Injection Therapies for Rotator Cuff Disease

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KEYWORDS

• Injection • Therapy • Rotator cuff • Calcific tendinitis • Corticosteroid • Prolotherapy • Platelet-rich plasma • Stem cell

KEY POINTS

- Numerous injection therapies have been used for the treatment of rotator cuff disease, including corticosteroid, prolotherapy, platelet-rich plasma, stem cells, and ultrasound-guided barbotage for calcific tendinitis.
- Although the cornerstone of injection therapy consists of administration of corticosteroids, its efficacy remains debatable in terms of pain relief, improvement in range of motion, and return of shoulder function.
- Existing evidence on prolotherapy, platelet-rich plasma, and stem cell injection therapies for the treatment of rotator cuff disease remains limited.
- Ultimately, improved understanding of the underlying structural and compositional deficiencies of the injured rotator cuff tissue is needed to identify the biological needs that can potentially be targeted with injection therapies.

INTRODUCTION

Shoulder pain is common among the general population, with a reported prevalence of 6.9% to 34.0%,[1] and comprises the third leading musculoskeletal complaint behind back and neck complaints as reasons for physician consultation.[2] Rotator cuff disease accounts for a large proportion of shoulder complaints, especially with increasing age.[3–5] Depending on the patients' precise pathologic conditions, age, activity level, symptoms, level of dysfunction, and findings on physical examination and imaging, a wide variety of treatment modalities have been described for rotator cuff disease. Nonoperative modalities include activity modification, nonsteroidal antiinflammatory drugs (NSAIDs), physical therapy, and various injection therapies. Operative management is generally reserved for select patients or when nonoperative modalities have been exhausted.

Historically, the injection therapy of choice was corticosteroids; however, more recently numerous other injectable therapies have been used for rotator cuff disease, including platelet-rich plasma (PRP), stem cells, and prolotherapy. The purpose of this review is to summarize the current evidence for each type of injection therapy reported in the relevant literature. Although injection therapies are also frequently used in other shoulder conditions, such as adhesive capsulitis (frozen shoulder) and osteoarthritis, these conditions are not discussed in this review.

INDICATIONS

Injections can be used for both diagnostic and therapeutic purposes in rotator cuff disease. For patients presenting with shoulder pain, history and physical examination alone is frequently diagnostic. However, when patients present with shoulder weakness and are unable to participate in a thorough examination because of pain, a subacromial injection consisting of local anesthetic with or without corticosteroids will aid in differentiating between weakness caused by impingement (with improvement in strength

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after injection) or true rotator cuff tear (no change in strength after injection). From a therapeutic standpoint, injections for symptom relief are generally offered for patients with significant symptoms unrelieved by a trial of NSAIDs. The diagnoses in which injection therapies are frequently used are subacromial impingement, degenerative rotator cuff tendinopathy, and calcific tendinitis.

Subacromial impingement is a common diagnosis that represents a spectrum of severity from bursitis to rotator cuff tendinopathy to full-thickness tears, which comprise the 3 Neer stages of the impingement process.[6] The subacromial space refers to the area between the coracoacromial arch and the humeral head where the supraspinatus tendon and biceps lie.[3] The pathology in subacromial impingement originates from compression of the rotator cuff against the lateral acromion most prominently during the arc of shoulder abduction leading to bursitis and cuff inflammation.[7] Predisposing structural factors to subacromial impingement include a type III or hooked acromion,[8,9] acromial spurs as a result of ossification of the coracoacromial ligament insertion,[10] and acromioclavicular joint arthritis.[11] When symptoms are consistent with subacromial impingement and there is absence of acute injury or radiographic findings, patients may be indicated for a subacromial injection.[3] Alternatively, intrinsic rotator cuff tendinopathy leading to thickening of the rotator cuff is also thought to contribute to subacromial impingement and can itself be a cause of shoulder pain. Intrinsic causes of rotator cuff tendinopathy include diminished vascular supply, age-related degeneration, and tensile forces leading to mechanical failure.[6]

