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Review Article

Hylonome

Injectable agents derived from or targeting vascularity: has clinical acceptance in managing tendon disorders superseded scientific evidence?

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Abstract

Objectives: To report outcomes after sclerosing, platelet-rich plasma (PRP) and autologous blood injection therapies as a treatment for tendinopathy. **Methods:** We searched Pubmed for clinical trials on sclerosing, PRP and autologous blood injections for tendinopathy. We scored the quality of the studies using a modified Coleman Methodological Score (CMS) with 9 criteria, which results in a final score between 0 and 90. **Results:** We included 14 studies involving 328 tendons on sclerosing (mean CMS: 52; range 31-77), 6 studies involving 143 tendons on PRP (CMS: 57; 43-73) and 5 studies involving 160 tendons on autologous blood injections (CMS: 58, 50-68). Across treatments, the results appear promising, but as reflected by the low methodology scores, the majority of studies are non-randomized, retrospective, with small sample size or of short duration. Two of three RTCs on sclerosing injections reported better outcomes in the treatment group, while two RCTs on PRP injections show conflicting results. The only available RTC on autologous blood injections has only 8 weeks follow-up. **Conclusions:** There is a need for large-scale RTCs with appropriate follow-up and study size to determine the efficacy of sclerosing, platelet-rich plasma and autologous blood injection therapies as a treatment for tendinopathy.

Keywords: Tendinopathy, Sclerosing, Platelet-rich Plasma, Autologous Blood, Therapy

Tendon problems represent a major cause of musculoskeletal morbidity. Chronic tendon pathology (tendinopathy) occurs frequently in athletes, and studies have estimated that 30-50% of all sports lesions are painful tendon injuries[1] that affect professional and recreational athletes in various anatomical locations. A cross-sectional study among Norwegian female and male elite athletes from nine different sports with different loading patterns documented that the overall prevalence of current symptoms of patellar tendinopathy was 14%; in addition, 8% reported previous symptoms[2]. The prevalence differed between sports according to the performance characteristics and was highest in jumping sports like volleyball (45%) and basketball (32%). Other tendinopathies are associated with other sports, such as in the shoulder and elbow regions in throwing sports.

Tendinopathies are well known to be difficult to treat[3,4], not seldom causing log-term disability and sometimes ending the sports or work career. Surgery is often advised, although the evidence base is limited[5,6]. However, recent research has spurred widespread use of various forms of novel injections therapies, like sclerosing injections, PRP injections and autologous blood injections.

The pathophysiology of chronic tendinopathies involves the presence of degenerative changes, including disorganized collagen fibers, increase in ground substance and neovascularity[7-10]. The precise cause of degeneration and pain in tendinopathy is not clear. Mechanical, vascular, neural and "failure of healing" models have been proposed[11-17]. There is no cellular evidence of inflammation in chronic Achilles tendinopathy[11,18,19], although inflammation may play a role in the early phases of the condition[17,20].

Sclerosing therapy

Ultrasound has shown to be well-suited to examine tendons, and is an established and reliable method today[21-23]. Combining

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ultrasound and color Doppler, neovascularisation was demonstrated inside and outside the area with structural tendon changes in chronic painful Achilles tendon, but not in pain-free Achilles tendons[10], suggesting a relationship between the neovascularisation and pain. Based on the hypothesis that the neovessels and the accompanying nerves were responsible for the pain, sclerosing injection therapy was developed to destroy the vasculoneural in-growth using the sclerosing agent polidocanol[24,25]. Polidocanol injections has been used for many years to treat varicose veins and teleangiectasias[26], and have been demonstrated to have few side effects[27]. Polidocanol has a sclerosing and a local anaesthetic effect, and the active substance is an aliphatic non-ionised nitrogen-free surface anaesthetic.

Autologous blood injection

The hypothesis for the mechanism of tendon regeneration is that transforming growth factors and fibroblast growth factors carried in the blood act as humeral mediators to induce a healing cascade and promote tendon repair[28]. Based on this hypothesis, investigators proposed that an injection of autologous blood might accelerate tendon repair[29,30]. Autologous blood is drawn from the patient, and then injected in the affected tendon within a short time.

