

Systematic Review

High- versus Low-dose Steroid Injection for Adhesive Capsulitis (Frozen Shoulder): A Systematic Review and Meta-analysis

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Background: Intraarticular steroid injections are a commonly used and proven treatment for frozen shoulder; however, there is no scientific basis for a certified dose.

Objectives: This study aimed to identify the difference between high- and low-dose steroid injections treatments and suggest an appropriate dose.

Study Design: Systematic review and meta-analysis.

Methods: The MEDLINE, EMBASE, and Cochrane electronic databases were searched through February 15, 2023 for eligible randomized controlled trials. The effects of high- and low-dose steroid injections were calculated as standardized mean differences (SMD) in pain, shoulder range of motion (ROM), and functional improvement. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate evidence quality.

Results: Four studies with 274 patients were included in the final analysis. The meta-analysis showed that improvement in pain (SMD, 0.10; 95% CI, -0.12 to 0.32), ROM (SMD, 0.07; 95% CI, -0.05 to 0.19), and functional improvement (SMD, 0.08; 95% CI, -0.10 to 0.26) did not differ significantly between the high- and low-dose steroid injections. Subgroup follow-up analyses also showed no clinically significant differences in SMD for pain, ROM, and functional scale measurement in any subgroups (after 3 weeks, 6 weeks, and one year). One article described that, although there was no significant difference in adverse events frequency between the high- and low-dose groups, flushing tended to occur more frequently in the high-dose group.

Limitations: Limitations are the small number of studies included in the meta-analysis, no disease stage considered, and a short follow-up period.

Conclusions: This meta-analysis suggests there are no significant differences between the high- and low-dose steroid groups in pain, ROM, or functional improvement. Therefore, considering the side effects of high-dose steroids, starting with low-dose steroids is recommended. However, further studies are needed to establish exact protocols according to disease severity.

Key words: Frozen shoulder, adhesive capsulitis, steroids, triamcinolone acetonide, injections, intraarticular, optimal dose, meta-analysis, randomized controlled trial

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Shoulder pain is a common health problem with a lifetime prevalence of 6.7%–66.7% (1-4). Common conditions that can result in shoulder pain are rotator cuff disorder, frozen shoulder, shoulder instability, and shoulder arthritis (4). Frozen shoulder, also known as adhesive capsulitis, is a pathologic process involving contracture of the glenohumeral capsule (5). Frozen shoulder presents as pain, restriction of passive shoulder range of motion (ROM), and dysfunction of the affected shoulder (6,7). Frozen shoulder affects about 2% of the general population, with a higher incidence among women and those aged 40–60 (8). Individuals with type 1 diabetes mellitus have a 40% chance of developing this condition in their lifetimes, while up to 29% of those with type 2 diabetes mellitus may also be affected (9). Frozen shoulder is also associated with prolonged immobilization, thyroid disease, stroke, myocardial infarction, and autoimmune disease (10).

The prevailing notion is that frozen shoulder arises mainly from capsular fibrosis and a decrease in capsular volume resulting from an inflammatory response (11). Clinically, frozen shoulder treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs) and oral or intraarticular steroids for anti-inflammatory effects, hyaluronic acid injection for viscosupplementation, hydraulic distension to increase joint volume, and physical therapy, depending on the pathophysiologic cause (5,7). Among treatments, intraarticular steroid injections are effective and safe for frozen shoulder with an effect that may last as long as 24–36 weeks (12).

Intra-articular steroid injections target the lesion site of the inflammatory process in the humeral joint. High concentrations of glucocorticoids induce immunosuppressive and anti-inflammatory responses through membrane protein modification, adenosine triphosphate (ATP) production, and ion cycling in the cell membrane (13,14). In addition, when glucocorticoids enter the cytoplasm, they bind to glucocorticoid receptors and stop the transcription of target genes, thereby reducing pro-inflammatory mediators (cytokines, chemokines, adhesion molecules) and modulating anti-inflammatory and metabolic pathways (15). As a result, patients may see improvements in pain due to reduced inflammatory processes and improvements in ROM due to reduced inflammatory capsular fibrosis. There is also increasing use of triamcinolone, a synthetic corticosteroid that exerts anti-inflammatory effects by inhibiting arachidonic acid synthesis and has relatively fewer mineralocorticoid side effects than other corticosteroids (16).

However, many studies reported used different types of steroids (triamcinolone acetonide, glucocorticoid, or prednisolone) at varying dosages (17-20). Due to the lack of certified doses, many doctors tend to choose doses based on personal experience rather than scientific evidence. High doses of steroids increase local (atrophy of subcutaneous fatty tissue, local depigmentation of skin, tendon rupture) and systemic (irregular menstruation, hot flashes, high blood sugar) complications; therefore, finding the right dose is important (21). We defined the high-dose group as a full, one-vial dose (e.g., triamcinolone acetonide 40 mg or methylprednisolone 40 mg, etc.) and the low-dose group as a half- or quarter-vial dose (e.g., triamcinolone acetonide 20 mg or triamcinolone acetonide 10 mg or methylprednisolone 20 mg or methylprednisolone 10 mg, etc.). The purpose of this study was to find out whether the pain scale, (ROM, and functional improvement were different according to high- and low-dose steroid injections for frozen shoulder.

METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement (22,23). The PRISMA checklist is provided in Supplementary Material S1. This review protocol was registered with the International Prospective Register of Systematic Reviews (no. CRD42022319343).

Search Strategy and Study Selection Process

We searched for articles in the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases published through February 15, 2023. Key terms used in the search were: (“shoulder pain” or “frozen shoulder” or “adhesive capsulitis”) AND (“intra-articular injection” or “steroid injection” or “shoulder injection”). The search strategies used for each database are shown in Supplementary Material S2.

Study inclusion criteria followed the population, intervention, comparison, outcome, and study design (PICOS) framework. Population (P): Patients diagnosed with frozen shoulder and treated with intraarticular steroid injections. Intervention (I): One full vial of high-dose steroid injection. Comparison (C): Low-dose steroid injection, administered in one-half or one-fourth vial doses. Outcome (O): Objective assessment tool scores for pain, range of motion, and functional improvement. Study Design (S): Randomized controlled trial reporting mean, standard deviation, and the P

value of mean difference for each treatment group outcome.

Studies with the following were excluded from the analysis: 1) populations with shoulder pain from causes other than frozen shoulder; 2) interventions other than intraarticular steroid injections; 3) a control group that received a placebo or a conservative treatment rather than a low-dose intraarticular steroid injection; 4) outcomes were not objective assessment scores or lacked data such as means, standard deviations, and *P* values; and 5) the study design was a review, an editorial, or other nonclinical trial design. Two reviewers (SJK, JMP) independently reviewed the titles and abstracts of the retrieved articles to determine their eligibility. Disagreements were resolved through discussion with a third reviewer (JS). Studies that did not meet the inclusion criteria were excluded.

Data Extraction Process

The following information was extracted from the included studies: first author, year of publication, trial design, patient demographics, intervention drug (triamcinolone acetonide or methylprednisolone acetate), steroid dose, sample size (total and per arm), scales and measures used to evaluate interventional efficacy, baseline and endpoint outcome measures, follow up duration, and adverse events.

Treatment effectiveness was measured in 3 dimensions: pain, ROM, and functional improvement. The pain portion was extracted from patient-reported Visual Analog Scale or Numeric Rating Scale score data. For ROM, data obtained by measuring flexion, extension, abduction, internal rotation, and external rotation of the shoulder joint with a goniometer were extracted. The functional part was extracted from the Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons, and Simple Shoulder Test performed on the patients. All results were extracted as continuous data; if there were repeated measurements during each follow-up period, all time points were extracted separately. Data values displayed only graphically in the study were extracted using Image J software. For studies providing insufficient data, the mean and SD of the change from baseline was calculated with reference to Chapter 6 of the Cochrane Handbook, version 6.3 (The Nordic Cochrane Centre for The Cochrane Collaboration).

Quality Assessment

We assessed study quality using the Revised Co-

chrane Risk of Bias Tool for Randomized Trials (RoB2). Two reviewers (SJK, JMP) performed the scoring independently. The RoB2 has 5 parts (randomization process, deviation from intended intervention, omission of outcome data, outcome measurement, and selection of reported outcomes), with each rated as low, some concern, high risk of bias, and no information (24). Discrepancies in the ratings were resolved through discussion among the investigators. The risk of bias figure was generated using the RobVis Tool, a web application that supports visualization (25). The certainty of the evidence in our meta-analyses was evaluated using The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool, which assesses evidence in 5 domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence is categorized as high, moderate, low, or very low (26).

Statistical Analysis

To determine the agreement level between 2 reviewers for study inclusion, the Cohen's κ statistic was employed. A meta-analysis obtained the effect size of steroid dose-dependent effects. A fixed-effects model was used since the samples were homogeneous because all patients were diagnosed with frozen shoulder. Effect size was calculated based on the mean pre to post change in the high dose group minus the mean pre to post change in the low dose group, divided by the pooled pretest standard deviation (27). The standardized mean difference (SMD) and 95% CI were calculated for each study, and the results were pooled.

The degree of heterogeneity was assessed using the I^2 statistic, which ranges from 0% to 100% with cutoff values of 25%, 50%, and 75% representing low, medium, and high levels of heterogeneity, respectively (28). Publication bias was assessed by visual inspection of funnel plots and Egger's test (29). All statistical tests were 2-sided; values of $P < 0.05$ were considered statistically significant. All analyses were conducted using Stata version 17 (Stata Corp LP).

RESULTS

Study Identification and Characteristics

A total of 1,108 studies were identified in the initial search. After duplicate removal, 709 studies remained. After title and abstract screening, 6 articles remained and were subjected to full screening. One article was excluded for being an editorial; another was excluded

due to patients having shoulder pain other than frozen shoulder. Finally, 4 studies were included in the final meta-analysis.

The degree of agreement on full-text review was calculated with a κ score (κ : 0.571, standard error = 0.353), showing moderate agreement among reviewers. A flow chart of the study selection process is shown in Fig. 1.