Calcific tendinitis is another common rotator cuff condition that should be discussed as a separate entity from subacromial impingement and degenerative rotator cuff tendinopathy. The term *calcific tendinitis* refers to calcium deposition, predominately in the form of hydroxyapatite in the rotator cuff tendons, most frequently the supraspinatus.[12,13] Calcific tendinitis is reported to occur in 2.5% to 7.5% of healthy shoulders, preferentially affecting women and patients in the fifth decade of life.[14] Symptomatically, patients may have a range of presentations from subacute to acute shoulder pain depending on the stage of the disease and the body's immune response to the calcific deposits and, rarely, fevers due to rupture of calcifications into local tissue. Calcific tendinitis is thought to be a self-limited disease that is generally managed with physical therapy and NSAIDs; however, for severe cases, pain and dysfunction can become significant, warranting more invasive treatment modalities, such as ultrasound-guided barbotage.[15]

CORTICOSTEROIDS

Corticosteroid injections are widely used in orthopedics and general practice and traditionally have been the cornerstone injection therapy in a variety of shoulder conditions.[16] A survey showed that 96% of practitioners, including primary care physicians and physiatrists, think that subacromial corticosteroid injections are efficacious in managing rotator cuff tendinitis.[17] Frequently used corticosteroids in the literature are methylprednisolone and triamcinolone, which are thought to have equivalent potency, followed by betamethasone and dexamethasone, which are proportionally more potent than both methylprednisolone and triamcinolone and, thus, are administered in smaller doses.[16,18,19] Most of the literature on injection therapies for rotator cuff disease focuses on corticosteroids; however, although some studies have reported efficacy in reducing pain and improving function, there is little reproducible evidence.

Historical studies from the 1980s and 1990s reported conflicting results regarding the efficacy of subacromial steroid injection over NSAIDs with respect to improvement in pain, function, or range of motion (ROM), as reported in a 2003 Cochrane systematic review.[19] Although several studies report a benefit of subacromial steroid injection over placebo at short-term time points (4–6 weeks), there was significant heterogeneity among populations and methodologies, precluding pooled analysis across various studies. Of note, a 1990 double-blinded randomized controlled trial (RCT) by Adebajo and colleagues[20] reported an improvement in visual analog scale (VAS) pain score of 3.6 points and an improvement active abduction of 45° versus control at the final follow-up in patients receiving triamcinolone versus placebo injection, both of which were statistically and clinically significant. A similar study by Petri and colleagues[21] reported statistically significant improvements in pain scores as well as an improvement in active shoulder abduction of 28°. A 1996 double-blind RCT by Blair and colleagues[22] corroborated this trend, reporting a 14° improvement in forward elevation compared with controls at 28 weeks. However, numerous other studies have reported no statistical differences in pain scores, ROM, or functional scores compared with placebo.[23–26] A Cochrane

systematic review comparing steroid injections and concomitant oral NSAIDs to NSAIDs alone yielded no difference in pain, function, and abduction ROM at various time points.[19]

Similar to the Cochrane review, a more recent systematic review by Koester and colleagues[16] in 2007 concluded that although there are existing data to suggest that subacromial corticosteroid injections relieve pain, increase ROM, and improve function in patients with rotator cuff disease, most studies are limited by methodological flaws leading to little reproducible evidence. Importantly, the investigators noted that when interpreting results from randomized studies, a distinction must be made between clinical and statistical significance. All but one randomized study reported statistically significant differences in pain scores on the magnitude of 0.5 to 1.0 points (centimeters) on the VAS scale, which were deemed clinically insignificant.[16,20–27] Only 2 of 8 studies included that reported on ROM yielded results that reached a minimal clinically important difference (MCID)[20,21] as indicated by a difference in VAS pain score by greater than 0.9 to 1.3 cm.[16,28,29] For ROM, a concrete cutoff for clinical relevance has not established; however, it must be noted ROM assessments have poor interobserver and intraobserver reliability leading to variations up to 10° to 15°.[16,30,31]

A more recent RCT studying the effectiveness of corticosteroid injections versus hyaluronic acid versus placebo in patients with subacromial impingement showed that at the 3-, 6-, and 12-week follow-up, patients receiving corticosteroids had improved pain and functional scores compared with those receiving hyaluronic acid but similar results to the placebo group.[32] Specifically, at 12 weeks, there was a reduction in VAS score of 7% in the hyaluronic acid group, 28% in the corticosteroid group, and 23% in the placebo group; by 26 weeks, there was no difference among any of the groups.

A 2016 meta-analysis of subacromial corticosteroid injections for pain due to rotator cuff tendinosis pooled 726 patients from 11 studies and found no significant reduction in pain compared with placebo at 3 months.[33] However, they did note a statistically significant relief in pain at a magnitude of a standardized mean difference VAS score of 0.52 (corrected for variability in pooling) in corticosteroid injection compared with placebo between 4 and 8 weeks, which they classify as minimally to mildly clinically relevant. Furthermore, they found that multiple injections in succession do not provide an added benefit over a single injection at any time point.