Platelet-rich plasma (PRP) injections

Platelet-rich plasma is defined as a sample of autologous blood with high concentrations of platelets. Platelets are a major player in the clotting cascade, and contain granules that secrete different types of growth factors. These growth factors play an important role in the normal healing response[31], and cell culture studies have provided evidence that PRP can stimulate processes associated with tendon healing[32,33]. Based on this, PRP injections is given to patients with tendinopathies to provide tendon repair. The purported mechanisms of PRP treatment have been reviewed recently by Engebretsen et al[34]. PRP is prepared by taking a sample of autologous, anticoagulated blood, and separating blood cells from leukocytes and platelets using a centrifuge or filter. The PRP preparation contains the noncellular components of plasma, including clotting factors, and is then injected to the affected tendon.

Anti-doping regulations

An important consideration for the use of PRP or autologous blood injections has been the antidoping regulations. Until recently, the World Anti-Doping Agency prohibited the use of intramuscular PRP injections[35]. All other routes of administration, such as intra-articular, intra- or peritendinous were permitted and required only a declaration of use[35]. Concerns regarding IGF-1 and its potential ergogenic aid exist, but they appear to be unfounded. The unbound IGF-1 in PRP or autologous blood has an inadequate half-life to exert systemic effects, and its concentrations are reported subtherapeutic by a factor of 500 and thus unlikely to produce systemic anabolic actions[36]. Consequently, platelet-derived preparations were removed from the prohibited list for 2011, and PRP is now permitted by all routes of administration[37].

Literature review

The available literature was reviewed using Pub Med. The search was performed using the terms "(sclerosing therapy OR sclerosing OR sclerosing injection) AND (tendon OR tendinopathy OR tendinosis OR epicondylitis)", "(platelet rich plasma) AND (tendon OR tendinopathy OR tendinosis OR epicondylitis" and "(autologous blood injection) AND (tendon OR tendinopathy OR tendinosis OR epicondylitis)". We restricted the search to papers in English, clinical trials and studies on humans.

All abstract were read, and papers not containing data on outcome of the treatment on tendinopathies were excluded. We also excluded single case reports. The first search using the selected search terms resulted in 158 articles (68 on sclerosing injections, 68 on PRP injections and 22 on autologous blood injections). After restricting the search, we ended up with 29 articles (16 on sclerosing injections, 7 on PRP injections and 6 on autologous blood injections). All these articles were read, but 4 had to be excluded according to the exclusion criteria. At the end, 25 articles (see Tables 2, 3 and 4) were included; 14 on sclerosing injections, 6 on PRP injections and 5 on autologous blood injections.

Methodological assessment

Our analysis was based on the Coleman Methodology Score (CMS), which we used for assessing the methodological quality of the studies. The CMS, which was originally developed for grading clinical studies in patellar and Achilles tendinopathy[5,38], assesses methodology using 10 criteria, resulting in a maximum score of 100. We modified the methodology score by excluding the category describing the number of different procedures because there were no differences in procedures in the different injection therapies (Table 1). Our modified CMS included 9 criteria, given a total CMS of between 0 and 90, were 90 is maximal score and indicates a perfect study design.

Literature review - Sclerosing injections

The 14 studies on sclerosing injections included are described in detail in Table 2. Four were randomized clinical trials, 8 were prospective case series and 2 had a retrospective study design. The total number of tendons included was 338, and the total number of tendons receiving sclerosing injections was 328. The mean duration of follow up was 11.7 months. All studies used the sclerosing agent polidocanol; we could not find any studies on any of the other sclerosing agents.

The majority of the studies had significant methodological limitations, as reflected by the mean CMS of 52 (range 31 through 77). The main limitations were related to small study size, short

Table 1. Modified Coleman Methodology Score.

