Effects of Sodium Hyaluronate in the Treatment of Rotator Cuff Lesions

A Systematic Review and Meta-analysis

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Background: Rotator cuff pathology is a common cause of pain and shoulder dysfunction. Several nonoperative treatment modalities have been developed for rotator cuff lesions, but their relative efficacy is not well-established.

Purpose/Hypothesis: The purpose of this systematic review and meta-analysis was to evaluate the efficacy and safety of sodium hyaluronate (SH) in the treatment of patients with rotator cuff lesions. It was hypothesized that SH would be found to be more effective than other nonoperative regimens.

Study Design: Systematic review; Level of evidence, 3.

Methods: We searched various databases to identify eligible studies that evaluated the effects of SH on the pain and shoulder dysfunction attributed to rotator cuff lesions. Outcome measures were pain visual analog scale (VAS) score; Constant score; University of California, Los Angeles (UCLA) score; satisfaction rate; complications; and factors affecting the pain VAS score. Outcomes were reported as weighted mean difference (WMD) or risk ratio.

Results: A total of 9 studies were identified for data analysis. Compared with patients treated with other nonoperative treatments (controls), those treated with SH had significantly improved pain VAS scores at 1 week (WMD = −0.95; 95% CI, −1.75 to −0.16; $P = .019$), 2 weeks (WMD = −1.05; 95% CI, −2.07 to −0.03; $P = .044$), 3 weeks (WMD = −1.49; 95% CI, −2.88 to −0.11; $P = .035$), and 4 weeks (WMD = −2.12; 95% CI, −4.05 to −0.19; $P = .031$). The Constant score was significantly improved in the SH group versus controls at 2 weeks (WMD = 3.25; 95% CI, 2.36 to 4.13; $P < .001$), 3 months (WMD = 20.28; 95% CI, 0.54 to 40.03; $P = .044$), and 6 months (WMD = 5.58; 95% CI, 0.94 to 10.21; $P = .018$). The UCLA score and satisfaction rate did not differ significantly between the 2 groups. No complications associated with SH were reported in the included studies. Metaregression analysis showed that, except for study design (coefficient = −1.64; 95% CI, −2.64 to −0.63; $P = .002$), none of the variables (sample size, tear type, control treatments) significantly predicted the difference in VAS pain score between SH and other treatments.

Conclusion: The present meta-analysis demonstrated that SH was effective in treating patients with rotator cuff lesions.

Keywords: meta-analysis; sodium hyaluronate; rotator cuff tear

Rotator cuff pathology is a common orthopaedic disorder that might result in pain, progressive loss of function, and diminished quality of life.[26] The ultimate goals of rotator cuff repair are to relieve pain and restore function. Nonoperative therapy is the mainstay treatment modality in patients with rotator cuff lesions without complete tears.[1] For patients exhibiting persistent symptoms after rehabilitation or the use of nonsteroidal anti-inflammatory drugs, the most predominant nonoperative treatment is the subacromial injection of anesthetics or corticosteroids.[22] Although these treatment modalities are effective in relieving shoulder pain, several adverse effects, such as gastrointestinal bleeding and liver or kidney toxicity, still attract a lot of attention.[10,15,23]

Sodium hyaluronate (SH) is a polysaccharide secreted into the normal joint space by type B synoviocytes or fibroblasts, and its viscoelastic properties are essential for lubrication and chondroprotective effects.[27] As a result of its properties, SH has been used as an antiadhesive agent in tendon surgery[9,29] and in abdominal surgery for reducing adhesions and postoperative ileus as well as in gynecological surgery for minimizing infertility.[8,16] Moreover, as an alternative intra-articular regimen for osteoarthritic knee joints,[5] SH has shown effects on the shoulder pain or rotator cuff tears.[13,25,28] Blaine et al[3] performed a randomized, double-blind, controlled trial in patients with persistent

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shoulder pain. They reported that SH was highly effective and well-tolerated for osteoarthritis and persistent shoulder pain that was refractory to other standard nonoperative approaches.[3]

Although multiple studies have assessed the effect of SH in patients with rotator cuff lesions, their results remain conflicting. Therefore, we performed this systematic review and meta-analysis to evaluate the efficacy and safety of SH treatment in patients with rotator cuff lesions.

METHODS

Search Strategy

The reporting of this meta-analysis follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[20] Electronic literature searches were conducted using PubMed, Embase, Web of Science, China National Knowledge Infrastructure, and SinoMed from their inception to October 11, 2021. Search terms used were "rotator cuff tears," "rotator cuff injuries," "cuff tears," "hyaluronic acid," "sodium hyaluronate," "hyaluronate," and "viscosupplementation." The search had no restrictions on publication status or language. In addition, we performed a manual search of reference citations of identified publications to search for potentially relevant studies.