Our meta-analysis included a total of 4 studies of 274 patients with frozen shoulder. All high-dose groups received 40 mg of triamcinolone acetonide ($n = 137$). In most studies, the low-dose group received 20 mg of triamcinolone acetonide; in one study (30) 10 mg of triamcinolone acetonide was administered. The low-dose groups had 2 more patients than the high-dose groups ($n = 139$). The average patient age was between 52 (31) and 60 (32) years. All studies included both men and

women. Frozen shoulder symptom duration ranged from 2.4 months (32) to 18.1 months (33). Detailed characteristics of the included studies are shown in Table 1.

Risk of Bias Assessment and Publication Bias

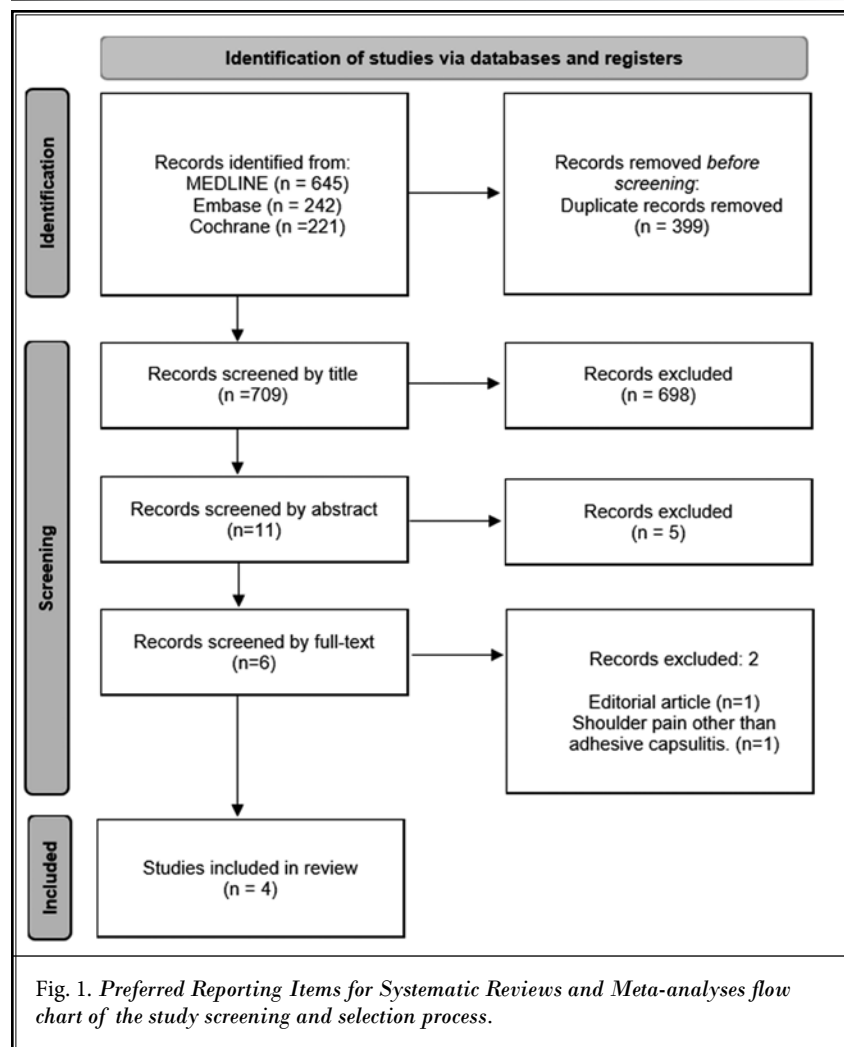
Of the 4 included studies, 2 were rated as having a low risk of bias and the other 2 were rated to be of some concern for a risk of bias. All 4 studies were randomized and double-blind and the effect of intervention knowledge was small; therefore, there was a low risk of deviation from the intended intervention bias and detection bias. In 2 studies (30,33) intervention outcomes data were missing due to patient loss to follow-up, and missing outcome bias was assessed to be of some concern. Two studies (30,33) did not specify a prerandomized study protocol, so selection bias was evaluated to be of some concern (Fig. 2).

The funnel plot and Egger's test revealed no significant evidence of publication bias in terms of pain ($P = 0.941$), ROM ($P = 0.105$) and functional improvement ($P = 0.719$) (Fig. 3).

Effect of High- and Low-dose Steroid Injections on Pain Improvement

Our meta-analysis showed no clinically important difference in the SMD for pain between the high- and low-dose steroid injection groups (SMD, 0.10; 95% CI, -0.12 to 0.32). The duration of follow-up differed among studies, varying from 3 weeks to more than one year. A subgroup analysis of the follow-up period showed no clinically important difference in the SMD for pain in any subgroups (after 3 weeks, 6 weeks, and one year).