Part A – Only one score to be given for each of the six sections		**Score**
1. Study size (N) (if multiple follow-up, multiply N by number of times subjects followed up)	>60	10
	41-60	7
	20-40	4
	<20, not stated	0
2. Mean follow up (months)	>24	5
	12-24	2
	<12, not stated or unclear	0
3. Type of study	Randomized controlled trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
4. Diagnostic certainly (use of preoperative US, MR or postoperative histopathology to confirm diagnosis	In all	5
	In >80%	3
	In <80%, no, not stated or unclear	0
5. Description of procedure given	Adequate (technique stated and necessary details of that type of procedure given)	5
	Fair (technique only stated without elaboration)	3
	Inadequate, not stated or unclear	0
6. Description of post-injection rehabilitation	Well described with >80% of patients complying	10
	Well described with 60-80% of patients complying	5
	Protocol not reported or <60-80% of patients complying	0
Part B – scores may be given for each of the three sections if applictable		
1. Outcome criteria	Outcome measures clearly defined	2
	Timing of outcome assessment clearly stated (e.g. at best outcome after surgery or at follow up)	2
	Use of outcome criteria that has reported good reliability	3
	Use of outcome with good sensitivity	3
2. Procedure for assessing outcomes	Subjects recruited (results not taken from surgeon's files)	5
	Investigator independent of surgeon	4
	Written assessment	3
	Completion of assessment by subjects themselves with minimal investigator assistance	3
3. Description of subject selection process	Selection criteria reported and unbiased	5
	Recruitment rate reported >80% or	5
	<80%	3
	Eligible subjects not included in the study satisfactorily accounted for or 100% recruitment	5

duration of follow up, and incomplete descriptions of patient recruitment as well as selection and rehabilitation procedures.

The studies were heterogenous regarding the site of the tendinopathy. Eight of the studies investigated the Achilles tendon, two the patellar tendon, two the lateral elbow, one the supraspinatus and one the extensor pollicis brevis/abductor pollicis tendons.

In one case the sural nerve was affected with paresthesia and numbness, and four papers did not explicitly report on complication due to sclerosing injection therapy.

Most of the case series studies[25,38-46] whether prospective or retrospective, report promising results with less pain and/or improved function in the majority of patients receiving sclerosing treatment. However, these results are difficult to interpret, as the effects observed can not necessarily be attributed to the intervention without a control group to compare to. In some cases, interpretation is also confounded by patients undergoing other treatment modalities prior to final assessment, such as surgery. An example is Sterkenburg et al[47], who retrospectively assessed the effects of sclerosing treatment on Achilles tendinopathy after

Table 2. Studies on sclerosing injections.

