European Journal of Musculoskeletal Diseases
ISSN 2038-4106 print - ISSN 2975-044X online

Review

HYALURONIC ACID INJECTIONS FOR TENNIS ELBOW: A SYSTEMATIC REVIEW

D. Tarantino[1], B. Corrado[1*], R. Mottola[1], R. Gnasso[1], S. Palermi[1], F. Sirico[1], C. Ruosi[1], R. Saggini[2], R. Pellegrino[3] and R. Aicale[4]

[1]Department of Public Health, University of Naples Federico II, Naples, Italy
[2]Department of Psychology, e-Campus University, Novedrate, Italy;
[3]Department of Scientific Research, Campus Ludes, Off-Campus Semmelweis University, Lugano, Switzerland
[4]Department of Musculoskeletal Disorders, Faculty of Medicine and Surgery, University of Salerno, Baronissi, Italy

Correspondence to:
Bruno Corrado, MD PhD
Department of Public Health,
University of Naples Federico II,
80131 Naples, Italy
e-mail address: bruno.corrado@unina.it

ABSTRACT

Tennis elbow is a tendinopathy of the lateral elbow that causes pain and functional limitation. This systematic review investigates the effects of hyaluronic acid injections for treating tennis elbow. A systematic search of scientific electronic databases (CENTRAL, EMBASE, MEDLINE, PEDro, Web of Science, Scopus, PubMed, and CINAHL) was performed up to October 2023 with no restrictions of time and language. This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Inclusion criteria were articles that reported clinical outcomes about the use of hyaluronic acid for tennis elbow alone or in comparison with other injectable drugs. Outcome measures were the Visual Analogue Scale, handgrip strength, and the Quick-Disabilities of the Arm, Shoulder, and Hand score. Two independent authors performed the search and evaluated the articles. The inter-rater reliability in the quality assessment was evaluated using Cohen's kappa coefficient. The Modified Coleman Methodology Score was used to evaluate the methodological quality of the articles included in this systematic review. A total of seven articles were included with the overall quality of the included articles being evaluated as fair. Despite using different kinds of hyaluronic acid and injection protocols, and different scores applied, each included study showed clinically relevant improvements. Hyaluronic acid injections resulted in being superior to placebo but inferior in the short-term compared to other injections. Given the high heterogeneity of the included studies, we cannot conclude which kind of hyaluronic acid and injection protocol is the best for treating tennis elbow. Hyaluronic acid injections for treating tennis elbow seem safe and effective in reducing pain, improving function, and allowing a faster return to pain-free sports activities especially in the long term. High-quality and prospective long-term follow-up studies are needed to confirm the articles' outcomes in this systematic review.

KEYWORDS: *tennis elbow, TE, lateral epicondylitis, epicondylitis, hyaluronic acid, HA, injections*

Received: 10 April 2024
Accepted: 12 May 2024

ISSN 2038-4106 print
ISSN 2975-044X online

INTRODUCTION

Tennis elbow (TE), also defined as lateral elbow tendinopathy (1, 2), is a widespread painful and non-inflammatory condition that affects the tendon insertion or myotendinous junction of wrist muscle extensors (3). It causes subacute and chronic symptoms of pain at the lateral epicondyle and elbow disability and sometimes of the entire upper limb (4, 5).

TE occurs in a range of 1% and 3% of the general population and typically affects subjects between 30 and 60 years without gender difference (3). TE is usually considered a self-limiting condition, with most patients recovering in 6–24 months (6), even if symptom recurrence persists for many years in approximately 20% of cases (4, 7). Despite the classic relationship to the practice of tennis, only 5% to 10% of total cases of this disease affect practitioners of this sport (8), especially those who practice tennis at an amateur level, who often practice tennis without athletic and technical preparation, or with inadequate sports equipment (9).

The main clinical manifestation of TE is hyperalgesia during elbow active range of motion and during palpation of the lateral epicondyle area, which is exacerbated by prono-supination of the forearm (10). Specific tests for TE, such as Cozen's and Mill's tests, are also usually performed to reproduce the pain experienced by the patient (11).
Moreover, patients affected by TE complain of painful handgrip with consequent functional limitation, disability in activities of daily living, time lost at work, and poor quality of life (12, 13). Ultrasound (US) evaluation and, eventually, magnetic resonance imaging (MRI) are usually performed as an adjunct to the physical examination (14-16).