Study Eligibility Criteria

Studies were included if they fulfilled the following criteria: (1) randomized controlled trial (RCT), cohort study, or case-control study; (2) patients with clinical diagnosis of rotator cuff lesions; (3) SH compared with placebo and/or other therapy methods; and (4) outcomes reported included pain visual analog scale (VAS) score, Constant score, University of California, Los Angeles (UCLA) score, satisfaction rate, and complications.

Data Extraction and Quality Assessment

The extracted data contained mainly the following: (1) study information: first author's name, year of publication, country, and sample size; (2) patient information: age, sex, rotator cuff disease characteristics, duration of follow-up, injection approach, and dosage of SH; and (3) outcome measures (mean ± SE): pain VAS score, Constant score, UCLA score, satisfaction rate, complications, and factors affecting the pain VAS score.

We applied the Newcastle-Ottawa Scale (NOS) to assess the methodological quality for nonrandomized trials.[31] The NOS assesses 9 methodological items in 3 domains: selection of study groups, comparability of groups, and ascertainment of exposure and outcomes.[31] Scores range from 0 to 9 points. Studies were classified as being high quality if the score was >5 points.[31]

We assessed the risk of bias of RCTs using the method recommended by Cochrane.[11] This method contains the following domains: random sequence generation; allocation concealment; blinding of outcome participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective reporting and other bias.[11] Based on the assessment criteria, a study was graded as having high, low, or unclear risk of bias.

Statistical Analysis

The statistical analysis was performed using Stata Version 12.0 software (Stata). Heterogeneity among the included studies was assessed using the Cochrane Q and I^2 statistics,[12] in which $P < .1$ or $I^2 > 50\%$ indicated significance.[12] For continuous variables, weighted mean differences (WMDs) with 95% CIs were expressed to calculate the effect estimate; for dichotomous variables, risk ratios (RRs) with 95% CIs were used to calculate the overall estimate. The fixed-effect model was used when no significant heterogeneity was identified[17]; otherwise, the random-effects model was used.[6] Sensitivity analysis was performed to explore the potential sources of heterogeneity when significant heterogeneity was found. Subgroup analysis was performed based on the control treatment and dosage of SH. The Egger and Begg tests were conducted to evaluate publication bias.[2,7] A $P < .05$ was the threshold for statistical significance, except where otherwise specified.

Metaregression Analysis

The outcome differences among studies might be influenced by the clinical variables (study design: prospective/retrospective cohort or RCT; sample size: <50 or ≥50; tear type: complete or without complete; and control treatments: normal saline, rehabilitation therapy, steroid, oral drug). To identify whether the different results were influenced by the variables, we performed metaregression analyses. In this model, outcomes were regarded as a dependent variable (y) and the above-mentioned covariates as independent variables (x).

RESULTS

Study Selection

The initial screening retrieved 2863 records from the databases, of which 2184 were removed because they were

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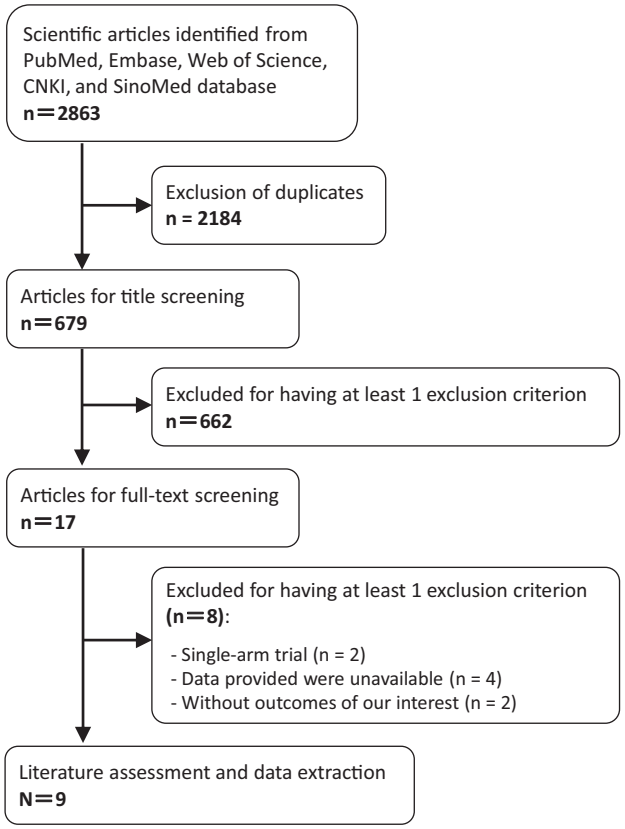

Figure 1. Eligibility of studies for inclusion in meta-analysis. CNKI, China National Knowledge Infrastructure.