Two studies (31,32) that followed up patient pain scale scores after 3 weeks showed no clinically important intergroup difference (SMD, 0.03; 95% CI, -0.44 to 0.50). Two studies (30,31) that followed up patient pain scores after 6

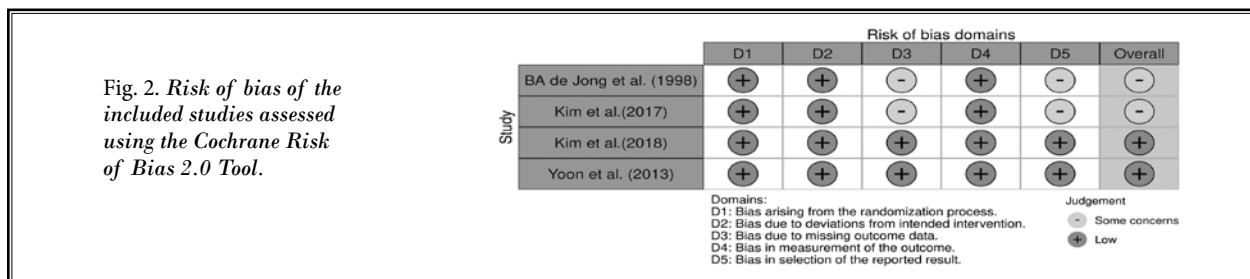


Steroid Injection Dose for Frozen Shoulder

Table 1. Main outcomes of the studies included in this systematic review and meta-analysis.

Author	Study Design	Factor	High-dose Group	Low-dose Group	Method	Follow-up Duration	Outcome Variable	Conclusion
de Jong et al. (1998)	RCT	Steroid type, dose	Triple injection of TA 40 mg	Triple injection of TA 10 mg	Posterior approach	6 weeks	VAS score Sleep disturbance Functional impairment Movement restriction	The 40 mg dose group showed significantly greater improvement in pain, sleep disturbance, and ROM than the 10 mg dose group.
		No. of participants	25	32				
		Age	55.0 ± 9.1	54.5 ± 9.1	Blind injection			
		Men/Women	9/15	13/19				
		Symptom duration (mos)	8.0 ± 6.2	6.8 ± 4.0				
Kim et al. (2017)	RCT	Steroid type, dose	Single injection of TA 40 mg	Single injection of TA 20 mg	Posterior approach	3 weeks, 6 weeks, 12 weeks, 6 months, 12 months	VAS score ROM American Shoulder and Elbow Surgeons score Simple Shoulder Test Blood glucose level Fructosamine level Glycated hemoglobin	Triamcinolone is an effective method for improving ROM and clinical function. No significant difference was noted between doses. A lower dose is recommended in diabetics, as short-term glucose levels may increase with high doses.
		No. of participants	76	71				
		Age	57.4	56.34	Ultrasound-guided Injection			
		Men/Women	23/53	18/53				
		Symptom duration (mos)	17.6	18.1				
Kim et al. (2018)	RCT	Steroid type, dose	Single injection of TA 40 mg	Single injection of TA 20 mg	Posterior approach	3 weeks	Pain NRS ROM SPADI	NRS and SPADI scores showed significant improvement in both dose groups. There was no statistically significant difference between groups. The change in passive ROM did not differ significantly between groups.
		No. of participants	16	14				
		Age	55.6 ± 11.8	60.7 ± 10.0	Ultrasound-guided Injection			
		Men/Women	4/12	3/13				
		Symptom duration (mos)	3.3 ± 2.4	2.4 ± 2.0				
Yoon et al. (2013)	RCT	Steroid type, dose	Single injection of TA 40 mg	Single injection of TA 20 mg	Posterior approach	One weeks 3 weeks, 6 weeks, 12 weeks	VAS score ROM SPADI	SPADI and VAS scores in flexion, abduction, and internal rotation showed significant improvement in both groups. No significant intergroup differences were noted.
		No. of participants	20	20				
		Age	54.2 ± 5.1	52.2 ± 3.8	Ultrasound-guided Injection			
		Men/Women	10/10	12/8				
		Symptom duration (mos)	5.5 ± 2.5	4.7 ± 2.1				