Different conservative treatments have been proposed for TE, such as pharmacological therapy, systemic and/or local treatments (corticosteroid injections, botulinum toxin, hyaluronic acid, autologous blood, and platelet-rich plasma) (4, 17, 18), manual therapy (19-21), therapeutic exercise (22), physical modalities (such as laser therapy) (23, 24), elbow braces, dry needling (25), acupuncture, and watchful waiting (12). Surgery is usually recommended for those patients with persistent pain and disability after a course of conservative therapy (26, 27). However, no consensus about the best treatment for improving pain and function in people with TE has been reached (5). Among conservative treatments, injection therapy is widely used for the treatment of patients with TE (28-30), with hyaluronic acid (HA) peritendinous injections representing an emerging treatment option that, anyway, lacks strong evidence to support its use.

HA was shown to regulate the tendinopathic tissue repair process through several pathways modulating the main phases of tendon healing (i.e., inflammation, cellular migration, and angiogenesis) (31-36). All these properties supported HA as a conservative treatment for tendinopathies (29, 34, 37-40).

Several studies evaluated the effects of peritendinous injections of HA for TE (41-44), showing promising results in pain control and functional improvement (5).

The aim of the present study was to systematically review the effects of HA injections for treating TE in athletic and non-athletic populations, alone or in combination with other management modalities, in short- and mid-term follow-up, and comparison, with other kinds of injections. We hypothesized that HA injections may improve clinical and functional conditions in patients affected by TE.

METHODS

Study design

The present systematic review and related procedures were organized and conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (45-47). The PRISMA flow chart can be retrieved in Fig. 1, while the PRISMA checklist can be retrieved from Appendix A. The research protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42023457108.

Eligibility criteria

This review included randomized clinical trials, prospective studies, and case-series studies, with at least a 4-week follow-up. Articles such as editorials, technical notes, letters to authors, narrative reviews, systematic reviews, case reports, and animal or cadaveric studies that did not report clinical outcomes about the use of HA for TE were excluded.

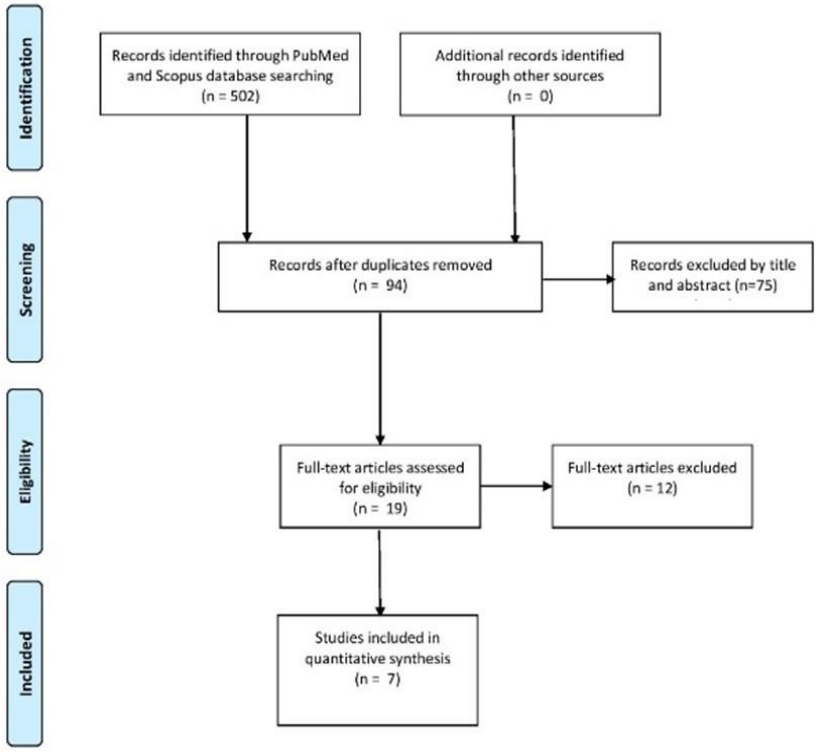

Fig. 1. *PRISMA flowchart.*

Information sources

Potential studies were identified by searching electronic databases, including Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, PEDro, Web of Science, Scopus, PubMed, and CINAHL. A systematic search of all databases was performed from their inception to September 2023, with no language limitations. Reference lists of relevant studies were also screened for additional possible studies.

Search strategy

The strategy had two components, including terms for HA and TE. Keywords for the population were “Tennis Elbow” [MeSH] OR “Elbow Tendinopathy” [MeSH] OR lateral epicondyle*[all fields] OR epicondylitis*[all fields]; keywords for the intervention were “Hyaluronic acid” [MeSH] OR sodium hyaluronate [all fields] OR hyaluronan [all fields].