duplicate records. The remaining 679 were screened for title or abstract, and a further 662 were excluded. Of the 17 publications left for full-text information review, 8 were removed for various reasons (single-arm trial, data provided were unavailable, or outcomes not of our interest). Ultimately, 9 studies met the eligibility for assessment (Figure 1).[§]

Characteristics of Eligible Studies and Quality Assessment

The characteristics of the included studies are listed in Table 1. Of the 9 studies, 4 were conducted in China, 2 in Italy, 1 in Korea, 1 in Japan, and 1 in Iran. The studies were published between 2001 and 2021, and 6 of them were designed as prospective RCTs,[4,14,19,21,25,30] 2 as prospective cohort studies,[18,27] and 1 as retrospective cohort study.[24] The sample sizes varied from 40 to 120 patients. The treatment regimen in control group varied greatly, with normal saline in 6 studies,[4,14,19,21,27,30] and physiotherapy, steroid, and oral drug in 1 study each.[18,24,25] The mean age of enrolled patients in each study ranged from 30 to 80 years, and 54.41% of the enrolled patients were male. Most patients had shoulder pain for >1 month, with a maximum duration of 25.72 ± 7.82 months.

The results of the risk-of-bias analysis are presented in Figure 2. Overall, 4 studies were regarded as low risk of bias,[4,19,21,30] 1 as unclear risk of bias,[25] and 1 as high risk of bias.[14] The reason for the trial with high risk of bias was that blinding was not performed in the patients and they were aware of which treatment group they were allocated to.[14] The reason for the trial with unclear risk of bias was that how the blinding of patients and study personnel was performed was not adequately reported in the study.[25] The NOS scores for 3 cohort studies were all >5 points, which demonstrated that they were of high quality.

Pain VAS Score

Eight studies reported pain VAS scores.[4,14,18,19,21,24,27,30] Compared with those treated with other nonoperative therapies, patients treated with SH had a significantly improved VAS score at 1 week (WMD = −0.95; 95% CI, −1.75 to −0.16; $P = .019$), 2 weeks (WMD = −1.05; 95% CI, −2.07 to −0.03; $P = .044$), 3 weeks (WMD = −1.49; 95% CI, −2.88 to −0.11; $P = .035$), 4 weeks (WMD = −2.12; 95% CI, −4.05 to −0.19; $P = .031$) and 3 months (WMD = −1.30; 95% CI, −2.41 to −0.19; $P = .022$) (Figure 3). However, this difference was not significant at 5 weeks (WMD = −1.16; 95% CI, −2.97 to 0.65; $P = .210$), 6 weeks (WMD = −0.50; 95% CI, −1.25 to 0.24; $P = .187$), and 6 months (WMD = 0.01; 95% CI, −0.26 to 0.27; $P = .963$) (Figure 4).

Data analysis for VAS score at 3 months identified a significant heterogeneity across the included studies ($I^2 = 97.6\%$; $P < .001$). Therefore, sensitivity analysis was performed by excluding the trial with outlier.[27] This action did not change the overall estimate substantially (WMD = −0.36; 95% CI, −0.45 to −0.27; $P < .001$), and the heterogeneity was still seen ($I^2 = 87.3\%$; $P < .001$). The exclusion of the trial with small sample size did not largely alter the overall estimate (WMD = −0.41; 95% CI, −0.50 to −0.32; $P < .001$) and heterogeneity ($I^2 = 97.9\%$; $P < .001$).[18] This demonstrated that these 2 studies were not responsible for the heterogeneity.

Subgroup analysis based on the control treatments showed that SH significantly improved the pain VAS score as compared with normal saline (WMD = −0.98; 95% CI, −1.36 to −0.60; $P < .001$), rehabilitation therapy (WMD = −1.46; 95% CI, −2.43 to −0.49; $P = .003$) and oral drug (WMD = −2.13; 95% CI, −3.32 to −0.94; $P < .001$).

Subgroup analysis based on the dosage of SH showed that SH significantly improved the pain VAS score when it was administrated with a dosage of 25 mg (WMD = −0.40; 95% CI, −0.49 to −0.32; $P < .001$), 12 mg (WMD = −1.45; 95% CI, −1.74 to −1.16; $P < .001$), 20 mg (WMD = −2.17; 95% CI, −2.75 to −1.59; $P < .001$), and 5 g (WMD = −0.26; 95% CI, −0.51 to −0.02; $P = .036$).

Constant Score

Six studies reported Constant scores.[4,18,19,21,24,27] Patients in the SH group achieved a greater Constant score than those in the control group at 2 weeks (WMD = 3.25; 95%

[§]References 4, 14, 18, 19, 21, 24, 25, 27, 30.