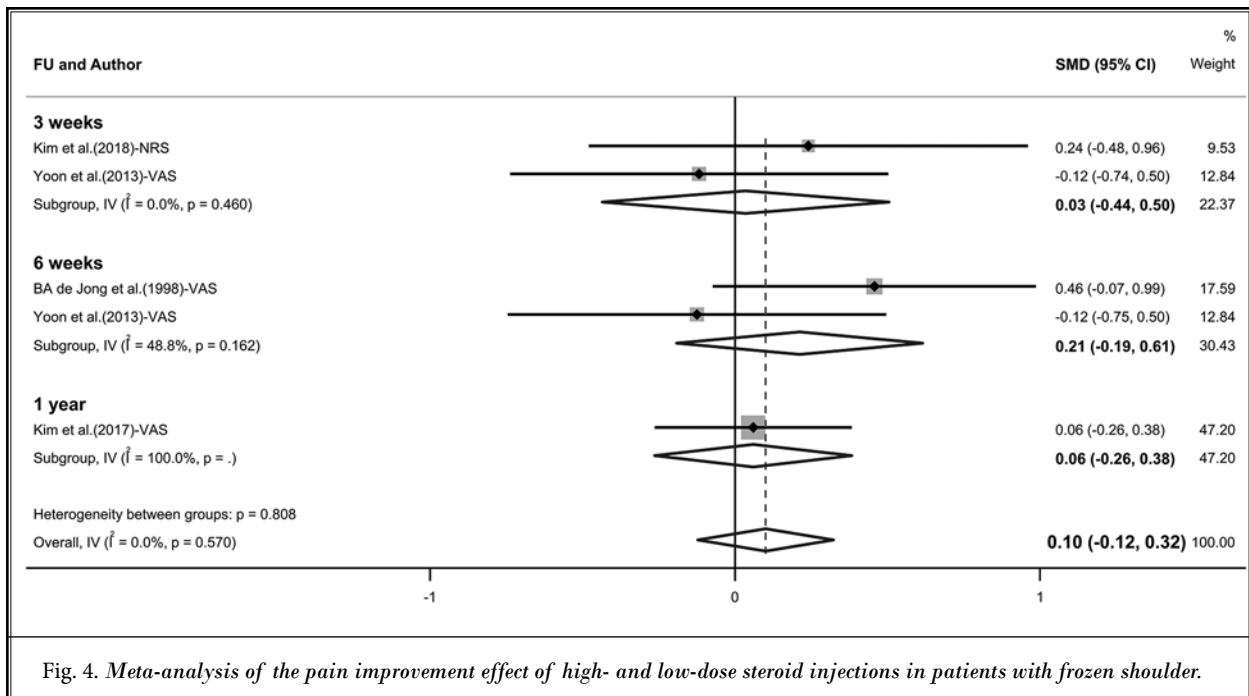
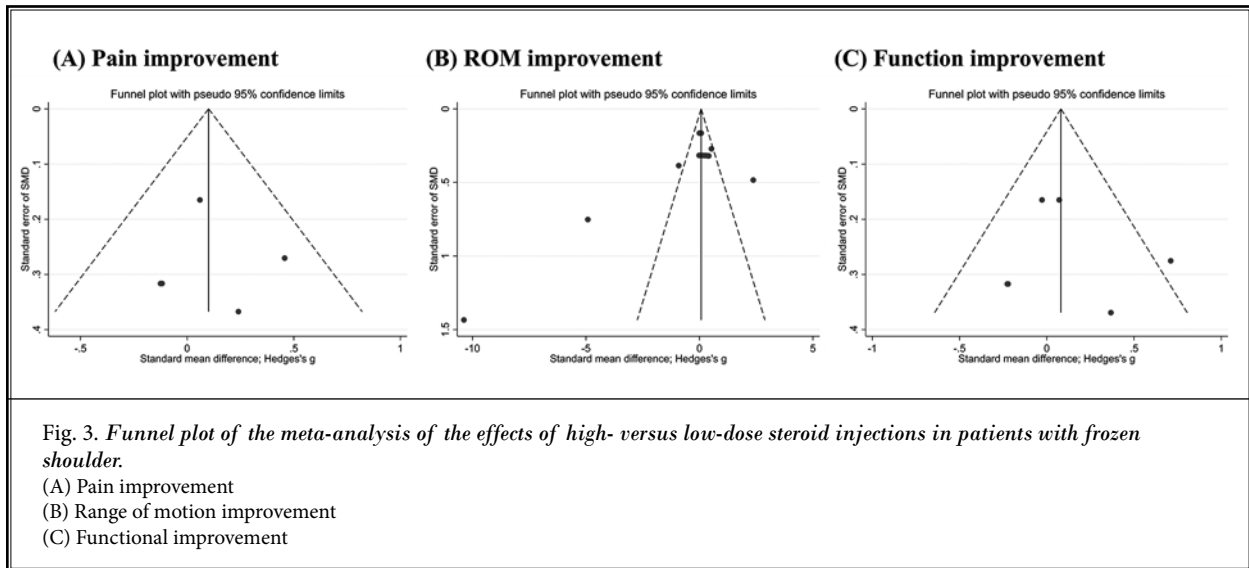
NRS, Numeric Rating Scale; RCT, randomized controlled trial; ROM, range of motion; SPADI, Shoulder Pain and Disability Index score; TA, triamcinolone acetone; VAS, Visual Analog Scale



weeks showed no clinically beneficial effect on pain score (SMD, 0.21; 95% CI, -0.19 to 0.61). One study (33) that followed up patient pain scores at more than one year showed no clinically important difference (SMD, 0.06; 95% CI, -0.26 to 0.38) (Fig. 4). According to the GRADE system, the quality of the evidence for pain improvement was considered moderate and downgraded for imprecision (Table 2).

Effect of High- and Low-dose Steroid Injections on Shoulder ROM Improvement

Our meta-analysis of ROM showed no clinically important intergroup difference (SMD, 0.07; 95% CI, -0.05 to 0.19). In a subgroup analysis of the follow-up period, 2 studies (31,32) that followed up patient pain scale scores after 3 weeks showed no clinically important intergroup difference in pain scores (SMD, 0.02; 95% CI, -0.23 to 0.27).



At 6 weeks of follow-up, 2 studies (30,31) showed no clinically beneficial effect on ROM (SMD, 0.23; 95% CI, -0.02 to 0.48). At more than one year of follow-up, one study (33) showed no significant intergroup difference (SMD, 0.03;

95% CI, -0.13 to 0.19) (Fig. 5). The quality of the evidence for shoulder ROM improvement according to the GRADE system was considered low and downgraded due to inconsistency and imprecision (Table 2).