Types of participants

This study included participants diagnosed with TE, defined as pain during palpation of the lateral epicondyle area exacerbated by prono-supination of the forearm or gripping and with or without confirmatory hypoechoic lesions on ultrasonography (48).

Types of interventions

For inclusion, HA had to be administered to at least one group in the RCTs. Studies in which the effects of HA alone could not be evaluated (such as a mixture of HA and another drug compared with HA alone or another drug) would not be included.

Types of comparison controls

Comparison groups were classified into active and inactive controls according to the Cochrane Handbook for Systematic Reviews of Interventions (49). Inactive control was defined as no treatment, standard care, or waiting list control, including watchful waiting, bracing, and usual care (50). Active control was defined as using different injection solutions such as corticosteroids (CS) (51), platelet-rich plasma injection 18, dextrose prolotherapy (DPT) (50, 52), and normal saline (53).

Outcome measures

The primary outcome of interest was pain reduction measured with the Visual Analogue Scale (VAS, 0-10). Secondary outcomes included the handgrip strength in kilograms and the Quick-Disabilities of the Arm, Shoulder, and Hand (Q-DASH) scores (where available). Other scores were evaluated case-by-case depending on the ones used in the included studies. The outcomes were evaluated at baseline, and final follow-up for each included study.

Study selection and data extraction

Two independent authors (D.T. and R.A.) performed the search and evaluated the articles. Experienced researchers in systematic reviews (D.T., R.P., F.S., B.C., C.R., R.A.) solved cases of doubt. Initially, investigators read article abstracts, selected the relevant ones according to inclusion and exclusion criteria, and then compared results with the other investigators. After two weeks, the same studies were read again to confirm the agreement. No disagreement was observed among the investigators.

One investigator (R.A.) extracted the data from the full-text articles to Excel (Microsoft, USA) spreadsheet structured tables to analyze each study in a descriptive fashion. The number of sample sizes, type of management, and HA used time of follow-up, clinical and functional outcome before and after treatment, adverse events, and complications were extracted from the retrieved articles and collected in Table I.

Table I. *A summary of the outcomes of the selected studies.*

Study name	Type of study	N. patient	Follow-up	Groups	HA used	Intervention	Scores at baseline	Scores at last follow-up	Adverse events
Apaydin et al. (2020)	RCT	32	6 and 12 weeks	HA (*n*=16) vs DPT (*n*=16)	30 mg/2 mL 1500 kDa	Single injection at baseline	**HA group** **VAS (rest):** 5.19 ± 1.1 **VAS (activity):** 7.25 ± 0.8 **VAS (night):** 6.08 ± 1.4 **Q-DASH:** 53.1 ± 12.5 **Grip strength:** 18.13 ± 8.6 **DPT group** **VAS (rest):** 4.94 ± 2.0 **VAS (activity):** 7.00 ± 1.5 **VAS (night):** 6.31 ± 2.3 **Q-DASH:** 53.2 ± 18.7 **Grip strength:** 19.87 ± 9.0	**HA group** **VAS (rest):** 2.44 ± 1.7** **VAS (activity):** 4.06 ± 2.3** **VAS (night):** 2.75 ± 2.0** **Q-DASH:** 24.7 ± 10.1** **Grip strength:** 22.94 ± 8.5** **DPT group** **VAS (rest):** 1.06 ± 0.8*,** **VAS (activity):** 2.19 ± 0.8*,** **VAS (night):** 1.19 ± 0.7*,** **Q-DASH:** 9.7 ± 6.4*,** **Grip strength:** 27.19 ± 9.6**	Injection site pain lasting 1-2 days (3 patients in the HA group, 4 patients in the DPT group)
							Significant improvement at last follow-up; DPT was favoured over HA for improvements for pain with activity, pain at night, and pain at rest. Q-DASH scores improved significantly more in the DPT group.		