TABLE 1
Baseline Characteristics of Patients in the Included Studies[a]

Lead Author (Year)	Country	Study Design	Treatment Arms	Patient Sex; Side Affected	Age, y, mean ± SD	Disease Duration, Months, mean ± SD	NOS Score
Tagliafico (2011)[27]	Italy	Prosp cohort	(1) SH (n = 30) (2) Untreated (n = 60)	(1) 10 M/23 F; 15 R/15 L (2) 26 M/34 F; 31 R/29 L	(1) 72 ± 6.2 (2) 71 ± 6.1	NR	6
Shibata (2001)[25]	Japan	Prosp RCT	(1) SH (n = 38) (2) Steroid (n = 40)	(1) 27 M/11 F; 25 R/13 L (2) 28 M /12 F; 29 R /11 L	(1) 59.5 ± 9.1 (2) 62.4 ± 8.6	(1) 5.8 ± 5.4 (2) 4.7 ± 5.7	NA
Oh (2011)[21]	Korea	Prosp RCT	(1) SH (n = 40 (2) Normal saline (n = 40)	(1) 20 M /20 F; 37 R /3 L (2) 19 M /21 F; 39 R /1 L	(1) 59.2 ± 8.1 (2) 60.2 ± 8.3	NR	NA
Chou (2010)[4]	China	Prosp RCT	(1) SH (n = 25) (2) Normal saline (n = 26)	(1) 16 M /9 F; 12 R /13 L (2) 19 M /10 F; 17 R /9 L	(1) 51.16 ± 7.84 (2) 52.38 ± 8.95	(1) 12.5 ± 15.1 (2) 11.7 ± 17.86	NA
Merolla (2013)[18]	Italy	Prosp cohort	(1) SH (n = 25) (2) Physiotherapy (n = 23)	(1) 14 M /11 F; 16 R /9 L (2) 12 M /11 F; 13 R /10 L	(1) 49 ± 2.35 (2) 51 ± 2.64	(1) ≥4 (2) ≥4	6
Moghtaderi (2013)[19]	Iran	Prosp RCT	(1) SH (n = 20) (2) Normal saline (n = 20)	(1) 8 M /12 F; NR (2) 6 M /14 F; NR	(1) range, 30-80 (2) range, 30-80	(1) ≥6 (2) ≥6	NA
Wang (2018)[30]	China	Prosp RCT	(1) SH (n = 49) (2) Normal saline (n = 49)	(1) 30 M /19 F; NR (2) 26 M /23 F; NR	(1) 53.92 ± 6.88 (2) 53.92 ± 6.88	(1) 25.72 ± 7.82 (2) 25.72 ± 7.82	NA
Shen (2015)[24]	China	Retrosp cohort	(1) SH (n = 23) (2) Oral drug (n = 23)	(1) NR; NR (2) NR; NR	(1) range, 35-65 (2) range, 35-65	(1) ≥3 (2) ≥3	5
Jiang (2021)[14]	China	Prosp RCT	(1) SH (n = 60) (2) Normal saline (n = 60)	(1) 40 M /20 F; 26 R /34 L (2) 36 M /24 F; 30 R /30 L	(1) 52 ± 9 (2) 52 ± 9	(1) 1.23 ± 0.17 (2) 1.23 ± 0.17	NA

[a]F, female; L, left; M, male; NA, not available; NOS, Newcastle-Ottawa Scale; NR, not reported; Prosp, prospective; R, right; RCT, randomized controlled trial; Retrosp, retrospective; SH, sodium hyaluronate.

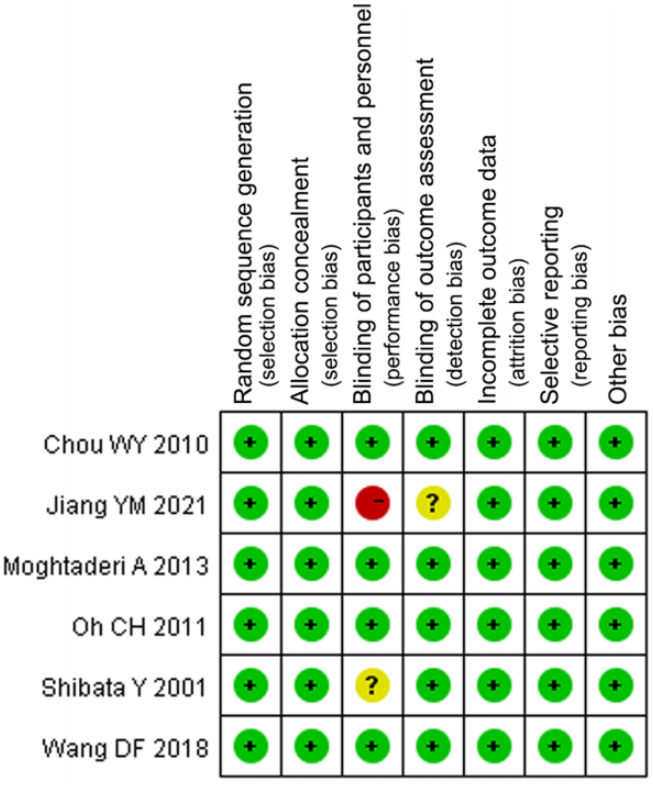

Figure 2. Risk-of-bias summary. Green, low risk; red, high risk; yellow, unclear risk.