Study	Tendon	Study size	Follow-up	Type of study	Treatment	Outcome measure	Results	A 1	A 2	A 3	A 4	A 5	A 6	B 1	B 2	B 3	Sum CMS
Sterkenburg et al. (2010)	Achilles	n=53	2.7-5.1 years	Retrospective case series	Polidocanol injections	Pain (none, minimal, same, more); VISA-A; VAS	VISA-A score: ~82; Pain: 70% none, 20% minimal, 2.5% same, 7.5% more; 21 of 40 tendons had undergone additional treatment.	7	5	0	5	5	0	10	15	13	60
Knobloch et al. (2008)	Extensor pollicis brevis/ abductor pollicis	n=3	~1 month	Prospective case series	Polidocanol injections & eccentric training	DASH score; VAS (pain during extension)	DASH: 61 to 14; VAS: 7 to 1 (of 10).	0	0	10	5	3	5	8	0	0	31
Zeisig et al. (2008)	Lateral epicondyle	n=34	~12 months	RCT (double blinded; crossover after 3 months)	Polidocanol injections vs. placebo (lidocaine & adrenaline)	VAS (pain during grip activities); Treatment satisfaction (yes/no); Voluntary grip strength (hand dynamometer)	3 & 12 months: No group differences in satisfaction, pain or strength, both groups less pain and higher grip strength. Overall: 27 of 34 satisfied with treatment at 12 months.	4	2	15	5	5	5	7	11	15	69
Clementson et al. (2008)	Achilles	n=25 (26 tendons)	~12 months case series	Retrospective injections	Polidocanol	Subjective outcome (completely recovered, improvement, no result, worse); Activity level	9 of 25 completely recovered, 10 improvement, 6 no result.	4	0	0	5	5	0	7	6	15	42
Willberg et al. (2008)	Achilles	n=48 (52 tendons)	~14 months	RCT (double blinded; crossover after 3 months)	Polidocanol injections: 5 mg/ml vs. 10 mg/ml	VAS (pain during tendon loading activity); Treatment satisfaction (yes/no)	All patients were satisfied after receiving 5 injections (5 tendons), 4 injections (8 tendons), 3 injection (12 tendons), 2 injections (12 tendons) or 1 (15 tendons); VAS: Significantly reduced pain; No between-group differences.	7	2	15	5	5	0	7	10	5	56
Alfredson et al. (2007)	Achilles	n=19	~6 months	Prospective case series	Polidocanol injections (n=9) vs. US-guided open surgery (n=10)	Treatment satisfaction (yes/no)	Polidocanol injections: 6 of 9 patients satisfied; Surgery: 10 of 10 satisfied.	0	0	10	5	5	0	7	11	5	43
Hoksrud et al. (2006)	Patellar	n=33 (42 tendons)	~12 months	RCT (double blinded; crossover after 4 months)	Polidocanol injections (n=17) vs. placebo (lidocaine & adrenaline; n=16)	VISA-P score; VAS	4 months: VISA-P & VAS improved in polidocanol group, no change in placebo group; 12 months (after crossover): VISA-P improved from 54 to 77 (n=42).	4	2	15	5	5	10	10	11	15	**77**
Alfredson et al. (2006)	Supraspinatus	n=15	~8 months	Prospective case series	Polidocanol injections	VAS (pain during daily horizontal arm activity); Treatment satisfaction (yes/no)	VAS: 79 to 21 for satisfied patients (14 of 15).	0	0	10	5	5	0	7	11	15	**53**

Table 2. (cont.)

Study	Tendon	Study size	Follow-up	Type of study	Treatment	Outcome measure	Results	A 1	A 2	A 3	A 4	A 5	A 6	B 1	B 2	B 3	Sum CMS
Lind et al. (2006)	Achilles	n=42	~24 months	Prospective case series	Polidocanol injections	VAS (pain during tendon loading activity); Treatment satisfaction (yes/no)	8 months: VAS 75 to 10 for satisfied patients (37 of 42); 24 months: VAS 75 to 7 for satisfied patients (38 of 42); 4 patients received surgical treatment.	7	2	10	5	5	0	7	11	5	**52**
Zeisig et al. (2006)	Lateral epicondyle	n=11 (13 tendons)	~8 months	Prospective case series	Polidocanol injections	VAS (pain during extensor activity); Treatment satisfaction; Grip strength (hand dynamometer)	VAS: 75 to 34; Treatment satisfaction: 86 of 100; Strength: 32 to 40 kg.	0	0	10	5	5	10	10	11	15	**66**
Alfredson & Öhberg (2005)	Achilles	n=20	3 months	RCT (double blinded; crossover after 1 injection)	Polidocanol injections (n=10) vs. placebo (lidocaine & adrenaline, n=10)	VAS (pain during activity); Treatment satisfaction (yes/no)	After one injection: VAS improved in polidocanol group, no change in placebo group; 3 months (after cross over): VAS improved in both groups; 19 of 20 patients were satisfied with treatment.	4	0	15	5	5	0	7	11	5	**52**
Alfredson & Öhberg (2005)	Patellar	n=15	6 months	Prospective case series	Polidocanol injections	VAS (pain during tendon loading activity); Treatment satisfaction (yes/no)	VAS: 81 to 10 for satisfied patients (12 of 15); 57 for unsatisfied patients (3 of 15).	0	0	10	5	5	0	7	11	5	**43**
Öhberg & Alfredson (2003)	Achilles	n=11	8 months	Prospective case series	Polidocanol injections	VAS (pain during tendon loading activity); Treatment satisfaction (yes/no)	VAS: 85 to 14 for satisfied patients (8 of 11); 58 for unsatisfied patients (3 of 11).	0	0	10	5	5	0	7	11	5	**43**
Öhberg & Alfredson (2002)	Achilles	n=10	6 months	Prospective case series	Polidocanol injections	VAS (pain during tendon loading activity); Treatment satisfaction (yes/no)	VAS: 74 to 8 for satisfied patients (8 of 10); 71 for unsatisfied patients (2 of 10).	0	0	10	5	5	0	7	11	5	**43**

2.7 to 5.1 years of follow up (Table 2). Although the results appear to be good, as many as 21 of 40 tendons they were able to follow up of the 53 tendons included had undergone additional treatment at some point. Treatment contamination like this was reported in two of the case series[44,47].