Fogli et al. (2017)	PRS	26	1, 2, 8 weeks	HA (*n*=26)	20 mg/2 mL 500-730 kDa	3 injections (one a week for 3 weeks in a row)	**HA group** **VAS:** 8.19 ± 0.79	**HA group** **VAS:** 1.74 ± 2.17**	No complications
							Significant pain relief and reduction in tendon thickness and neovascularization in US evaluations at each follow-up.		
Petrella et al. (2010)	RCT	331	1, 2, 4, 12, 52 weeks	HA (*n*=165) vs placebo (*n*=166)	1% HA/1.2 cc	2 injections (one at baseline and one after one week)	**HA group** **VAS (rest):** 8.5 ± 11.1 **VAS (grip):** 9.8 ± 1.1 **PGS:** 0.3 ± 1.1 **PANF:** 1.1 ± 2.1 **PGA:** 1.1 ± 1.0 **Grip strength:** 49.2 ± 1.1 **Placebo (saline) group** **VAS (rest):** 8.4 ± 1.6 **VAS (grip):** 9.6 ± 0.4 **PGS:** 0.4 ± 1.1 **PANF:** 1.7 ± 2.2 **PGA:** 0.9 ± 1.2 **Grip strength:** 47.9 ± 0.4	**HA group** **VAS (rest):** 2.4 ± 1.4** **VAS (grip):** 2.9 ± 1.4** **PGS:** 4.8 ± 0.9** **PANF:** 4.6 ± 0.3** **PGA:** 4.7 ± 0.5** **Grip strength:** 65.7 ± 1.8** **Placebo (saline) group** **VAS (rest):** 7.7 ± 1.3*,** **VAS (grip):** 9.1 ± 1.1*,** **PGS:** 1.1 ± 1.8*,** **PANF:** 0.9 ± 1.9*,** **PGA:** 1.3 ± 0.7*,** **Grip strength:** 45.6 ± 1.3*,**	Pain during injection (3 patients in the HA group, 5 patients in the placebo group)
							Significant improvements in VAS and grip strength at each follow-up in the HA group. Statistically significant improvement in PGS, PANF and PGA were observed in the HA group.		
Stirma et al. (2020)	CSE	12	4 and 12 weeks	HA (*n*=12)	12 mg/1.2 mL	2 injections (one at baseline and one after one week)	**HA group** **VAS (rest):** 5.9 ± 2.6 **VAS (active):** 8.1 ± 1.6 **MEPS:** 61.3 ± 15.5 **Cozen's test:** 12 positives **Mill's test:** 12 positives	**HA group** **VAS (rest):** 2.1 ± 3.3** **VAS (active):** 3.6 ± 4.0** **MEPS:** 85.0 ± 21.2** **Cozen's test:** 5 positives **Mill's test:** 5 positives	No complications
							Significant improvement in VAS and MEPS at final follow-up.		
Khan et al. (2018)	CSE	45	4 weeks	HA (*n*=45)	1% HA/1 cc	2 injections (one at baseline and one after one week)	**HA group** **VAS:** 8.73 ± 1.07	**HA group** **VAS:** 6.42 ± 1.06**	Not reported
							Significant improvement in VAS at follow-up.		
Yalcin et al. (2022)	RCT	80	6 and 12 weeks	HA (*n*=40) vs CS (*n*=40)	30 mg/2 mL 2000 kDa	Single injection at baseline	**HA group** **VAS (rest):** 6.34 ± 0.73 **VAS (grip):** 7.2 ± 0.81 **Q-DASH:** 54.61 ± 8.11 **Grip strength:** 19.95 ± 4.46 **CS group** **VAS (rest):** 6.39 ± 0.8 **VAS (grip):** 7.54 ± 0.99 **Q-DASH:** 59.27 ± 9.03 **Grip strength:** 21.25 ± 3.43	**HA group** **VAS (rest):** 3.88±1 **VAS (grip):** 4.22±1.1 **Q-DASH:** 38.36±7.39 **Grip strength:** 37.1±2.54 **CS group** **VAS (rest):** 4.07±1.08 **VAS (grip):** 4.41±0.97 **Q-DASH:** 43.22±10.34 **Grip strength:** 38.82±3	Not reported
							Significant improvements in VAS, Q-DASH and grip strength were found in both group at six but not at 12 weeks, with changes being more prominent in the CS group. Within group comparison could not be performed due to the lack of data from the original article.		

Zinger et al. (2022)	PRS	18	12, 24, 52 weeks	HA (*n*=18)	16 mg/2 cc 800–1200 kDa	3 injections (one every two weeks)	**HA group** **VAS (rest):** 7.64 ± 1.21 **Q-DASH:** 53.7 ± 18.9 **PRTEE:** 67.0 ± 14.6	**HA group** **VAS (rest):** 1.43 ± 1.19** **Q-DASH:** 22.5 ± 17.1** **PRTEE:** 28.1 ± 15.8**	No complications
							Significant improvement in VAS, Q-DAH and PRTEE at final follow-up.		

