and Search Method

We performed the prescreening process to reach all possible injection methods with the key term (**Injection**) listed below and made sure that no any injection method would be left out. Afterward we started the specific terminology searching for each specific injection.

Text words with key terms for electronic databases:

1. **PubMed, The Cochrane Collaboration Central Register of Controlled Clinical Trials and Cochrane Database of Systematic Reviews:**
   - **Injection:**
     ("rotator cuff" OR subacromial OR sub-acromial OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor")
     AND (injection)
     NOT (arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis" OR "frozen shoulder" OR rat OR mice OR animal)
   - **Steroid:**
     ("rotator cuff" OR subacromial OR sub-acromial OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor")
     AND (steroid* OR corticosteroid* OR glucocorticoid* OR corti* OR hydrocorti*)
     NOT (arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis" OR "frozen shoulder" OR rat OR mice OR animal)
   - **Nonsteroidal anti-inflammatory drugs (NSAIDs):**
     ("rotator cuff" OR subacromial OR sub-acromial OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor")
     AND (NSAID* OR Nonsteroid* OR Non-steroid* OR "Tenoxicam" OR keto*)
     NOT (arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis" OR "frozen shoulder" OR rat OR mice OR animal)
   - **Hyaluronic acid (HA):**
     ("rotator cuff" OR subacromial OR sub-acromial OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor")
     AND (Hyaluron* OR HA OR viscosupplement*)
     NOT (arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis" OR "frozen shoulder" OR rat OR mice OR animal)
   - **Botulinum toxin**
     ("rotator cuff" OR subacromial OR sub-acromial OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor")
     AND (Botulin* OR BOTOX*)
     NOT (arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis" OR "frozen shoulder" OR rat OR mice OR animal)
   - **Platelet-rich plasma (PRP):**
     ("rotator cuff" OR subacromial OR sub-acromial OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor")
     AND (autologous OR platelet or plasma OR PRP OR platelet rich plasma OR platelet gel OR platelet derived growth factors OR platelet concentrate OR PRGF OR ACP OR autologous conditioned plasma OR platelet lysate OR platelet rich fibrin OR platelet rich membrane)
     NOT (arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis" OR "frozen shoulder" OR rat OR mice OR animal)
   - **Prolotherapy:**
     ("rotator cuff" OR subacromial OR sub-acromial OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor")
     AND (prolotherapy OR prolo* OR Dextrose*)
     NOT (arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis" OR "frozen shoulder" OR rat OR mice OR animal)
2. **EMBASE and Scopus:**
   - **Injection:**
     #1 "rotator cuff"/exp OR "rotator cuff"
     #2 "subacromial"/exp OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor"
     #3 #1 OR #2
     #4 "injection" OR injection* OR "injection"/exp
     #5 arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis"/exp OR "rat"/exp OR "mice"/exp OR "animal"/exp
     #6 #3 AND #4 NOT #5
   - **Steroid:**
     #1 "rotator cuff"/exp OR "rotator cuff"
     #2 "subacromial"/exp OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor"
     #3 #1 OR #2
     #4 "steroid"/exp OR steroid* OR corticosteroid* OR glucocorticoid* OR corti* OR hydrocorti*
     #5 arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis"/exp OR "rat"/exp OR "mice"/exp OR "animal"/exp
     #6 #3 AND #4 NOT #5
   - **Nonsteroidal anti-inflammatory drugs (NSAIDs):**
     #1 "rotator cuff"/exp OR "rotator cuff"
     #2 "subacromial"/exp OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor"
     #3 #1 OR #2
     #4 "NSAID"/exp OR Nonsteroid* OR Non-steroid* OR "Tenoxicam" OR "keto"
     #5 arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis"/exp OR "rat"/exp OR "mice"/exp OR "animal"/exp
     #6 #3 AND #4 NOT #5
   - **Hyaluronic acid (HA):**
     #1 "rotator cuff"/exp OR "rotator cuff"
     #2 "subacromial"/exp OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor"
     #3 #1 OR #2
     #4 Hyaluron* OR HA OR "HA"/exp OR viscosupplement*
     #5 arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis"/exp OR "rat"/exp OR "mice"/exp OR "animal"/exp
     #6 #3 AND #4 NOT #5
   - **Botulinum**
     #1 "rotator cuff"/exp OR "rotator cuff"

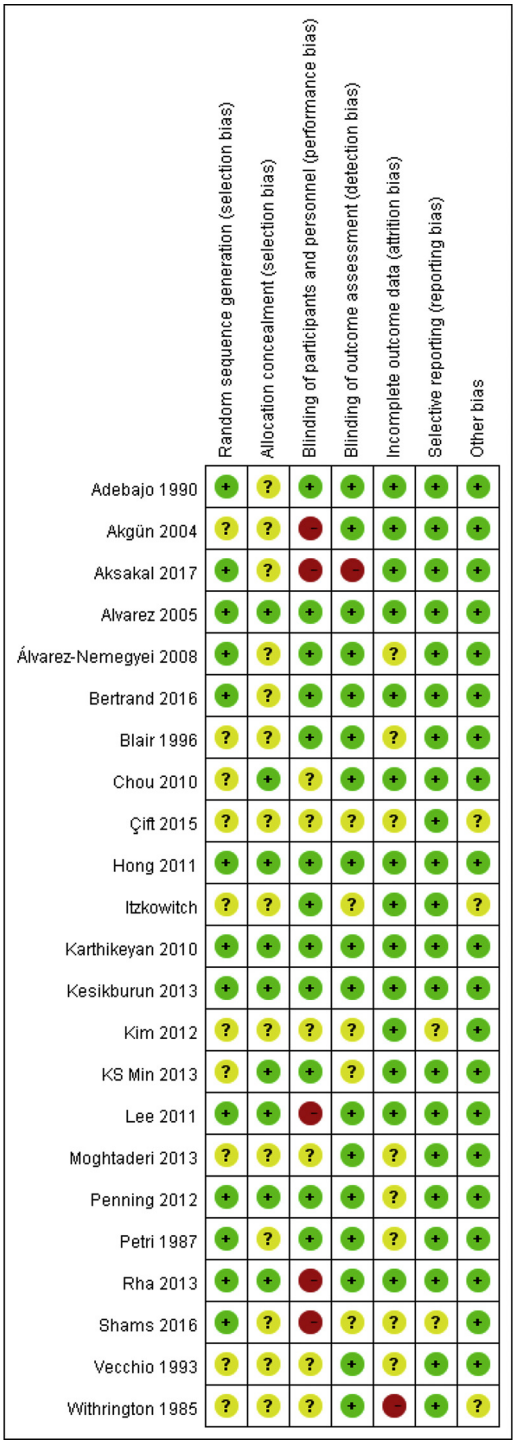
#2 "subacromial"/exp OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor"
#3 #1 OR #2
#4 Botulin* OR "Botulin"/exp OR BOTOX*
#5 arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis"/exp OR "rat"/exp OR "mice"/exp OR "animal"/exp
#6 #3 AND #4 NOT #5