Table 2. Summary of findings and quality of evidence assessment using the GRADE approach.

Outcome measure	Summary of Findings			Quality of Evidence Assessment (GRADE)					
	No of patients (trials)	Effect size (95% CI)	I ² %	Risk of bias ^a	Inconsistency ^b	Indirectness ^c	Imprecision ^d	Publication bias ^e	Quality of evidence ^f
Pain improvement	314 (5)	0.10 (-0.12, 0.32)	0	Not Serious	Not Serious	Not Serious	Serious	Not Serious	Moderate
Shoulder ROM improvement	1045 (19)	0.07 (-0.05, 0.19)	86.4	Not Serious	Serious	Not Serious	Serious	Not Serious	Low
Functional improvement	461 (6)	0.08 (-0.10, 0.26)	38.3	Not Serious	Not Serious	Not Serious	Serious	Not Serious	Moderate

^a Risk of bias based on the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2). ^b Downgraded if significant unexplained heterogeneity (I² > 50%, P < 0.10) not explained by meta-regression or subgroup analysis. ^c Downgraded if there were any factors related to patients, interventions, or results that limited the generalizability of the results. ^d Downgraded if the 95% CI crossed the benefit or harm. ^e Downgraded if there was evidence of publication bias using Egger's test. ^f Because all included studies were meta-analyses of randomized clinical trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded according to prespecified criteria. Quality is graded as high, medium, low, and very low.

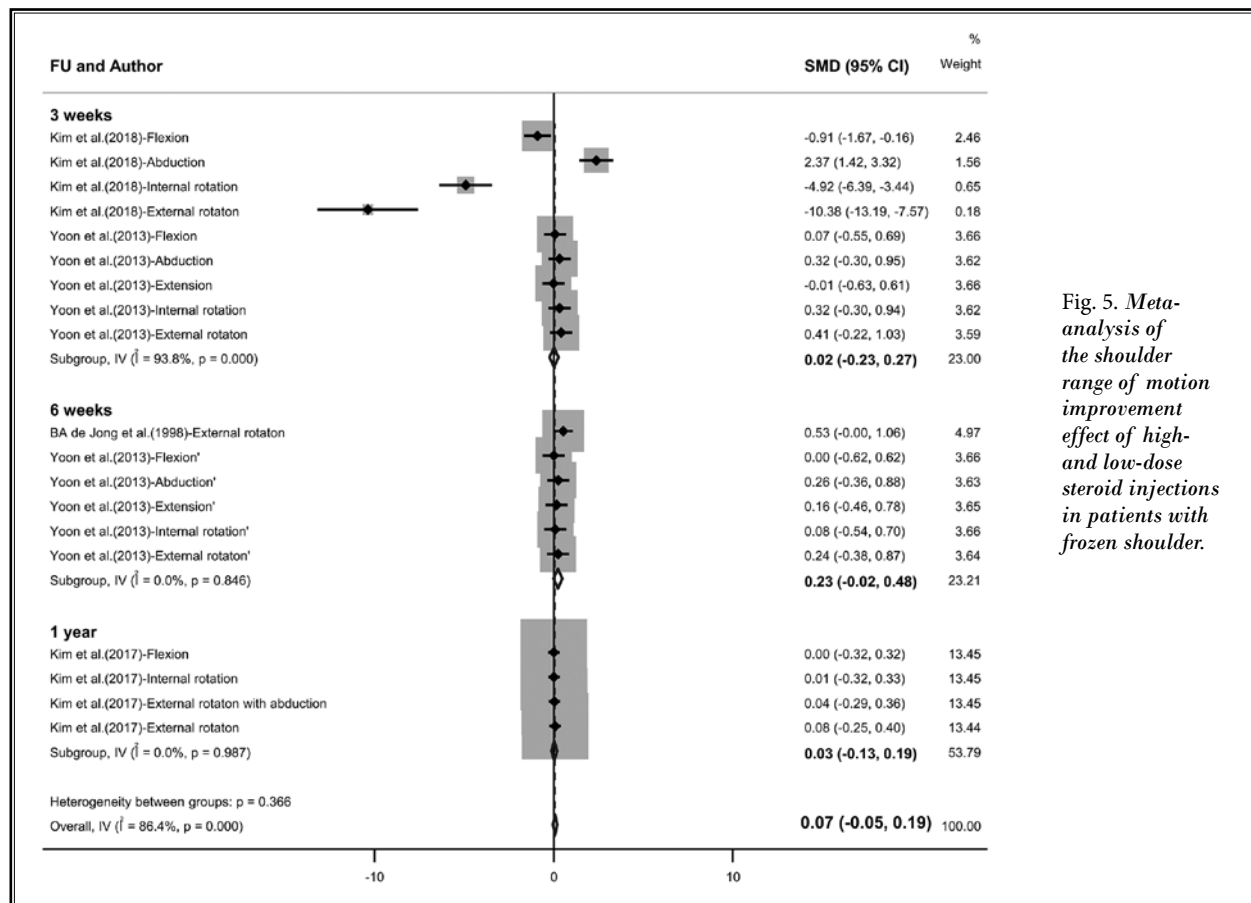


Fig. 5. Meta-analysis of the shoulder range of motion improvement effect of high- and low-dose steroid injections in patients with frozen shoulder.