CI, 2.36-4.13; $P < .001$), 3 months (WMD = 20.28; 95% CI, 0.54-40.03; $P = .044$), and 6 months (WMD = 5.58; 95% CI, 0.94-10.21; $P = .018$) (Figure 5).

The test for heterogeneity of Constant scores at 3 and 6 months was significant ($P < .001$). Therefore, sensitivity analysis was conducted by excluding 1 single study at each time point; however, the overall estimate and heterogeneity did not alter substantially (data not shown).

UCLA Score

Three studies reported UCLA scores.[14,25,30] Patients in the SH group had a similar effect in UCLA score to those in the control group at 4 weeks (WMD = 3.07; 95% CI, −1.15 to 7.28; $P = .154$) and 3 months (WMD = 2.62; 95% CI, −1.18 to 6.43; $P = .176$).

Patient Satisfaction

Three studies reported patient satisfaction.[4,21,25] The satisfaction rates in SH and control group were 57.03% and 48.48%, respectively, but this difference did not reach statistical significance (RR = 1.20; 95% CI, 0.96–1.49; $P = .109$).

Complications

Five studies reported no complications associated with SH injection,[4,18,19,21,25] such as flare reaction, infection, hemarthrosis, and synovitis, and the remaining 4 studies

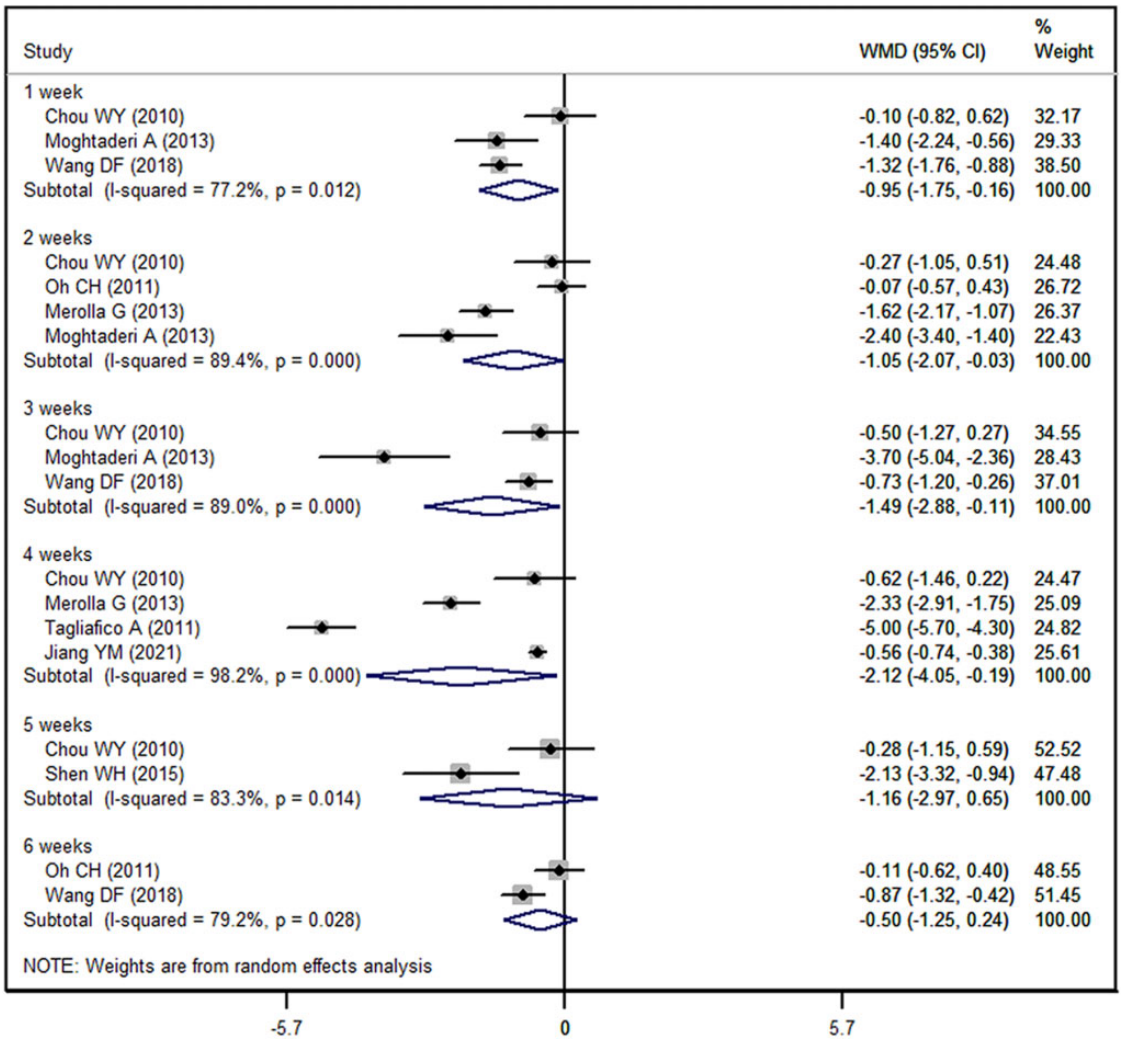

Figure 3. Forest plot showing the effect comparison between sodium hyaluronate and other treatments on pain visual analog scale score at 1, 2, 3, 4, 5, and 6 weeks postoperatively. WMD, weighted mean difference.

did not report whether there were complications affecting patients. Therefore, we were unable to perform meta-analysis to assess the safety of SH in rotator cuff tear.