- **Platelet-rich plasma (PRP):**
#1 "rotator cuff"/exp OR "rotator cuff"
#2 "subacromial"/exp OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor"
#3 #1 OR #2
#4 "autologous" OR "platelet" or "plasma" OR "PRP" OR "platelet rich plasma" OR "platelet gel" OR "platelet derived growth factors" OR "platelet concentrate" OR "PRGF" OR "ACP"
#5 arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis"/exp OR "rat"/exp OR "mice"/exp OR "animal"/exp
#6 #3 AND #4 NOT #5
- **Prolotherapy:**
#1 "rotator cuff"/exp OR "rotator cuff"
#2 "subacromial"/exp OR impinge* OR supraspinat* OR infraspinat* OR subscapular* OR "teres minor"
#3 #1 OR #2
#4 "prolotherapy" OR "prolotherapy"/exp OR prolo* OR Dextrose*
#5 arthroscop* OR arthroplas* OR acromioplas* OR "adhesive capsulitis"/exp OR "rat"/exp OR "mice"/exp OR "animal"/exp
#6 #3 AND #4 NOT #5

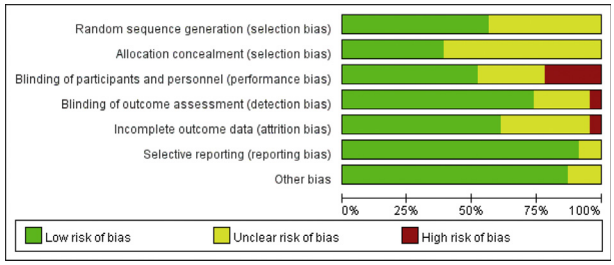
Data synthesis and analysis

Pooled $SD_{intervention}$ = the square root of {[(participant numbers $_{baseline}-1)*(SD_{baseline})^2+$(participant numbers$_{postintervention}-1)*(SD_{postintervention})^2]/[$(participant numbers$_{baseline}-1)$ + (participant numbers$_{postintervention}-1)]$}.

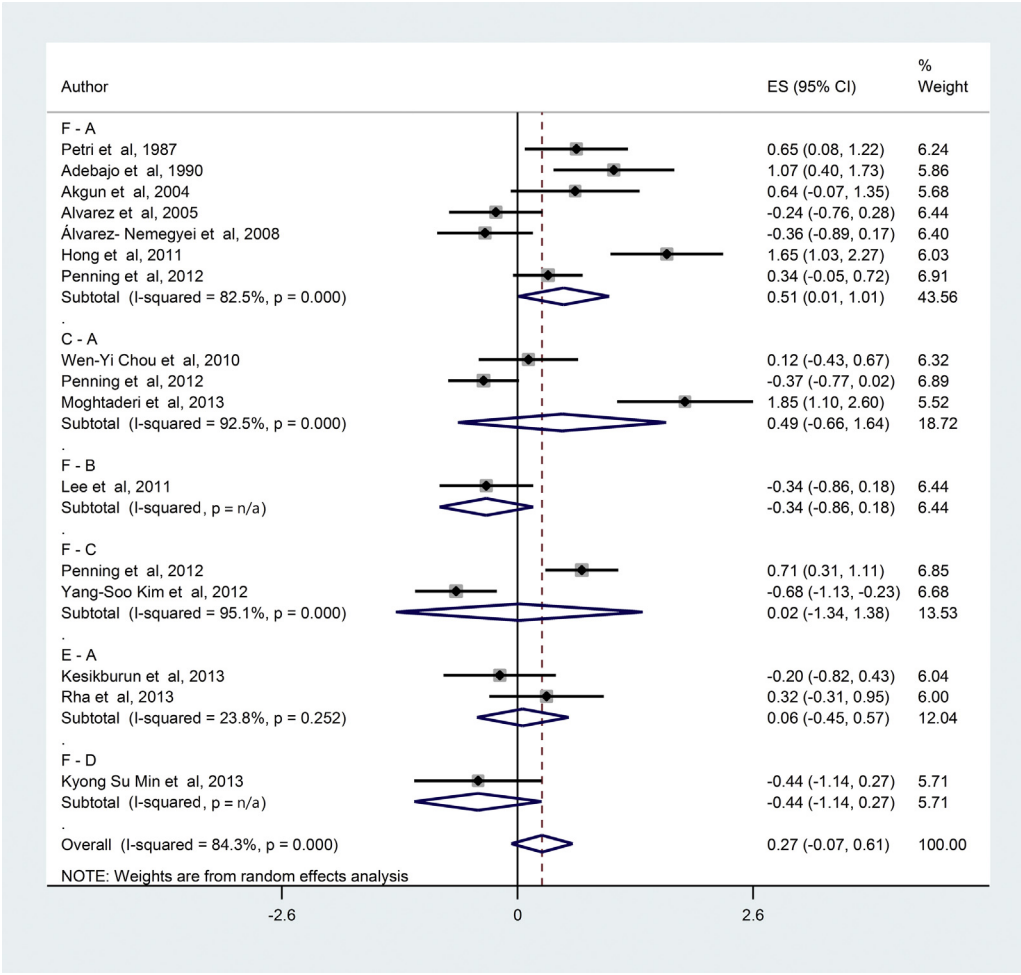
Pooled $SD_{between\text{-}interventions}$ = the square root of {[(participant numbers$_{first\ intervention}-1)*$(pooled $SD_{first\ intervention})^2+$(participant numbers$_{second\ intervention}-1)*$(pooled $SD_{second\ intervention})^2$]/[(participant numbers$_{first\ intervention}-1)+$(participant numbers$_{second\ intervention}-1)]$}.