Of the four randomized controlled trials, there are three comparing the results of patients receiving polidocanol injections to those of a placebo group receiving injections with lidocaine and adrenaline in patients with Achilles tendinopathy[48], patellar tendinopathy[49] and lateral epicondylitis[50]. Lidocaine was used to mimic the local anaesthetic effect of polidocanol and thus blind the patient, and adrenaline to cause vasoconstriction of the neovessels and thus blind the physician doing the color Doppler ultrasound-guided injections. In all of these studies, a large ma-

jority of patients were satisfied with treatment at their final follow-up. Another common denominator between the three studies is that the patients in the control group crossed over to polidocanol treatment after 3-4 months, and in the Achilles tendon[48] and patellar tendon trials[49] significantly better outcomes were reported in the sclerosing groups than the placebo groups. In contrast, no such difference was observed in the trial on lateral epicondylitis. Although these short-term effects may be interpreted as "proof of concept", it should be noted there are no placebo-controlled randomized trials available comparing polidocanol injections to placebo with medium- (6-12 months) or long-range follow-up (2 years or more) without contamination. One explanation for this is that may be that it is difficult to recruit athletes to randomized studies where they risk assignment to a placebo group for long periods of time.

In conclusion, although most studies investigating the effect of sclerosing injections with polidocanol have shown promising results, large-scale randomized controlled trials with longer follow-up are needed to determine their efficacy.

Literature review - PRP injections

The 6 studies on PRP injections included, two on the Achilles tendon, two on the patellar tendon and two the lateral elbow, are described in detail in Table 3. Two were randomized controlled trials, two studies were prospective case series, and two were non-randomized clinical trials. The total number of tendons included was 240, and the total number of patients receiving PRP injections was 143. The mean duration of follow up was 12 months.

As in the studies of sclerosing injections, there were significant methodological limitations with the majority of the PRP injection studies, as reflected by a mean CMS of 57 (range 43 through 73). As for the polidocanol studies, the main limitations were also related to small study size, short duration of follow up, and incomplete description of rehabilitation procedures and compliance.

Except for one case of local inflammation, no complications were reported after PRP injections. However, in two papers this was not explicitly reported.

Both of the case series[51,52] reported promising results with less pain or improved function in the majority of the patients receiving PRP injections. The two non-randomized clinical trials also report promising results with improved function and less pain[53,54]. In contrast, Filardo et al[53] studied patients with Achilles tendinopathy and did not detect any differences in 6-month outcomes between a group receiving PRP injections in addition to physiotherapy and a control group receiving physiotherapy alone. However, it should be noted that the groups differed at the outset, as the patients in the PRP group had severe chronic patellar tendinopathy who had failed previous therapies. The patients in the control group were offered physical therapy as their first therapy; thus, the PRP group probably represent more resistant cases.

Without appropriate control groups, the results from the case series and non-randomized studies are difficult to interpret. However, two recent randomized controlled trials have investigated the effect of PRP injections on lateral epicondylitis and Achilles tendinopathy, respectively. Peerbooms et al[55] investigated the effect on the lateral elbow, by comparing the 12-month outcome in 51 patients receiving PRP injections to 49 patients receiving corticosteroid injections. Significantly better outcomes were observed in the PRP group than the corticosteroid group, reporting a 73% success rate in the PRP group vs. 49% in the corticosteroid group.