Metaregression Analysis

The metaregression analysis was performed only for the VAS because of insufficient data on SH. Results demonstrated that none of the variables (sample size, tear type, control treatments), except study design (coefficient = −1.64; 95% CI, −2.64 to −0.63; $P = .002$), significantly predicted the difference in VAS score between SH and other treatments (Table 2).

Publication Bias

The assessment of publication bias did not appear significant (Egger test, $P = .138$; Begg test, $P = .451$).

DISCUSSION

In the present meta-analysis, we systematically assessed the efficacy and safety of SH in the treatment of patients with rotator cuff lesions. The results, based on 9 clinical trials, demonstrated that SH was associated with a significant improvement in VAS score at 1, 2, 3, and 4 weeks, but not at 5 and 6 weeks or 6 months, as compared with controls. The Constant score was improved significantly with the treatment of SH from 2 weeks to 6 months. However, in comparison with other nonoperative treatments, SH did not improve UCLA score or satisfaction rate.

To the best of our knowledge, this is the first meta-analysis assessing the efficacy and safety of SH on rotator cuff lesions. We found that SH improved VAS score significantly in the short term but not at long-term follow-up. The positive impact of SH on VAS score found in this study was in accordance with the findings of previous studies. Tagliafico et al[27] performed a prospective open-label nonrandomized trial in