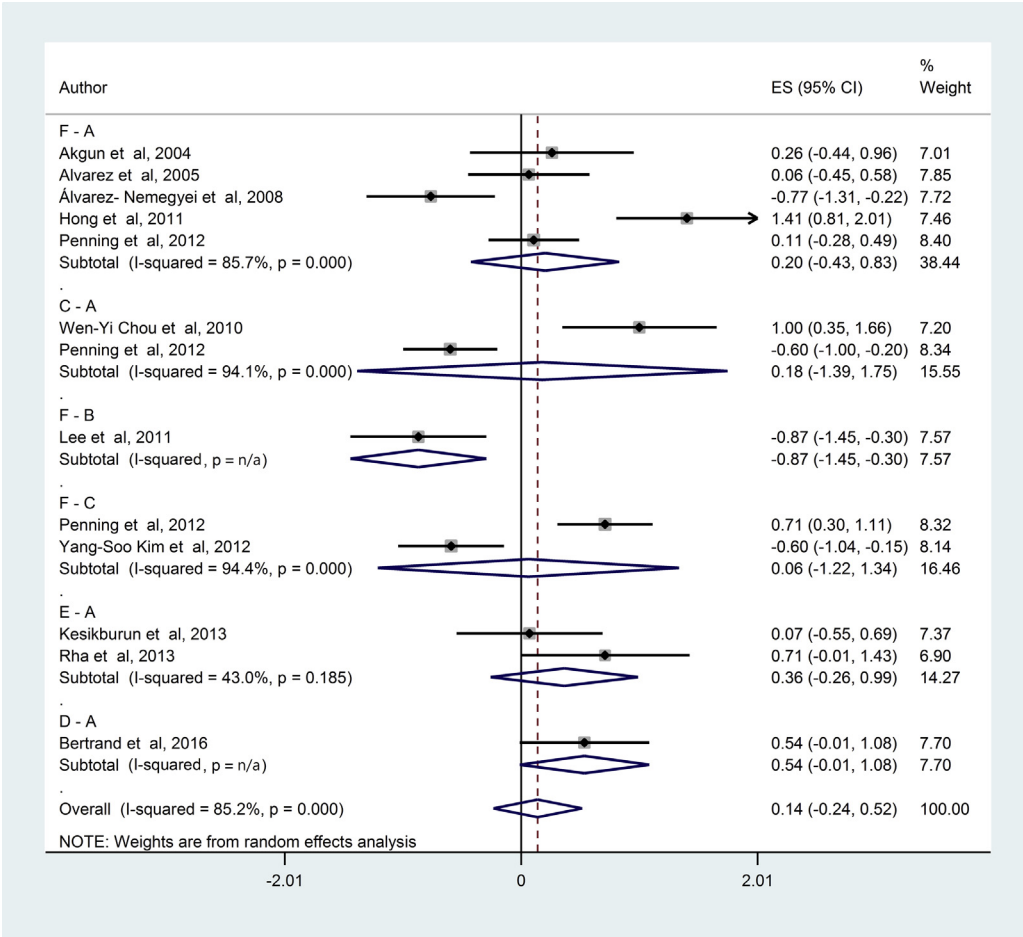
Supplemental Fig S1 Risk of bias summary: low risk of bias in green; high risk of bias in red; unclear risk of bias in yellow.



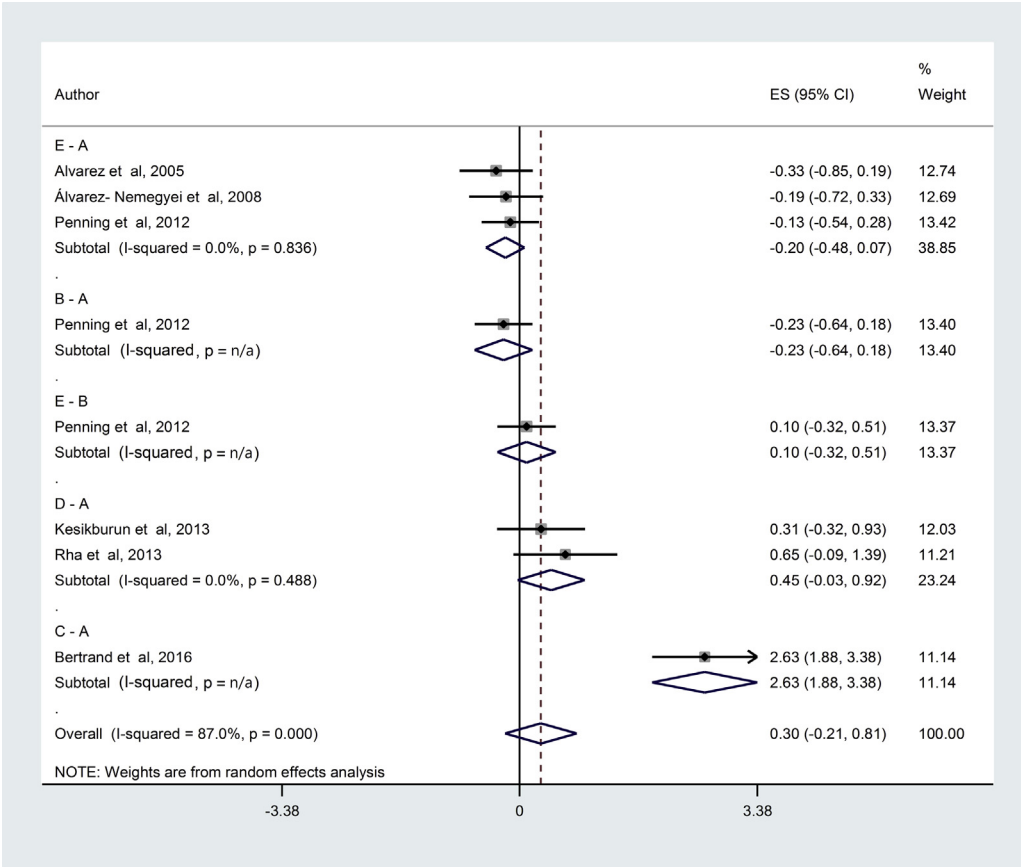
Supplemental Fig S2 Risk of bias graph: low risk of bias in green; high risk of bias in red; unclear risk of bias in yellow.