Effect of High- and Low-dose Steroid Injections on Functional Improvement

Our meta-analysis of functional improvement also showed no clinically important intergroup difference (SMD, 0.08; 95% CI, -0.10 to 0.26). A subgroup analysis of the follow-up period also showed no clinically important intergroup difference (3 weeks of follow-up: SMD, 0.03; 95% CI, -0.44 to 0.50; 6 weeks of follow-up: SMD, 0.31; 95% CI, -0.10 to 0.72; one year of follow-up: SMD, 0.02; 95% CI, -0.21 to 0.25) (Fig. 6). According to the GRADE system, the quality of the evidence for functional improvement was considered moderate and downgraded for imprecision (Table 2).

Safety and Adverse Events

One study (30) identified the side effects of intraarticular steroid injections including pain, flushing, menstrual irregularities, headache, and rash. No significant difference was noted in the frequency of side effects. However, flushing was somewhat more common and more severe in the high-dose group. Although not investigated as an adverse event in one study (33), secondary results showed that the high-dose group had significantly higher mean blood sugar levels at 6 weeks than the low-dose group. However, there

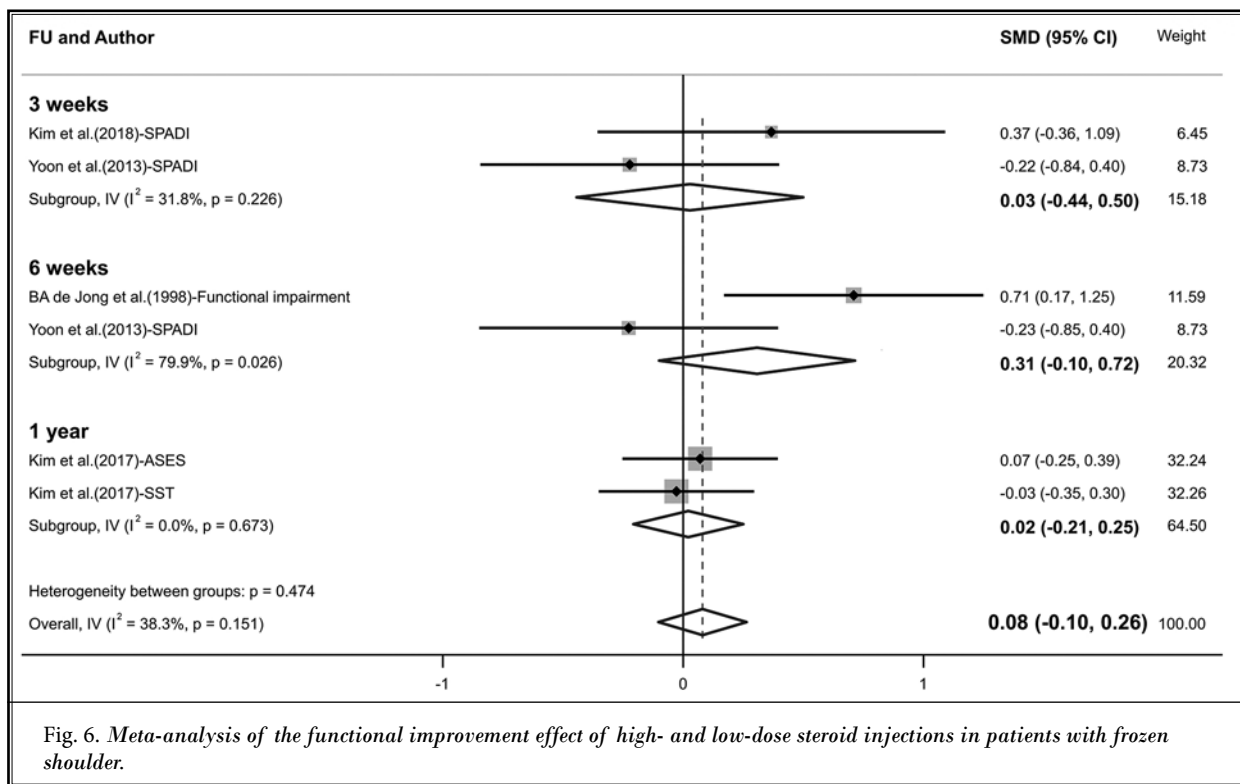
were no significant differences in blood glucose, fructosamine, and glycated hemoglobin levels before versus after the injections. There were no reports of safety in any studies or of adverse events in 2 studies (31,32).

DISCUSSION

This systematic review and meta-analysis compared the efficacy of different dosages of steroid injections in patients with frozen shoulder. Our results showed no clinically important difference in the low- versus high-dose steroid injection groups.

Pathological changes in frozen shoulder are considered inflammatory and fibrotic conditions (34). Intraarticular corticosteroids provide chemical clearance of synovitis and limit the subsequent development of fibrosis, reducing pain perception and leading to early acceleration of functional recovery (35).