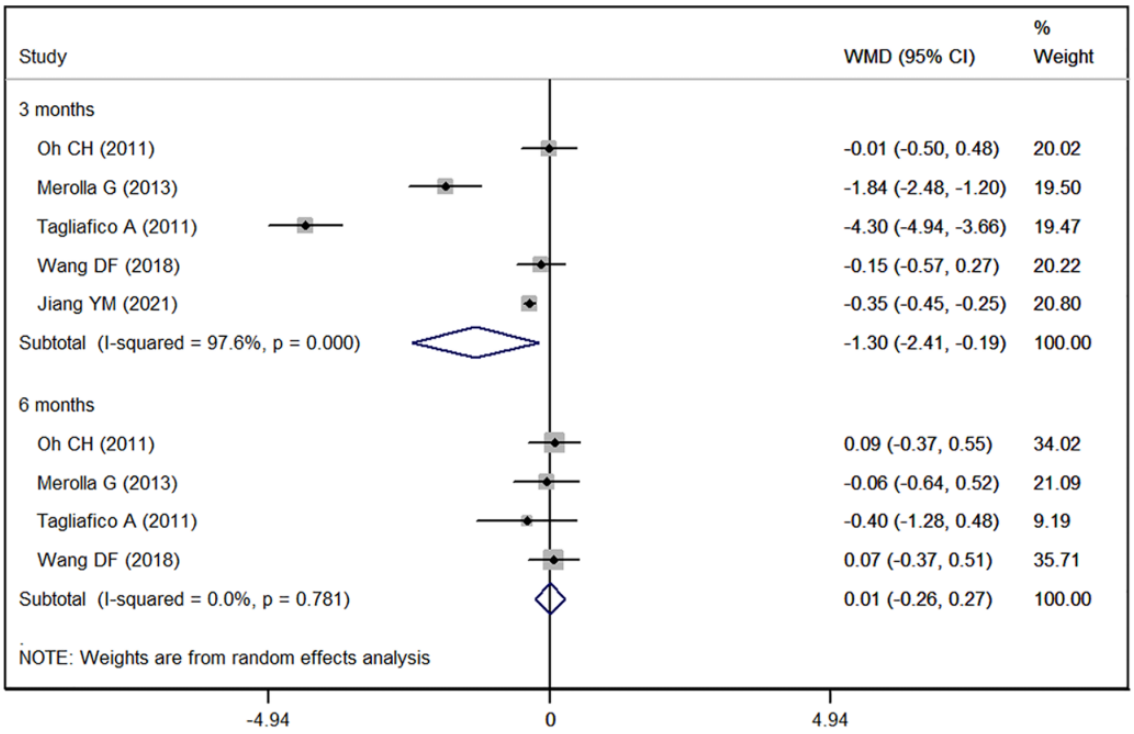

Figure 4. Forest plot showing the effect comparison between sodium hyaluronate and other treatments on visual analog scale score at 3 and 6 months postoperatively. WMD, weighted mean difference.

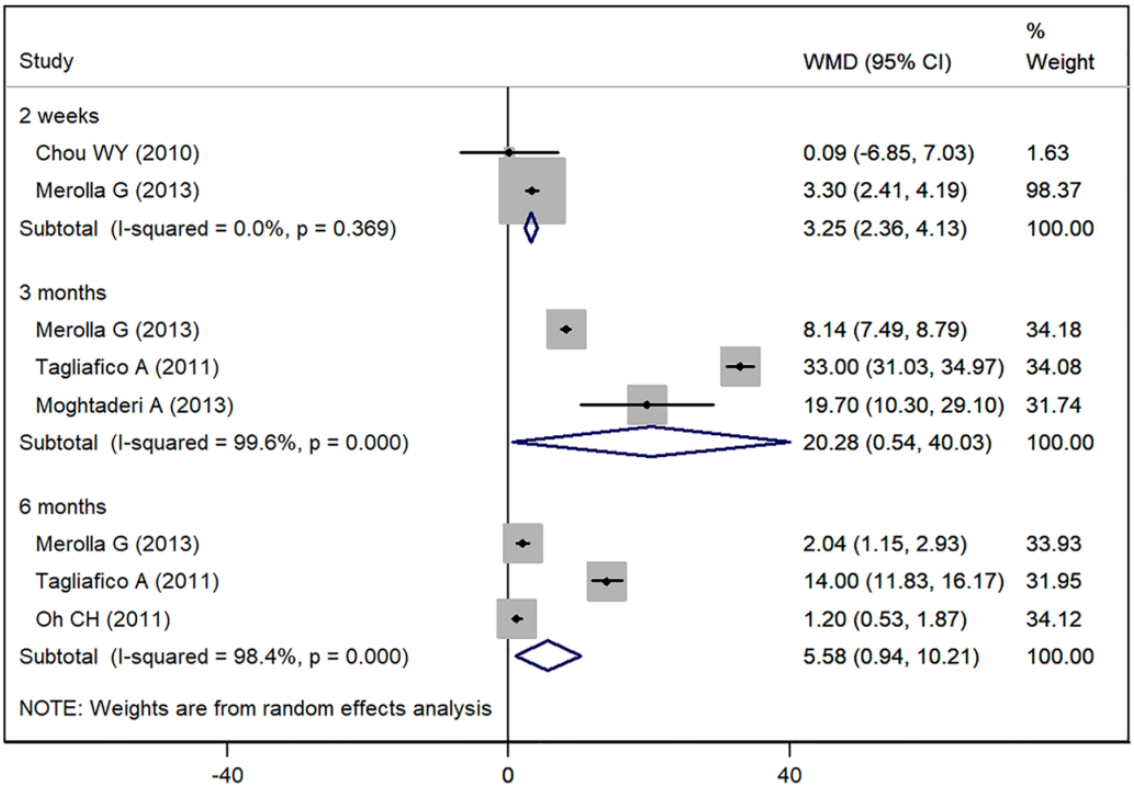

Figure 5. Forest plot showing the effect comparison between sodium hyaluronate and other treatments on Constant score at 2 weeks, 3 months, and 6 months postoperatively. WMD, weighted mean difference.

TABLE 2
Results of Metaregression Analysis for the Impact of Clinical Data on Pain VAS Score[a]

Variable	Coefficient (95% CI)	SE	t	P
Study design	−1.64 (−2.64 to −0.63)	0.49	−3.35	**.002**
Sample size	0.17 (−1.23 to 1.56)	0.68	0.24	.808
Tear type	0.95 (−0.39 to 2.29)	0.65	1.46	.157
Control treatment	−0.82 (−2.34 to 0.70)	0.74	−1.11	.278

[a]Boldface P value indicates statistical significance ($P < .05$). VAS, visual analog scale.