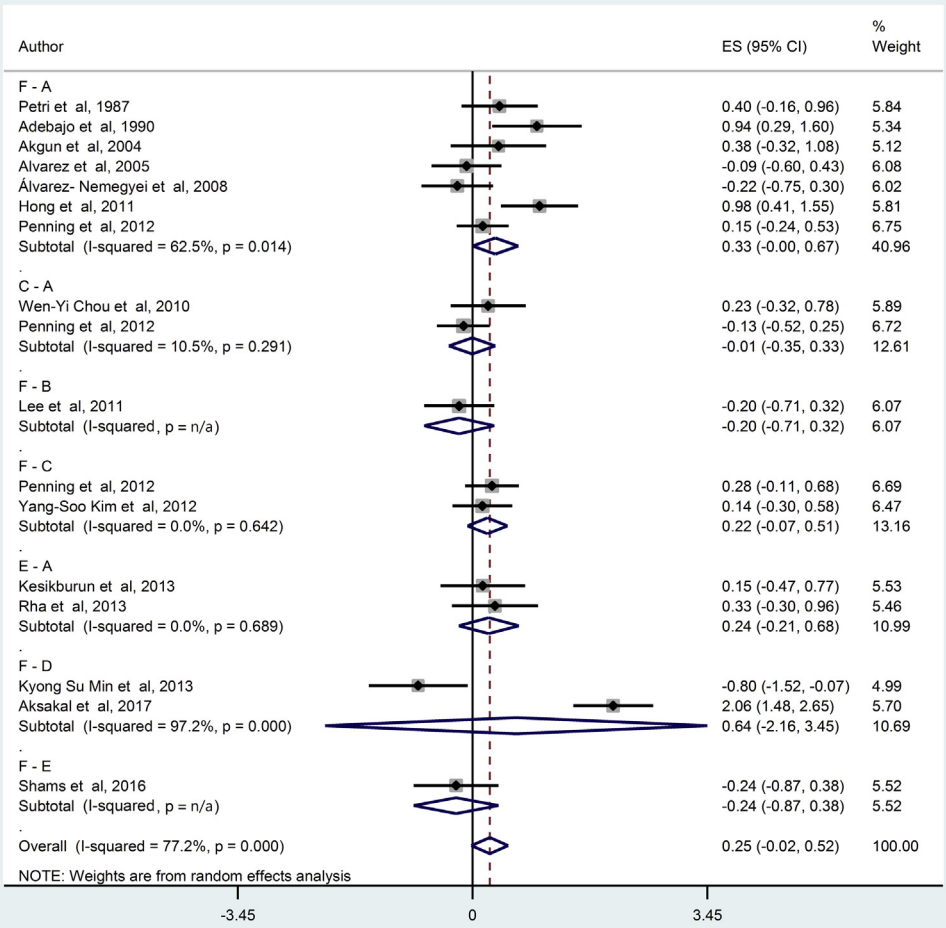
Supplemental Fig S3 The forest plot of pairwise meta-analysis: comparison between injection therapies in pain reduction at short term (3-6wk). A, placebo; B, botulinum; C, hyaluronic acid; D, nonsteroidal anti-inflammatory drug; E, platelet-rich plasma; F, steroid.



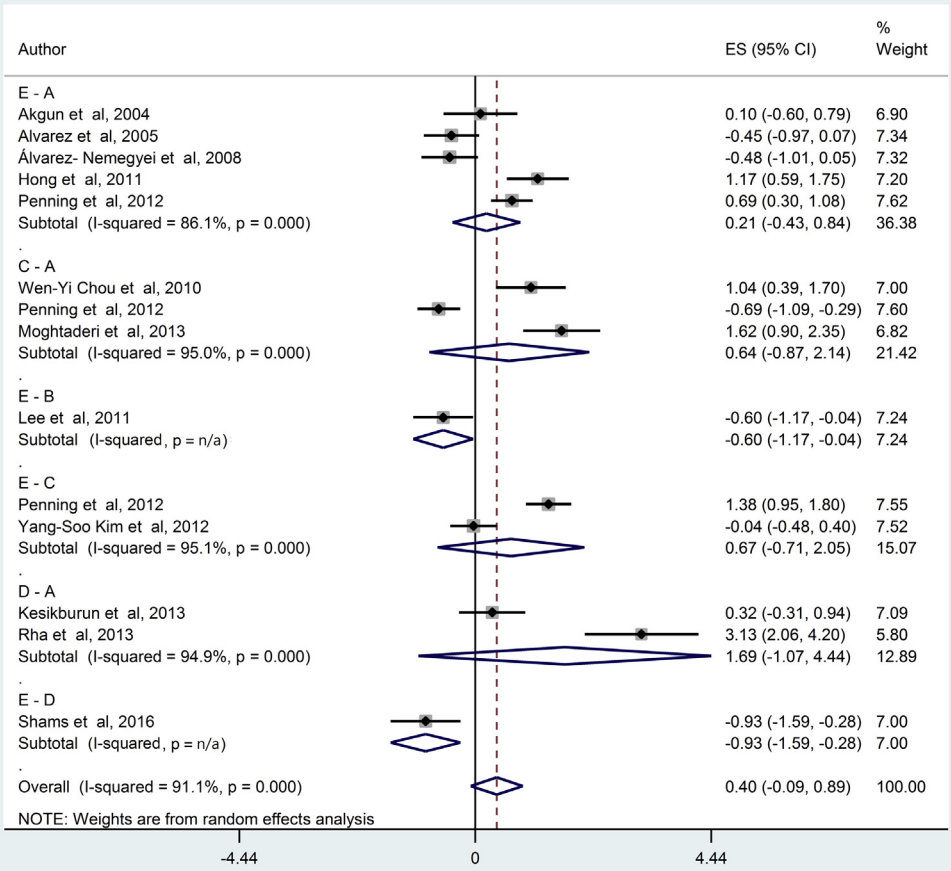
Supplemental Fig S4 The forest plot of pairwise meta-analysis: comparison between injection therapies in pain reduction at medium term (12wk). A, placebo; B, botulinum; C, hyaluronic acid; D, prolotherapy; E, platelet-rich plasma; F, steroid.