Finally, regarding subacromial corticosteroid injections, the accuracy of injection must be taken into account. Several studies have assessed injection accuracy and its impact on clinical outcomes (Table 1). A Japanese study using arthrographic evaluation concluded that injections using a lateral approach reached the subacromial space 70% of the time. Unintentionally, 21% were in the deltoid, 4% in the glenohumeral joint, and 5% subcutaneously.[34] A recent prospective study similarly reported an injection accuracy of 70%, although, among all injections, there was no difference in terms of pain, function, or patient satisfaction in patients who received accurate and inaccurate injections at 3 months.[35]

PROLOTHERAPY

Another injection therapy that has been described for the treatment of chronic painful rotator cuff tendinopathy is prolotherapy or hypertonic dextrose injection.[37] Although the exact mechanism of this type of treatment remains unclear, it is thought that injection of an irritant solution at painful ligament and tendon insertions stimulates local healing through proliferation of scar tissue.[38] Most of the literature on prolotherapy is limited to the treatment of knee osteoarthritis, and the literature on prolotherapy in the shoulder is limited to small retrospective series outside of North America. Lee and colleagues[39] conducted a retrospective case-control study among a heterogeneous Korean population with rotator cuff disease showing that prolotherapy injection led to improvement in VAS score, Shoulder Pain and Disability Index (SPADI) score, isometric strength, and active ROM compared with continued conservative management without injection. A similar study conducted in a Turkish population by Seven and colleagues[40] showed similar results with improvement in VAS, SPADI, and Western Ontario Rotatory Cuff Index at up to 1 year in patients treated with prolotherapy versus no injection. To the authors' knowledge, there are no comparative studies of prolotherapy with other injection therapies and no RCTs investigating prolotherapy in the literature. Further clinical data as well as an improved understanding of the exact mechanism of action of prolotherapy are needed.

PLATELET-RICH PLASMA

PRP injections locally deliver high concentrations of biological factors essential to the healing process to augment musculoskeletal tissue repair. As a result, the use of PRP for the treatment of

Table 1
Outcomes from recent level I studies of subacromial corticosteroid injection

Study (Type), Year	Location	N	Average Age (y)	Intervention and Control	Follow-up	Outcome Measures	Final Effect Size (Intervention-Control)	Other Notable Findings
McInerney et al,[24] (RCT), 2003	United Kingdom	98	49	Methylprednisolone vs bupivicaine[a]	3, 6, 12 wk	VAS Abduction	0 cm (P = .99) 1.4° (P = .8)	—
Akgun et al,[27] (RCT), 2004	Turkey	32	49	Methylprednisolone vs lignocaine[a]	1, 3 mo	VAS Constant score	0.1 (P>.05) 0 (P>.05)	Difference in VAS of 1.1 at 1 mo (P<.001)
Alvarez et al,[23] (RCT), 2005	Canada	58	55	Betamethasone vs xylocaine[a]	3, 6 mo	WORC ASES DASH	−8.0 (P = .38) −1.9 (P = .89) 0.3 (P = .86)	—
Hong et al,[36] (RCT), 2011	South Korea	54	50	Triamcinolone vs lidocaine[a]	2, 4, 8 wk	VAS Forward flexion Abduction	−2.7 cm (P<.05) 7° (P = .21) 23.5° (P<.05)	—
Penning et al,[32] (RCT), 2012	Netherlands	106	53	Triamcinolone vs lidocaine[a]	3, 6, 12, 26 wk	VAS Constant score	−0.1 cm (P>.05) −1.9 (P>.05)	Difference in VAS of 1.2 at 6 wk (P<.001)
Mohamadi et al,[33] (meta-analysis), 2017	Multicenter	726 (pooled)	Results: minimal to mild statistically and clinically significant improvement in pain at 4–8 wk, adjusted standardized mean difference VAS score 0.52, NNT = 5					

Abbreviations: ASES, American Shoulder and Elbow Surgeons standardized form; DASH, disabilities of the arm, shoulder, and hand; NNT, number needed to treat; WORC, Western Ontario Rotator Cuff Index.