De Vos et al.[56] compared the effect of PRP injections with placebo injections (saline) in 54 patients with Achilles tendinopathy. Both injection therapies were combined with eccentric exercises. They reported improvements in VISA-A score at 24 weeks in both groups, but no between-group differences. Given the additional use of eccentric exercises, which has been shown to be effective in several studies[57-60] it is not surprising that both groups showed improvements in VISA-A score.

In conclusion, although most studies investigating the effect of PRP injection therapy on patients with tendinopathy have shown promising results, the two randomized controlled trials available appear to show conflicting results. Large-scale randomized controlled trials with longer follow-up are needed to determine the efficacy of PRP injections in tendinopathy.

Literature review - Autologous blood injections

The five studies on autologous blood injections included are described in detail in Table 4. One investigated the patellar tendon, and there were three on the lateral and one the medial elbow. One was a randomized controlled trial and 4 were prospective case series. The total number of tendons included were190 and, of these, 160 received autologous blood injections. The mean duration of follow up was 8.5 months. No complications were reported, but one paper did not explicitly report on complications.

As for the two other injection therapies, the majority of the studies had methodological limitations, as reflected by the mean CMS of 58 (range 50 to 68). Similar to the other two injection therapies, the main limitations were related to small study size, short duration of follow up, and incomplete descriptions of rehabilitation procedure and compliance.

All of the prospective case series studies[29,61-63] report promising results with less pain and/or improved function in the majority of the patients receiving autologous blood injection therapy. But, as for the other case series mentioned above, these results are difficult to interpret, as the effect can not be attributed to the intervention without a control group to compare to.

The only randomized controlled trial available compared autologous blood injections to corticosteroid injections in a 60 patients[64]. All outcomes were significantly better after autologous blood injections compared to patients receiving corticosteroid injections, but the duration of follow up was only 8 weeks, and only the assessors were blinded to which procedure patients had undergone.

In other words, there is limited evidence available to assess the efficacy of autologous blood injection in tendinopathy.

Table 3. Studies on PRP injections.

Study	Tendon	Study size	Follow-up	Type of study	Treatment	Outcome measure	Results	A 1	A 2	A 3	A 4	A 5	A 6	B 1	B 2	B 3	Sum CMS
Peerbooms et al. (2010)	Lateral epicondyle	n=100	12 months	RCT (double blinded)	PRP injections (n=51) vs. corticosteroid injections (n=49)	VAS; DASH; Success rate (>25% reduction in VAS or DASH)	All outcomes significantly better in PRP group: VAS 70 to 25 for PRP group, 66 to 50 for corticosteroid group; DASH 161 to 55 for PRP group, 131 to 108 for corticosteroid group; Success rate 73% for PRP group, 49% for corticosteroid group.	10	2	15	5	5	0	10	11	15	**73**
De Vos et al (2010)	Achilles	n=54	~24 weeks	RCT (double blinded)	PRP injections & eccentric exercises (n=27) vs. placebo injections (saline) & eccentric exercises (n=27)	VISA-A; Satisfaction (poor, fair, good, excellent); Return to sport	No significant group differences in VISA-A, satisfaction or return to sport, but VISA improved in both groups.	7	2	15	0	5	5	10	11	13	**68**
Filardo et al. (2010)	Patellar tendon	n=31	6 months	Non-randomized clinical study	PRP injections & physiotherapy (n=15) vs. physiotherapy alone (n=16)	EQ VAS; Tegnér score; Pain level	No group differences in EQ VAS or pain level, but improvements in both groups; Greater improvement in Tegnér score in PRP group.	4	0	10	5	5	0	7	11	5	**47**
Gaweda et al. (2010)	Achilles	n=14 (15 tendons)	18 months	Prospective case series	PRP injections	VISA-A; AOFAS	Significant improvement in both scores; VISA-A: 24 to 96; AOFAS: 55 to 96.	0	2	10	5	5	0	10	11	5	48
Kon et al. (2009)	Patellar	n=20	6 months	Prospective case series	PRP injections	Tegnér; EQ VAS; SF 36 questionnaire	Significant improvement in all scores; EQ VAS 58 to 82; Tegnér 4 to 7.	4	0	10	5	5	0	7	11	5	47
Mishra & Pavelko (2006)	Lateral epicondyle	n=20	8 wks & ~25 months	Non-randomized clinical study	PRP injection (n=15) vs. placebo (bupivacaine & adrenaline, n=5)	VAS; Mayo elbow score	8 wks: Significantly better outcomes in PRP group: VAS 80 to 32 compared to 86 to 72 in placebo group; Mayo elbow score 50 to 76 in PRP group, 50 to 57 in placebo group. Further improvements in VAS and Mayo elbow score in PRP group after 6 & 25 months, no data given on placebo group.	4	2	10	0	5	0	10	11	15	57

Table 4. Studies on autologous blood injections.