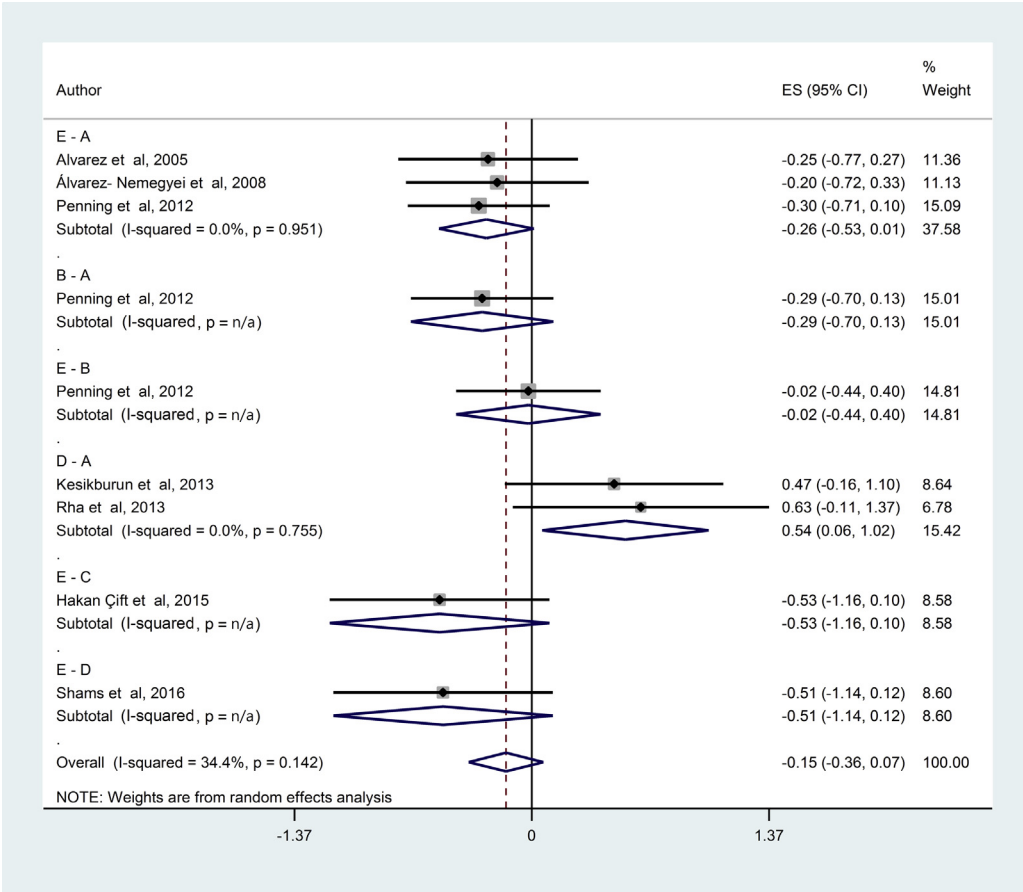
Supplemental Fig S5 The forest plot of pairwise meta-analysis: comparison between injection therapies in pain reduction at long term (over 24wk) after sensitivity analysis. A, placebo; B, hyaluronic acid; C, prolotherapy; D, platelet-rich plasma; E, steroid.



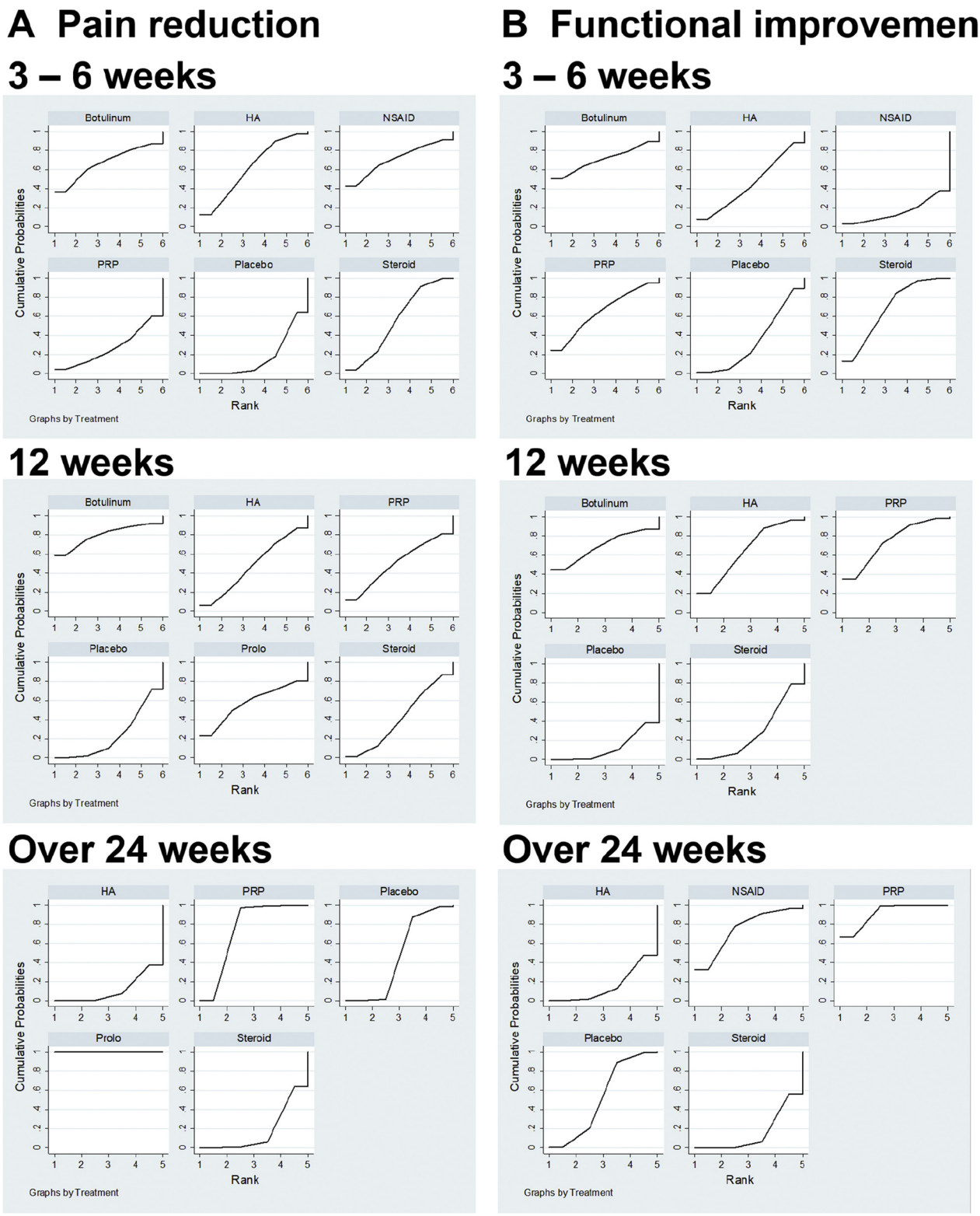
Supplemental Fig S6 The forest plot of pairwise meta-analysis: comparison between injection therapies in functional improvement at short term (3-6wk). A, placebo; B, botulinum; C, hyaluronic acid; D, nonsteroidal anti-inflammatory drugs; E, platelet-rich plasma; F, steroid.