P<0.05 (between groups**), **P<0.05 (**within group**). **HA**=hyaluronic acid; **DPT**=dextrose prolotherapy; **VAS**=visual analogue scale; **Q-DASH**=Quick-Disabilities of the Arm, Shoulder, and Hand (score between 0 and 100, with higher scores reflecting greater disability); **US**=ultrasound; **PGS**= patient global satisfaction using a 5 point categorical scale (0 = not satisfied, 5 = fully satisfied); **PANF**= patient assessment of normal function using a 5 point categorical scale (0 = no return to normal function, 5 = full return to normal function); **PGA**= physician's global assessment of elbow injury using a 5 point categorical scale (0 = poor patient elbow function and poor pain management, 5 = normal patient elbow function and normal pain management); **MEPS**=Mayo Elbow Performance Score (ranges from 0 to 100 with higher values indicating better results); **CS**= corticosteroid; **PRTEE**= Patient-Rated Tennis Elbow Evaluation (ranges from 0 meaning no pain and maximum function to 100 meaning maximum pain and minimum function); **RCT**=randomized clinical trial; **PRS**=prospective study; **CSE**=case series study.*

A second investigator (D.T.) independently double-checked the primary data extraction from all the articles. Doubts and inconsistencies were grouped and solved. All the authors participated in the drafting of the text.

All results compatible with each outcome domain in each study were sought. A *p*-value <0.05 was considered statistically significant. *P*-values are presented in Table I for a comparison of progression from baseline to the last follow-up within groups and a comparison of the between-group effects from baseline to the last follow-up.

The level of evidence analysis was determined using the Oxford Centre for Evidence-Based Medicine Levels of Evidence (54).

Quality assessment

The Modified Coleman Methodology Score (MCMS) was used to evaluate the methodological quality of the articles included in this systematic review (55). MCMS was used to assess the quality of the articles found in the present study, assessing methodology with 10 criteria, with a total score between 0 and 100 (which indicates that the study largely avoids chance, various biases, and confounding factors). Final score was categorized as excellent (85-100 points), good (70-84 points), fair (55-69 points), and poor (<55 points).

The MCMS criteria were modified to make them reproducible and relevant to the present systematic review. For example, we replaced the "description of surgical technique" criterion with "description of injection technique." Appendix B (56) reports more details about the MCMS (such as the definition for each criterion, the scoring system, etc.).

Two authors (D.T. and R.A.) independently applied the MCMS, and a final score was reached by consensus. The MCMS is calculated using ten different criteria (study size, follow-up, number of procedures, type of study, diagnostic certainty, description of the injection technique, rehabilitation and compliance, outcome criteria, outcome assessment, and selection process), with a maximum total possible score of 100 (55). Then, the agreement in the quality assessment between the two reviewers was evaluated using Cohen's kappa coefficient.

RESULTS

Eligible studies

After the initial literature search, 502 potentially relevant citations were retrieved. After the removal of duplicate records, 94 articles were identified. Then, following a first evaluation of titles and abstracts, 75 articles were not included since they did not investigate outcomes in the use of HA for TE. Finally, after further screening, other 12 articles were excluded as they did not conform to inclusion criteria, and a total of seven articles were included in the present systematic review (Fig. 1). Among the 12 excluded studies, one had only 1-week follow-up, so its outcomes could not be considered as reliable. Three articles were excluded because they combined HA with other drugs (such as chondroitin sulfate or CS) or physical therapy (such as laser therapy).

Quality of the included studies

The inter-rater (R.A. and D.T.) reliability in the quality assessment, evaluated using Cohen's K coefficient, was optimal (0.9). The raters were blinded to the other reviewer's ratings.

The results of the MCSMS are reported in Table II. There was a wide range of MCMS values, from 47 to 79, with a mean of 61.4±11.4 regarded as fair (55-69 points). Some of the selected studies presented some limits, therefore, a meta-analysis was not performed (Table II).