[a] Intervention injection also contained local anesthetic.

rotator cuff disease has been extensively studied through multiple RCTs and meta-analyses. However, it is important to note that there remains substantial variability in the methods of PRP production among commercial systems.[41–43] Furthermore, within a given separation technique, there is a high degree of intersubject and intrasubject variability in the composition of PRP produced.[44] This variability, along with the heterogeneity among studies regarding the means of administration, tear size, and repair technique (single or double row), make it difficult to draw any definitive conclusions on the efficacy of PRP treatment of rotator cuff disease.

Present level I studies report no difference in clinical outcomes in patients who received PRP injection for rotator cuff tendinopathy compared with controls.[45,46] In an RCT of patients with chronic rotator cuff tendinopathy randomized to arthroscopic acromioplasty alone or in combination with a PRP injection, reduced vascularity and cellularity and increased levels of apoptosis were noted in tissue biopsy specimens taken from PRP-treated patients.[45] Additionally, most level I and II studies report no differences in pain and functional scores in patients who received PRP injection as an augment to rotator cuff repair compared with controls.[47–51] In a meta-analysis, Warth and colleagues[47] showed a significantly decreased improvement in the constant score when PRP was injected over the surface of the repaired tendon as opposed to application at the tendon-bone interface; however, this difference was not greater than the threshold for an MCID. The effect of PRP treatment on retear rates after rotator cuff repair remains debatable. Of the studies that assessed the repair site integrity at least 6 months postoperatively, most demonstrated no difference in retear rates.[47,50–53] Nevertheless, some studies have shown that PRP applied at the tendon-bone interface resulted in significantly lower retear rates after the repair of medium to large tears.[47,54,55]

MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) derived from bone marrow (Fig. 1) and adipose (Fig. 2) have garnered the most attention for use in rotator cuff healing because of their multipotent potential and ability to exert paracrine effects, such as modulating and controlling inflammation, stimulating endogenous cell repair and proliferation, inhibiting apoptosis, and improving blood flow.[56,57] Like PRP augmentation therapy, continued research is needed to identify the optimal cell source and the ideal treatment protocol needed to drive cell differentiation and create an optimal healing environment that directs regeneration of the native fibrocartilaginous enthesis. Currently, only a few studies have examined the effect of augmentative MSC therapy on rotator cuff repair in humans, with early results suggesting a possible improvement in repair site healing.[58–60] In a level III study, Kim and colleagues[58] reported no difference in pain and functional scores in patients who received an injection of adipose-derived

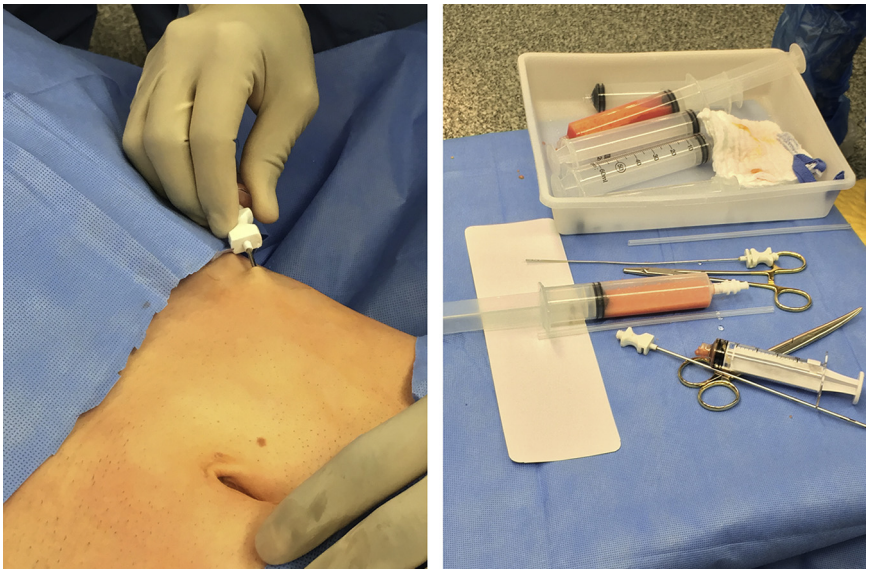

Fig. 1. Lipo-aspiration of the abdominal midsection. The lipo-aspirate is then processed to form an injectable solution containing MSCs.

Fig. 2. Bone marrow aspirate is taken from the iliac crest with the use of a needle. The bone marrow aspirate is then processed and concentrated to form an injection solution containing MSCs.

MSCs as an augment to rotator cuff repair compared with controls. However, MRI obtained at a minimum of 1 year indicated a significantly lower retear rate (14.3%) in patients treated with MSCs compared with controls (28.5%).