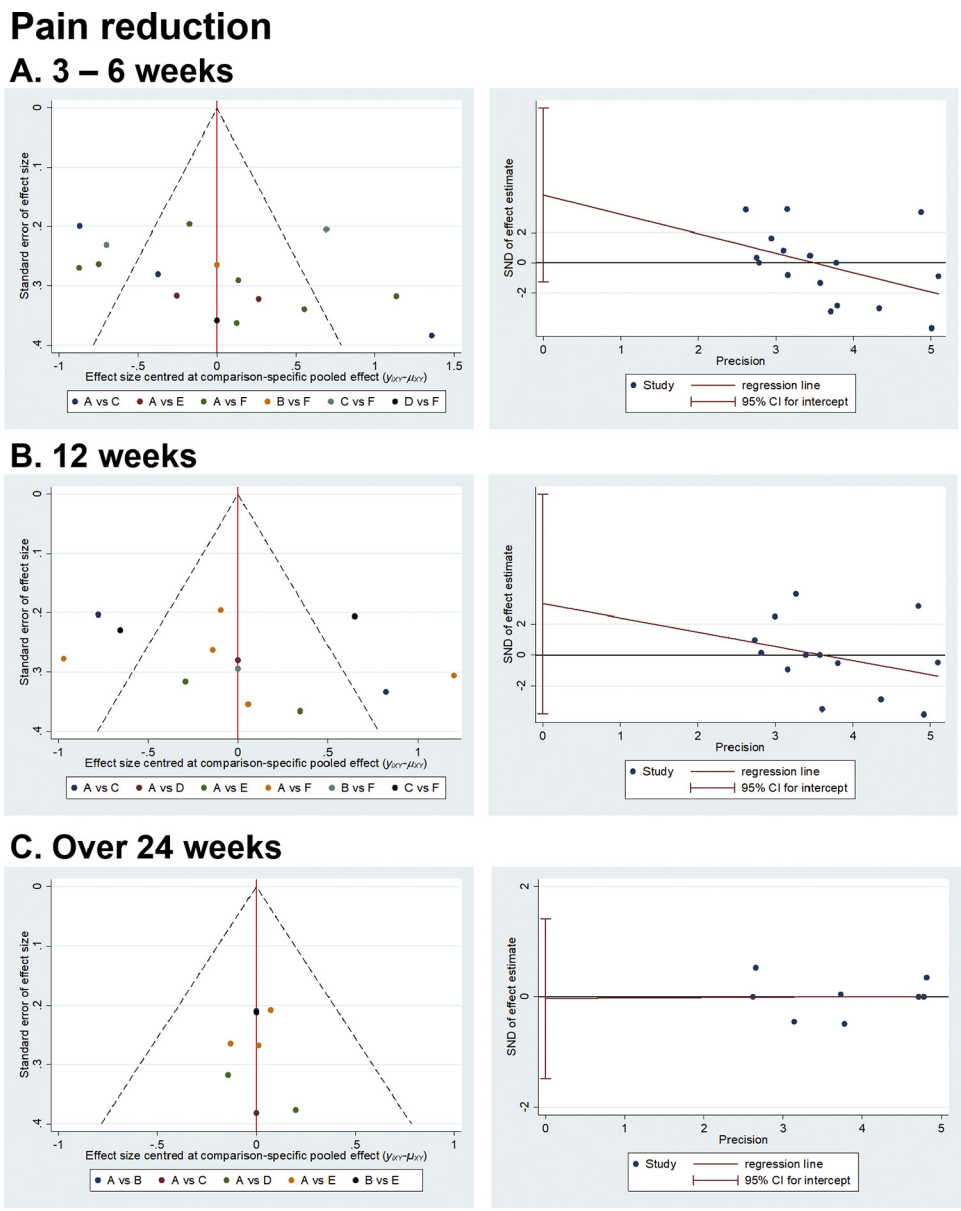
Supplemental Fig S7 The forest plot of pairwise meta-analysis: comparison between injection therapies in functional improvement at medium term (12wk). A, placebo; B, botulinum; C, hyaluronic acid; D, platelet-rich plasma; E, steroid.



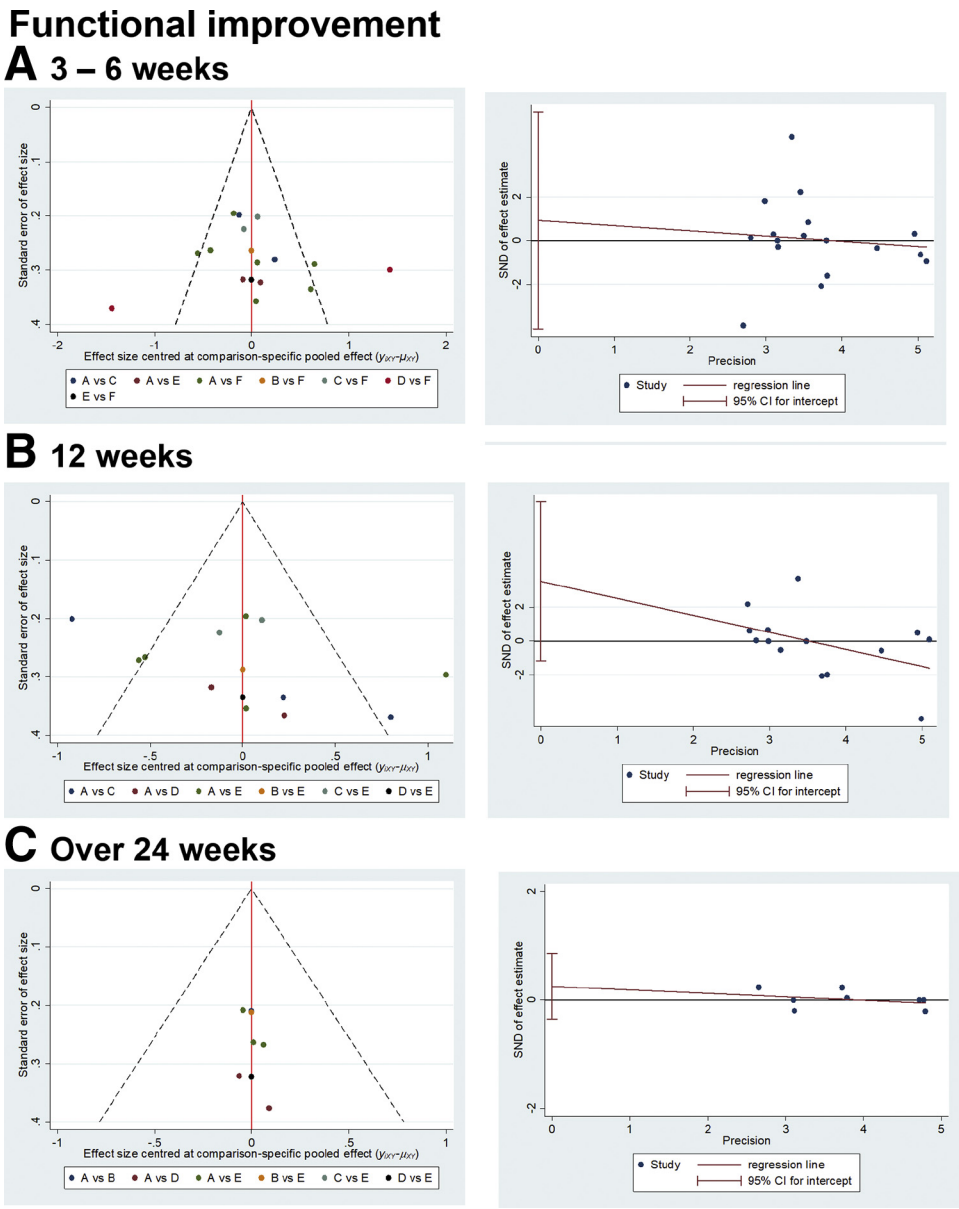
Supplemental Fig S8 The forest plot of pairwise meta-analysis: comparison between injection therapies in functional improvement at long term (over 24wk). A, placebo; B, hyaluronic acid; C, nonsteroidal anti-inflammatory drugs; D, platelet-rich plasma; E, steroid.