Table II. *Results of the Modified Coleman Methodology Score (MCMS) used to assess quality of the included.*

Article	Study size	Follow-up	N procedures	Type of study	Diagnostic certainty	Description of injection technique	Rehabilitation and compliance	Outcome criteria	Outcome assessment	Selection process	Total
Apaydin et al. 2020	4	0	7	15	5	10	0	10	12	5	68
Fogli et al. 2017	0	0	10	10	0	10	0	7	5	5	47
Petrella et al 2010	10	4	7	15	5	10	5	10	8	5	79
Stirma et al 2020	0	0	10	10	0	5	5	10	8	5	53
Khan et al 2018	4	0	10	10	0	10	0	7	5	5	51
Yalcin et al 2022	7	0	7	15	5	5	0	10	12	5	66
Zinger et al 2022	0	4	10	15	5	10	0	10	7	5	66
Maximum Score Possible	10	10	10	15	5	10	5	10	15	10	100
Mean ± Standard Deviation	3.6±3.9	1.1±1.95	8.7±1.6	12.85±2.7	2.85±2.7	8.6±2.4	1.4±2.4	9.1±1.5	8.1±2.9	5±0	61.4±11.4

Characteristics of the included studies

Detailed descriptions of the characteristics of the included studies are summarized in Table I. Of the seven articles retrieved, three were prospective and case series studies with no comparative group, reporting results after a different number of HA injections (two or three) (8, 57, 58). Three studies were RCTs, with one of them reporting outcomes comparing HA injections with saline (placebo) injections (43), one reporting outcomes comparing a single HA injection with a single dextrose prolotherapy injection (52), and one reporting outcomes comparing a single HA injection with a single CS injection (59).

One study was initially designed as an RCT comparing HA injections with saline (placebo) injections (4). Still, as the authors stated, they could not analyze the information from the saline-treated patients due to the high rate of loss to follow-up: for this reason, this study should be considered prospective.

The study period ranged from 58 to 52 weeks (4, 43). The total number of patients enrolled in the retrieved studies was 544, with a minimum of 12 patients 8 and a maximum of 331 patients (43).

A clinical diagnosis of pain from a minimum of three weeks 58 to a maximum of 12 months (8) at the lateral epicondyle during palpation and/or resisted wrist extension with the arm fully extended was also used in all the included studies (4, 8, 43, 52, 57-59).

When injections were performed using a US-guided approach, a US-based evaluation of the affected epicondyle was also performed (8, 57). Only in one study an MRI diagnosis of TE was performed (59). Only two studies reported using specific tests for clinical assessment of TE, such as Cozen's and Mill's tests (8, 59).

Adverse events

Adverse events with the use of HA were pain at the injection site pain lasting one to two days reported in the study by Apaydin et al. in which HA was compared to DPT (three patients in the HA group, four patients in the DPT group) (52), and pain during the injection reported study by Petrella et al. in which HA was compared to placebo (three patients in the HA group, five patients in the placebo group) (43).

Injection technique

Two studies used a US-guided injection technique (8, 57), while, in the other studies, the injections were delivered at the point of greatest tenderness (4, 43, 52, 58, 59) one centimeter distal to the lateral epicondyle (4, 43, 58) and with the affected arm flexed to 90° (8, 43, 58). In two studies, a single injection at baseline was performed (52, 59), while in the other studies, two (8, 43, 58) or three injections (4, 57) were administered.

Rehabilitation

Only one study mentioned the rehabilitation protocol followed after the injections, which consisted of standard home stretching and strengthening procedures guided by a physical therapist (8).

Primary and secondary outcomes evaluation

The initial assessment of patients was performed in all the included studies using the visual analog scale (a 0-score score means no pain and maximum function while a 10-score means maximum pain and minimum function), with including values going from 3/10 (52) to 7/10 (58).

In each study, VAS decreased at each follow-up more than the threshold for minimal clinically important difference (MCID) (60) compared to baseline. Interestingly, in four out of six studies with more than a single follow-up point (4, 8, 52, 57), the VAS decreased more in the long-term follow-ups than in the short-term follow-ups. Physical function was shown to be improved in all the secondary outcomes across all the included studies.

In the studies in which grip strength was assessed using a hand dynamometer (43, 52, 59), the scores increased at each follow-up compared to a baseline of more than the threshold for MCID (61, 62). In any case, only in one study (52) the grip strength constantly improved over time, while in the other two studies (43, 59), grip strength increased at the first follow-up (i.e., four weeks and six weeks, respectively) but then started to decrease until the last follow-up.

In three articles in which the Q-DASH was used (4, 52, 59), the scores decreased at each follow-up when compared to a baseline of more than the threshold for MCID (63), except at the 6-week follow-up in the study by Yalcin et al. (59) that did not reach the threshold. The Q-DASH constantly decreased over time. As for the VAS, Q-DASH scores decreased more in the long-term follow-ups than in the short-term follow-ups.

HA versus active controls

Studies by Apaydin et al. (52) and Yalcin et al. (59) showed that in their control groups (i.e. patients treated with injections of dextrose prolotherapy and CS, respectively) better outcomes in terms of pain and function were reached at 12 and six weeks, respectively.