ULTRASOUND-GUIDED NEEDLE THERAPIES FOR CALCIFIC TENDINITIS

Severe cases of calcific tendinitis that require invasive treatment modalities have traditionally been treated with subacromial corticosteroid injections; however, more recently, barbotage has become increasingly popular (Fig. 3).[15] Barbotage was first introduced in 1937[61] and involves image-guided insertion of a needle directly into a calcific deposit, followed by lavage (usually with normal saline) to dissolve the deposit.[15,62] The increasing use of ultrasound as an imaging alternative has made this technique radiation free and more accessible.[61]

A 2013 systematic review assessing the efficacy of ultrasound-guided needle treatments for calcific tendinitis included 11 articles and concluded that all studies in the literature were of low quality and that there was no difference in pain relief between needle lavage and other interventions.[63] A recent RCT in the Netherlands compared barbotage with subacromial corticosteroid injection and found that clinical and radiographic outcomes at 1 year were superior in the barbotage group.[15] Specifically, at 1 year they reported a 12.1-point improvement in the mean constant score, 6.5-mm improvement in calcification size decrease, and a greater proportion of total resorption in the barbotage group compared with the corticosteroid group. These results corroborate those from a previously reported prospective nonrandomized trial of ultrasound-guided barbotage versus control in Italy showing a 13.3-point improvement in the constant score and a 1.8-point improvement in the VAS score at 1 year.[62] In this study, significant improvements in the constant score and the VAS score were seen as early as 1 month and maintained beyond 1 year but were no longer present at the follow-up at 5 and 10 years.

Interestingly, some investigators think that some of the observed therapeutic effects of barbotage may be attributed to fenestration of the tendon causing a natural healing response.[64] A recent small randomized study in China

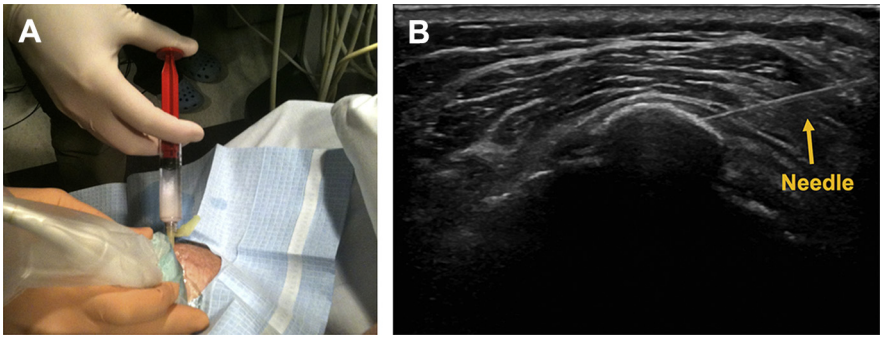

Fig. 3. (*A*) Ultrasound-guided barbotage of calcific tendinitis in the supraspinatus. (*B*) Ultrasound image demonstrating insertion of a needle directly into a calcific deposit, followed by lavage (usually with normal saline) to dissolve the deposit.

showed that patients undergoing ultrasound-guided barbotage versus ultrasound-guided fenestration experienced a similar degree of pain relief from 1 to 36 weeks.[65]

Although limited evidence does exist to support the use of ultrasound-guided needle therapies in calcific tendinitis of the shoulder, at least in the short-term, further high-quality studies are required to more definitively determine its efficacy and understand its mechanism of action. Apart from improved study quality, further studies should also aim to clarify whether certain patient populations (based on number and size of calcifications) may benefit more than others.[63]

SUMMARY

Rotator cuff disease affects a large proportion of the overall population and encompasses a wide spectrum of pathologies, including subacromial impingement, rotator cuff tendinopathy or tear, and calcific tendinitis. Various injection therapies have been used for the treatment of rotator cuff disease. Although the cornerstone of traditional injection therapy involves the administration of corticosteroids, the evidence on its efficacy remains debatable in terms of pain relief, improvement in ROM, and return of shoulder function. Several newer injection therapies have gained popularity, including prolotherapy, PRP, stem cells, and ultrasound-guided barbotage for calcific tendinitis. However, the existing evidence for each type of therapy is currently limited. Ultimately, improved understanding of the underlying structural and compositional deficiencies of the injured rotator cuff tissue is needed to identify the biological needs that can potentially be targeted with injection therapies.

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