95 elderly patients with massive rotator cuff tears, assigned to SH treatment (n = 30) and control (n = 60) groups.[27] Patients treated with SH showed a significant decrease in the VAS score at 1 month (1.9 ± 1.2 vs 6.9 ± 2.2; $P < .001$), 2 months (1.7 ± 1.2 vs 6.8 ± 2.5; $P < .001$), 3 months (2.3 ± 1.2 vs 6.6 ± 1.9; $P < .001$), and 4 months (3.3 ± 1.4 vs 7.8 ± 3.1; $P < .001$), as compared with controls.[27] However, after 5 months, the differences were not significant. Similarly, in another prospective randomized comparison study comparing arthroscopic repair combined with SH versus traditional arthroscopic repair,[30] significant improvements in VAS score were observed between the 2 treatments at short-term but not at long-term follow-up visits. In the latter study, the postoperative VAS scores at 1, 3, and 6 weeks in the combination group were 5.04 ± 1.15, 4.13 ± 1.25, and 3.15 ± 0.96, which was significantly better than the scores of 6.36 ± 1.08, 4.56 ± 1.14, and 4.02 ± 1.27 seen in the traditional group, respectively.[30] However, the difference between them was no longer significant at 12 weeks (3.09 ± 0.96 vs 3.24 ± 1.17) and 6 months postoperatively (2.65 ± 1.03 vs 2.58 ± 1.21).[30] The authors concluded that arthroscopic rotator cuff repair combined with SH could effectively alleviate pain in the short term.

Contrasting results were obtained by Chou et al[4] in a randomized, double-blind, placebo-controlled study that aimed to assess the effect of SH on rotator cuff lesion without complete tears. This latter trial enrolled 51 patients, of whom 25 had injections of 25mg/week of SH into the subacromial bursa for 5 consecutive weeks (SH group) and 26 received 2.5 ml of normal saline solution with the same injection protocol as the SH group (control group).[4] The VAS score was similar in both groups at 1 to 5 weeks after injection, but a significant difference was observed at the 6-week follow-up visit.[4] The authors hypothesized that the unexpected negative results might be due to the lack of information on the natural processes of symptomatic rotator cuff lesions without complete tears, and the scarcity of comparison with subacromial steroid injection.[4]

Our results showed that the Constant score in the SH group was better than that of the control group at 2 weeks, 3 months, and 6 months. Our results were in accordance with those of previous studies.[18,19,27] Merolla et al[18] compared the subacromial SH injections with rehabilitation therapy in patients with rotator cuff tendinopathy. A total of 48 patients were enrolled, of whom 25 received ultrasound-guided subacromial SH and 23 underwent rehabilitation therapy.[18] The Constant scores in the SH group at 3 and 6 months were 67.44 ± 1.09 and 59.04 ± 1.13, higher than 59.30 ± 1.21 and 57 ± 1.89 in the rehabilitation group ($P < .01$), respectively. With regard to the short-term effect of SH, Chou et al[4] reported that SH had similar Constant score with placebo. In that study, the Constant scores at 3, 4, and 5 weeks in the 2 treatments were 68.16 ± 13.92 versus 69.04 ± 9.75, 70.04 ± 14.62 versus 70.00 ± 10.58, and 71.2 ± 15.04 versus 71.62 ± 10.69, respectively.[4]

In the present study, the effect of SH on patient satisfaction was found to be the same as that of other treatments. The patients in SH group showed a satisfaction rate similar to those in the control group. Shibata et al[25] suggested that patients who do not place much pressure on their shoulders are more likely to be satisfied by the conservative treatments. Interestingly, their results were similar to ours; in our analysis, patients in the SH group achieved a satisfaction rate comparable with that of patients in the steroid group.

Limitations

Several limitations to this review should be acknowledged. First, some of the included studies had a relatively small sample size. As compared with larger trials, studies with small sample size are more likely to overestimate the treatment effect. Second, significant heterogeneity was identified in some outcomes. However, this is not surprising given the differences in study design, sample size, injection approach, time from symptoms to treatment, and treatment regimen. All these factors might have affected the overall estimate and contributed to the heterogeneity. Third, most of the included studies assessed the effects of SH at a short-term follow-up; therefore, we could not obtain data from these studies to evaluate the long-term effects of SH on rotator cuff lesion. Further long-term studies focusing on this topic are warranted.

CONCLUSION

The present study demonstrated that pain and shoulder function were improved significantly after SH treatment. Thus, SH is effective in treating patients with rotator cuff lesions and can be used as an alternative regimen in patients with rotator cuff lesions. Based on the promising results and potential limitations, more large-scale, randomized trials are needed to verify our findings and explore the long-term effects of SH in these patients.

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