In the study by Apaydin et al. (52) there were no significant differences between the groups at six weeks for pain ($p>0.05$). Each group demonstrated a substantial change in VAS score at six weeks. DPT was favored over HA for improvements from zero to 12 weeks for pain with activity ($p=0.04$), pain at night ($p=0.03$), and pain at rest ($p=0.04$). Q-DASH scores improved significantly from zero to 12 weeks in the DPT group ($p=0.04$). Each group significantly improved pain and Q-DASH over time ($p<0.001$).

In the study by Yalcin et al. (59) there were significant differences regarding pain at rest ($p=0.017$), pain with hand grip ($p=0.08$), Q-DASH ($p=0.001$), and grip strength ($p=0.004$) at the six-week follow-up favoring the CS group, but non-significant differences at the 12-week follow-up in the evaluated scores.

When HA injections were compared to placebo (saline injections) (43), pain at rest and after grip testing was significantly better using HA. These outcomes were also associated with significantly greater grip strength, patient global satisfaction, and assessment of normal elbow function in the HA group *versus* control. Physician global assessment of elbow injury was significantly better for the HA *versus* control. These differences persisted at each follow-up assessment. Time to return to pain-free and disability-free sport was 18 ± 11 days in the HA group, with this outcome not being achieved in any of the control group patients, meaning a faster return to pain-free sports activities compared to placebo.

DISCUSSION

The outcomes of the included studies highlighted the paucity of evidence on the effectiveness and safety of HA injections for TE. Despite the use of different types of HA and injection protocols, and different scores applied, each study evaluated in this systematic review showed that the administration of HA for the treatment of TE is safe and effective in reducing pain, improving function, and allowing a faster return to pain-free sports activities.

HA was shown to regulate the tissue repair process through several pathways modulating the main phases of tendon healing (i.e., inflammation, cellular migration, and angiogenesis) (31-36). All these properties supported HA as a conservative treatment for tendinopathies (29, 34, 37-40).

While the effectiveness of HA injections is well-established for treating osteoarthritis (OA) (64-67), its efficacy in managing tendinopathies is still debated (68).

A systematic review by Coombes et al. (51) about the use of peritendinous injections for tendinopathies showed that HA injections have moderate evidence of benefits in the short, medium, and long-term, while other kind of injectable drugs, such as CS, only give temporary relief. Another recent systematic review by Crimaldi et al. (32) about the use of HA for tendinopathies stated that although HA seems to be an effective therapeutic option for managing tendinopathies, further studies with a larger sample size are needed to confirm the available findings. Since few conservative treatments were proven effective for TE (4), HA injections may represent an effective and safe therapeutic option.

Despite the good outcomes reported by the studies included in this review, the use of HA alone for TE remains questionable, especially regarding its use for short-term pain relief. Apaydin et al. stated that the superiority of DPT injections over HA in the short term may be related to the fact that DPT is more effective in accelerating tendon healing and regeneration. In contrast, HA injection provides increasing tendon lubricity over a longer period of time (52).
For this reason, and given the lack of a hard scientific background, other treatments or combined treatments using HA and other drugs may be preferred.

One prospective RCT by Tosun et al. (69) evaluated the effects of a mixture of HA and chondroitin sulfate injections *versus* CS alone for the treatment of TE, reporting better pain and function scores at six months in the HA plus chondroitin sulfate group. Chondroitin sulfate has anti-inflammatory, viscoelastic, and hydration properties, which may contribute to the effectiveness of HA (70).

A prospective study by Saggini et al. (9) compared the effectiveness of injections of CS plus HA *versus* CS alone, showing that CS plus HA is more effective than CS alone in the long term (6 months). Mixing CS with HA may have the potential to undermine the accurate assessment of the effect of the HA for treating TE (71). Furthermore, the anti-inflammatory effects of CS may falsely exaggerate the beneficial effect of HA (44).

Recent evidence indicated that CS could have tenotoxic effects, increasing the risk of tendon or ligament rupture, increasing tenocyte necrosis, and decreasing cell viability (72-74). Furthermore, in a prospective, double-blind RCT by Lindenhovius et al. (75), steroid injections did not affect the self-limited course of lateral elbow pain.

These concerns lead to the use of other materials for injection therapies, such as platelet-rich plasma (PRP) (76) which has become popular despite insufficient scientific support since most of the literature on PRP contains low-quality studies (51, 77-79). Only one study, a double-blinded RCT (80), reported results comparing PRP to CS injection with a one-year follow-up for TE, finding a 73% success in the PRP group.