Supplemental Fig S9 Ranking—cumulative probability plot of multiple injection therapies in pain reduction (A) and functional improvement (B) at short term (3-6wk), medium term (12 wk), and long term (over 24wk). Abbreviations: HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; Prolo, prolotherapy; PRP, platelet-rich plasma.



Supplemental Fig S10 Publication bias: funnel plot (left) and Egger's test (right) in pain reduction at short term (A, 3-6wk), medium term (B, 12wk), and long term (C, over 24wk). A, placebo; B, botulinum; C, hyaluronic acid; D, nonsteroidal anti-inflammatory drug; E, platelet-rich plasma; F, steroid.



Supplemental Fig S11 Publication bias: funnel plot (left) and Egger's test (right) in functional improvement at short term (A, 3-6wk), medium term (B, 12wk), and long term (C, over 24wk). A, placebo; B, botulinum; C, hyaluronic acid; D, nonsteroidal anti-inflammatory drug; E, platelet-rich plasma; F, steroid.

Supplemental Table S1 Result of pairwise and network meta-analysis for pain reduction at medium term

	Pairwise Meta-analysis	Network Meta-analysis
Corticosteroid vs*		
PRP	ND	−0.16 (−1.47 to 1.14)
Prolotherapy	ND	−0.32 (−2.00 to 1.37)
HA	0.06 (−1.22 to 1.34)	−0.08 (−0.98 to 0.82)
Botulinum	−0.87 (−1.45 to −0.30)†	−0.87 (−2.43 to 0.69)
Placebo	0.20 (−0.43 to 0.83)	0.22 (−0.44 to 0.88)
PRP vs*		
Prolotherapy	ND	−0.15 (−2.07 to 1.76)
HA	ND	0.08 (−1.37 to 1.53)
Botulinum	ND	−0.71 (−2.74 to 1.33)
Placebo	0.36 (−0.26 to 0.99)	0.38 (−0.75 to 1.51)
Prolotherapy vs*		
HA	ND	0.23 (−1.56 to 2.03)
Botulinum	ND	−0.55 (−2.85 to 1.74)
Placebo	0.54 (−0.01 to 1.09)	0.54 (−1.01 to 2.09)
HA vs*		
Botulinum	ND	−0.79 (−2.59 to 1.01)
Placebo		0.30 (−0.60 to 1.21)
Botulinum vs*	0.18 (−1.40 to 1.75)	
Placebo	ND	1.09 (−0.60 to 2.78)

NOTE. The data was presented as standardized mean difference (SMD), with 95% confidence interval. In A intervention vs B intervention, positive SMD means better efficacy of A intervention; negative SMD means better efficacy of B intervention.
Abbreviations: HA, hyaluronic acid; PRP, platelet-rich plasma.
* Statistically significant results are shown.
† $P<.05$.

Supplemental Table S2 Result of pairwise and network meta-analysis for functional improvement at short term

	Pairwise Meta-analysis	Network Meta-analysis
Corticosteroid vs*		
PRP	−0.24 (−0.87 to 0.38)	−0.03 (−0.87 to 0.82)
NSAID	0.64 (−2.17 to 3.45)	0.70 (−0.27 to 1.67)
HA	0.22 (−0.07 to 0.51)	0.22 (−0.52 to 0.96)
Botulinum	−0.2 (−0.72 to 0.32)	−0.20 (−1.51 to 1.11)
Placebo	0.33 (0.00 to 0.67)†	0.32 (−0.14 to 0.79)
PRP vs*		
NSAID	ND	0.73 (−0.56 to 2.01)
HA	ND	0.25 (−0.81 to 1.31)
Botulinum	ND	−0.17 (−1.73 to 1.38)
Placebo	0.24 (−0.21 to 0.68)	0.35 (−0.45 to 1.15)
NSAID vs*		
HA	ND	−0.48 (−1.70 to 0.74)
Botulinum	ND	−0.90 (−2.53 to 0.73)
Placebo	ND	−0.38 (−1.46 to 0.70)
HA vs*		
Botulinum	ND	−0.42 (−1.93 to 1.08)
Placebo	−0.01 (−0.35 to 0.33)	0.10 (−0.64 to 0.84)
Botulinum vs*		
Placebo	ND	0.52 (−0.87 to 1.91)

NOTE. The data was presented as standardized mean difference (SMD), with 95% confidence interval. In A intervention vs B intervention, positive SMD means better efficacy of A intervention; negative SMD means better efficacy of B intervention.
Abbreviations: HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.
* Statistically significant results are shown.
† $P<.05$.