Study	Tendon	Study size	Follow-up	Type of study	Treatment	Outcome measure	Results	A 1	A 2	A 3	A 4	A 5	A 6	B 1	B 2	B 3	Sum CMS
Kazemi et al. (2010)	Lateral epicondyle	n=60	~8 weeks	RCT (single blinded)	Autologous blood (n=30) injections vs. corticosteroid injections (n=30)	VAS (pain previous 24 hrs); DASH; Nirschl score; grip strength; Tenderness (algometer)	All outcomes significantly better after autologous blood injections compared to corticosteroids	10	0	15	0	5	0	10	15	13	68
James et al. (2007)	Patellar	n=44 (47 tendons)	~14.8 months	Prospective case series	Autologous blood injections	VISA-P score	VISA-P increased: from 40 to 74.	7	2	10	5	5	0	10	11	5	55
Suresh et al. (2006)	Medial epicondyle	n=20	10 months	Prospective case series	Autologous blood injections	VAS; Nirschl score	Significant improvement in both scores: VAS from 8.0 to 2.2 and Nirschl score 6 to 1 in satisfied patients (17 of 20); 3 patients received surgical treatment.	4	0	10	5	5	0	10	11	5	50
Connell et al. (2006)	Lateral epicondyle	n=35	~6 months	Prospective case series	Autologous blood injections & dry needling	VAS; Nirschl score	Significant improvement in both scores: Median VAS from 9 to 0 and Nirschl score 6 to 0 in satisfied patients (33 of 35); 2 patients received surgical treatment.	4	0	10	5	5	0	10	15	13	62
Edwards (2003)	Lateral epicondyle	n=28	9.5 months	Prospective case series	Autologous blood injections	VAS; Nirschl score	Improvement in both scores: VAS 7.8 to 2.3; Nirschl score 6.5 to 2.0	4	0	10	0	5	0	10	15	13	57

Methodological considerations

To evaluate the methodology of the studies included, we chose the Coleman Methodology Score, as it is the only scoring scale developed specifically for tendinopathy and has been used in previous reviews on the topic[5,38]. However, the generally accepted 'ranking' of RCTs being superior, then prospective studies and retrospective case series as the weakest design is not always reflected in the scores given. One explanation is that some of the RCTs done on tendinopathy have small numbers and short follow-up and therefore the scores are relatively low.

The moderate to low CMS scores observed illustrate the difficulty of conducting controlled studies on athletes with tendinopathy. Ideally, we would like to have long-term data from randomized trials to inform clinical decisions. However, it seems highly unlikely that athletes, especially athletes performing at the elite level, would be willing to accept placebo treatment for a sufficient period. This is illustrated by three of the RTCs investigating outcome after sclerosing treatment, where patients were randomized to either immediate treatment with polidocanol injections or to delayed treatment, i.e. where placebo injections were given during an initial 12-16 week period[49,50,65]. Long-term RCTs against placebo treatment is probably not realistic in elite athletes with tendinopathy, and for this reason we may have to continue basing clinical decisions for tendinopathy on short-term outcomes or data from recreational athletes.

Conclusion

Injectable agents derived from or targeting vascularity, in the form of autologous blood and PRP injections or sclerosing therapy is a recent addition to the sports medicine physician's armamentarium. And although these therapies seem to have received clinical acceptance in managing tendon disorders, it seems that their widespread use has superseded the available scientific evidence. There is a clear need for large-scale randomized controlled trials with longer follow-up to determine their efficacy in tendinopathy.

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