Three recent systematic reviews and meta-analyses discouraged the use of CS and PRP for the treatment of TE (81-83), while favoring the use of electrophysiotherapy (such as laser therapy, shock wave therapy, and microcurrent application) even over physical therapy (81, 84).

One retrospective cohort clinical study by Pellegrino et al. (5) compared the effectiveness of a combined approach based on high-intensity laser therapy (HILT) and HA injections to therapeutic exercise alone on pain, muscle strength, and disability in patients with painful TE. The authors stated that a combined HA plus HILT treatment might be more effective than therapeutic exercise for people suffering from TE in the short-medium term.

These findings showed that when HA is combined with other pharmacological or physical conservative treatments, such as CS or electrophysiotherapy, the outcomes are better than those of single therapies alone (5, 9, 69).

Study limitations

The present review is not free from limitations. First, only three included studies are level-II studies and the others are level-IV studies. For this reason, the reported outcomes (especially those from level-IV studies, including a single group of patients) need to be interpreted cautiously due to the substantial risks of bias. Furthermore, there was high heterogeneity in the type of HA used and the number of injections performed, and even when the same injection protocol was used, the type of HA administered was different.

In some studies, molecular weight and concentration of the HA were not specified, so we cannot conclude which HA and injection protocol is the best choice for the conservative treatment of TE.

Finally, the heterogeneity of the study population with the absence of a control group in many investigations is an important limitation.

CONCLUSIONS

The administration of HA for the conservative treatment of TE shows a trend toward benefits in pain and functional outcomes, with few and minor side effects. In each study, the scores evaluated improved significantly with good results andoutcomes, especially in the long term. However, five articles were level-IV studies, preventingdefinitive recommendations regarding the indicationfor the use of HA for TE. Furthermore, when HA was compared to DPT or CS, it appeared inferior regarding pain and functional improvements in the short term. Prospective long term follow-up studies and RCTs are needed to confirm the outcomes of the included articles.

Funding:
This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflict of interest:
The authors state that they do not have any conflict of interest.

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Appendix A. *PRISMA checklist.*

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pages 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6-7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7
Study characteristics	17	Cite each included study and present its characteristics.	Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 8-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 11-13
	23b	Discuss any limitations of the evidence included in the review.	Page 13-14
	23c	Discuss any limitations of the review processes used.	Page 13-14
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not applicable
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 14

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Page 14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix B. *The Modified Coleman Methodology Score.*

Part 1: One score for each of the sections:

1.	Number of patients:	
	a. <30	0
	b. 30-50	4
	c. 51-10	7
	d. >100	10
2.	Mean follow-up	
	a. <12 months	0
	b. 12-36 months	4
	c. 37-60 months	7
	d. >61 months	10
3.	Surgical approach	
	a. Different approaches and outcome not reported separately	0
	b. Different approaches and outcome reported separately	7
	c. Single approach	10
4.	Type of study	
	a. Retrospective cohort study	0
	b. Prospective cohort study	10
	c. Randomized controlled trial	15
5.	Description of diagnosis	
	a. Described without percentage specified	0
	b. Described with percentage specified	5
6.	Description of surgical technique	
	a. Not stated/unclear – Inadequate	0
	b. Only stated – Fair	5
	c. Stated with details – Adequate	10
7.	Description of postoperative rehabilitation	
	a. Described	5
	b. Not described	0

Part 2: Scores can be assigned for each option of every section

1.	Outcome criteria	
	a. Outcome measures clearly specified	2
	b. Timing of outcome measures clear	2
	c. Outcome measures with reported reliability	3
	d. General health measure included	3
2.	Outcome assessment	
	a. Participants recruited	5
	b. Investigator independent of surgeon	4
	c. Written assessment	3
	d. Assessment completed by patients	3
3.	Description of participants selection process	
	a. Selection criteria reported and unbiased	5
	b. Recruitment rate reported (>90%)	5
	c. Recruitment rate reported (<90%)	0

The figure reporting the Modified Coleman Methodology Score was retrieved from the following article: Mancino, F.; Di Matteo, V.; Mocini, F.; Cacciola, G.; Malerba, G.; Perisano, C.; De Martino, I. Survivorship and Clinical Outcomes of Proximal Femoral Replacement in Non-Neoplastic Primary and Revision Total Hip Arthroplasty: A Systematic Review. BMC Musculoskelet. Disord. 2021, 22, 933, doi:10.1186/s12891-021-04711-w. This article is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, including images or other third party material.