Supplemental Table S3 Result of pairwise and network meta-analysis for functional improvement at medium term

	Pairwise Meta-analysis	Network Meta-analysis
Corticosteroid vs*		
PRP	−0.93 (−1.59 to −0.28)†	−0.53 (−1.39 to 0.33)
HA	0.09 (−0.21 to 0.38)	−0.41 (−1.11 to 0.29)
Botulinum	−0.61 (−1.17 to −0.04)†	−0.60 (−1.92 to 0.71)
Placebo	0.08 (−0.47 to 0.63)	0.18 (−0.34 to 0.70)
PRP vs*		
HA	ND	0.12 (−0.89 to 1.13)
Botulinum	ND	−0.07 (−1.64 to 1.50)
Placebo	0.48 (0.01-0.96)†	0.71 (−0.10 to 1.51)
HA vs*		
Botulinum	ND	−0.19 (−1.68 to 1.30)
Placebo	0.82 (−0.26 to 1.91)	0.59 (−0.08 to 1.26)
Botulinum vs*		
Placebo	ND	0.78 (−0.63 to 2.20)

NOTE. The data was presented as standardized mean difference (SMD), with 95% confidence interval. In A intervention vs B intervention to positive SMD means the better efficacy of A intervention; negative SMD means the better efficacy of B intervention.
Abbreviations: HA, hyaluronic acid; PRP, platelet-rich plasma.
* Statistically significant results are shown.
† $P<.05$.

Supplemental Table S4 Result of pairwise and network meta-analysis for functional improvement at long term

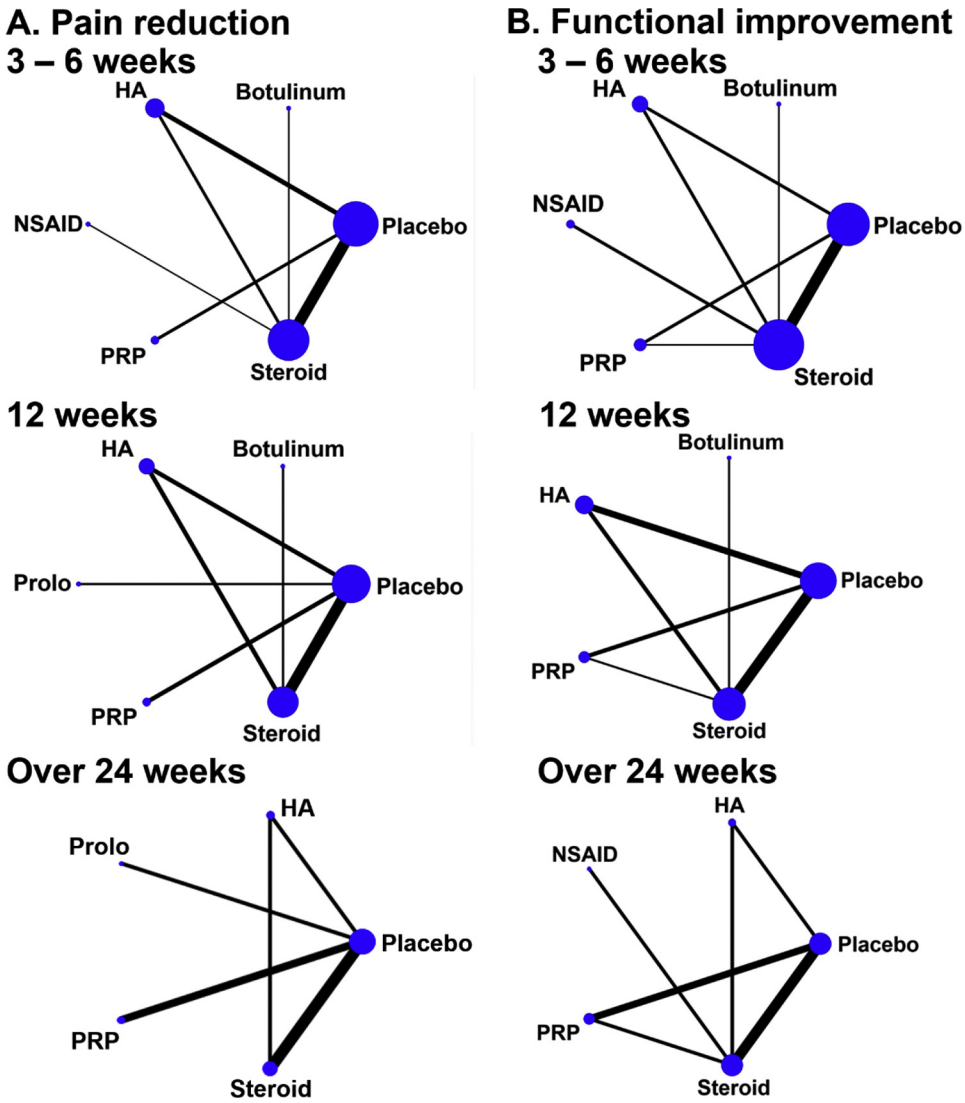
	Pairwise Meta-analysis	Network Meta-analysis
Corticosteroid vs*		
PRP	−0.51 (−1.14 to 0.12)	−0.67 (−1.09 to −0.26)†
NSAID	−0.53 (−1.16 to 0.10)	−0.53 (−1.16 to 0.10)
HA	−0.02 (−0.44 to 0.40)	0.02 (−0.36 to 0.40)
Placebo	−0.26 (−0.54 to 0.01)	−0.23 (−0.49 to 0.03)
PRP vs*		
NSAID	ND	0.14 (−0.61 to 0.90)
HA	ND	0.69 (0.17-1.22)†
Placebo	0.54 (0.06-1.02)†	0.44 (0.05-0.84)†
NSAID vs*		
HA	ND	0.55 (−0.19 to 1.29)
Placebo	ND	0.30 (−0.38 to 0.98)
HA vs*		
Placebo	−0.29 (−0.70 to 0.13)	−0.25 (−0.63 to 0.13)

NOTE. The data was presented as standardized mean difference (SMD), with 95% confidence interval. In A intervention vs B intervention, positive SMD means the better efficacy of A intervention; negative SMD means the better efficacy of B intervention.
Abbreviations: HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.
* Statistically significant results are shown.
† $P<.05$.

Supplemental Table S5 Meta-regression and inconsistency of pain reduction and functional improvement

	Pain Reduction			Functional Improvement		
	3-6 wk	12 wk	Over 24 wk	3-6 wk	12 wk	Over 24 wk
Meta-regression						
Age	0.392	0.772	0.662	0.001*	0.646	0.988
Symptom duration	0.773	0.279	0.668	<0.001†	0.124	0.794
Inconsistency						
Design	0.435	0.437	0.639	0.993	0.301	0.763
Loop	0.362	0.424	NA	0.923	0.658	0.498

* $P<.05$.
† $P<.001$.



Supplemental Fig S12 Network graph of multiple injection therapies in each outcome after sensitivity analysis: pain reduction (A) and functional improvement (B) at short term (3-6wk) to medium term (12wk) to and long term (over 24wk). Abbreviations: HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; Prolo, prolotherapy; PRP, platelet-rich plasma.