Many studies have shown that intraarticular steroid therapy is superior to other treatments for frozen shoulder. Compared to physical therapy alone, corticosteroid injections improved Shoulder Disability Questionnaire (19), SPADI (20), and ROM scores (36). Compared to ice pack application and intraarticular corticosteroid treatment, corticosteroid treatment provided an earlier return of shoulder motion (36) and im-



proved SPADI scores (20). Intraarticular corticosteroids showed superior results to oral glucocorticoids in more objective shoulder scores (Simple Shoulder Test, Constant-Murley score), ROM, and patient satisfaction (37). Intraarticular corticosteroids and manipulation under anesthesia demonstrated no significant differences in Constant-Murley score, Visual Analog Scale, and Short Form-36 (SF-36) health survey scores (38). Therefore, intraarticular injection treatment is preferred because of the risks associated with manipulation under anesthesia (38).

However, steroid injections may also cause local and systemic side effects from the steroid itself. In vitro (39) and animal model (40) studies have confirmed that corticosteroids inhibit chondrocyte proliferation and cartilage repair and can cause cartilage damage. Another local side effect is tendon rupture. In vitro studies have reported that triamcinolone acetonide inhibits collagen synthesis with chondrotoxic effects and inhibitory activity on human tenocytes (41,42). Moreover, clinical trials have confirmed that corticosteroids cause local side effects such as atrophy of the subcutaneous fat tissue, local depigmentation of the skin, and nerve lesions (21). Systemic side effects, such as an increased infection rate (43), weight gain (44,45), avascular necrosis of the bone, menstrual irregularities, hot flushes, and hyperglycemia in patients with diabetes mellitus (21) have also been reported. And finally, the long-term use of steroids can induce diabetes mellitus (46).

Our study reached an important conclusion that low-dose steroid treatment is recommended to reduce steroid side effects due to the lack of a significant difference between high- and low-dose steroids in the treatment of frozen shoulder. Of the 4 included studies, de Jong et al (30) was the only one to report that a low dose of triamcinolone acetonide (10 mg) had a better therapeutic effect than a high dose. The other study that used a low dose of triamcinolone acetonide (20 mg) showed no significant difference from high dose (40 mg). In summary, intraarticular treatment with 20 mg of triamcinolone acetonide is recommended for its therapeutic effect and its reduced chance of side effects.

Strengths and Limitations

The primary strength of this meta-analysis is that it is the first study to analyze the effects of high- versus low-dose steroid injections in patients with frozen shoulder, followed by a subgroup analysis of each effect by follow-up period.

There are a few limitations to this study. First, the total number of studies included in the meta-analysis was small. There was a study comparing methylprednisolone and triamcinolone acetonide by dose in a clinical trial for shoulder pain caused by subacromial bursa (47), but only a study comparing triamcinolone acetonide by dose in frozen shoulder. To reduce heterogeneity, we included only those studies in which shoulder pain was due to frozen shoulder and excluded those in which other causes were present.

Second, the disease stage of the included patients was not considered. Frozen shoulder has 3 known stages (48,49). The first stage, "freezing," is characterized by progressive pain and loss of motion that lasts up to 9 months. In the second phase, "frozen," which lasts 4–20 months, pain improves but stiffness persists and affects the patient's ability to perform activities of daily living. The third and final "thawing" stage involves gradual improvement in shoulder ROM that may take 5–26 months. Disease stage at the time of treatment may affect treatment efficacy. Although the symptom duration of the patients included in the study varied from 2.4 months (32) to 18.1 months (33), no information was provided about stage.

Third, the follow-up period was short. The longest follow-up period was one year (33), while the others were 3 weeks (32), 6 weeks (30), and 12 weeks (31). The disease course of frozen shoulder is unclear, but most patients report that, regardless of treatment, maximum improvement occurs at 2–4 years after treatment (50). Considering the course of the disease, it seems necessary to confirm the long-term treatment effects.

Fourth, studies with different injection frequencies were included. Three (31–33) of the 4 included papers were all single injections, and only one paper (30) described the use of an additional injection of the same dose one–2 weeks later. Since this was the only study in which a high dose showed a more significant effect than a low dose, a unified analysis of dose and number of injections is needed in the future. Therefore, future large-scale randomized controlled clinical trials and long-term follow-up studies are needed that analyze frozen shoulder stage, steroid type, injection method, and multiple consecutive treatments. Through such studies, a clear steroid injection treatment protocol can be developed.

CONCLUSIONS

This meta-analysis detected no significant differences in pain, ROM, and functional improvement be-

tween high- and low-dose steroid injection treatment in patients with frozen shoulder. These results were the same for all follow-up periods of 3 weeks, 6 weeks, and one year. Considering the side effects of high-dose steroids, a steroid dose of 20 mg is recommended as initial treatment in patients with frozen shoulder. However, since our study did not classify patients by disease severity, further studies are needed to confirm our findings.

Authors' Contributions

Study design: SJK, JMP, JMS. Initial screening: SJK, JMP. Full-text review and data extraction: SJK, JMP. Statistical analyses: SJK, JMP, JMS. Drafting of the initial manuscript: SJK, JMP, JMS, SYY, JIS, SCL. Contribution to and review of the final version of the manuscript: SJK, JMP, JMS, SYY, JIS, SCL.

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