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SYSTEMATIC REVIEW

Local corticosteroid *versus* autologous blood injections in lateral epicondylitis: meta-analysis of randomized controlled trials

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ABSTRACT

INTRODUCTION: Lateral epicondylitis is a common painful elbow disorder. Several approaches to treatment have been proposed, with a local injection of corticosteroids being the most frequently used. Recent insights into the pathophysiology encouraged the introduction of autologous blood injections as an alternative treatment method. The aim of this meta-analysis is to summarize quantitatively the evidence regarding the efficacy of corticosteroids and autologous blood injections for treatment of pain in lateral epicondylitis.

EVIDENCE ACQUISITION: Studies were considered eligible based on the following inclusion criteria: adult human, diagnosis of lateral epicondylitis, randomized controlled trials comparing corticosteroids *versus* autologous blood injections, pain assessment. Exclusion criteria were previous surgery for lateral epicondylitis or for other elbow disorders, concurrent treatment with drugs or physiotherapy, diagnosis of musculoskeletal systemic disorder. A systematic search of literature was performed according to the PRISMA statement. Effect size of each included study was calculated and analyzed in a random-effects model.

EVIDENCE SYNTHESIS: Four studies, enrolling total of 218 patients (139 females and 79 males), were included in quantitative analysis. At 2 weeks, there was a trend towards a reduction of VAS score in the corticosteroid group (WMD=2.12 [95% CI: 4.38 to 0.14], P=0.07). No significant differences were recorded in the medium-term (4-12 weeks; WMD=0.85 [95% CI: -0.44 to 2.15], P=0.19) and long-term (24 weeks; WMD=0.63 [95% CI: -2.40 to 3.66], P=0.68) follow-up.

CONCLUSIONS: Few high-quality trials compare the efficacy of corticosteroid and autologous blood injections in the control of pain related to lateral epicondylitis. Available data indicate that corticosteroids tend to reduce VAS score in short-term follow-up, although these data are not statistically significant. No differences were recorded in the medium and long term. Contrary to popular opinion among medical professionals, and despite pathophysiological cues, the currently available data offer no support for the effectiveness of autologous blood injections in medium- and long-term follow-up. Further studies are necessary to establish which treatment has more impact on pain in lateral epicondylitis. These data could be then used as a basis for practical guidelines and new protocols of treatment.

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Key words: Tennis elbow - Adrenal cortex hormones - Autologous blood transfusion - Pain management.

Introduction

Lateral epicondylitis, also known as tennis elbow, is a common complaint in musculoskeletal clinical practice. The prevalence of this disease is around 1-3% in the population between ages 45 and 55.[1] Lateral epicondylitis occurs as a result of repetitive stress and overuse of the wrist and usually affects the dominant arm. Age, sex, psychosocial factors, leisure- and occupation-based physical activities are considered to be risk factors. Common extensor tendon is the anatomical structure involved, with the extensor carpi radialis bre-

vis tendon typically compromised.[2] Different hypotheses have been proposed over the years to explain the etiology of this disorder. Histological studies showed that inflammation is not the main etiological event in the lateral epicondylitis.[3] Hence, attention was drawn to the degeneration of tendon attachment points caused by repetitive microtrauma. Indeed, new evidence justifies the use of the term "tendinosis", rather than "tendinitis", as the more appropriate term to describe the tennis elbow.

Currently, there is no consensus on the best treatment of elbow tendinosis. Even though the pathophysiological rationale for the use of corticosteroids has not been demonstrated, data from previous studies evidenced that corticosteroids could be useful in reducing pain in short-term follow-up, albeit a worsening of symptoms was observed in long term. Subsequently, injections of autologous blood or blood derivatives, such as platelet-rich plasma (PRP), abundant in growth factors and other mediators of regeneration, have been proposed as a treatment.[4] Injection of PRP represents a modern approach with a promising application in several musculoskeletal disorders, but its widespread use is limited by the specific technical requirements. Therefore, it remains an expensive and non-standardized option.

Previous studies [5-9] have attempted to summarize the available evidence on the effectiveness of different injection therapies, with most authors concluding that corticosteroids are advantageous in the short term, while autologous blood injection (ABI) may have a higher efficacy in the long term. However, these conclusions are limited to few methodologically different studies and need to be analyzed from a systematic point of view. Therefore, the aim of this meta-analysis is to compare the efficacy of these approaches in lateral epicondylitis-related pain reduction in the short- and long-term follow-up.

Evidence acquisition

The study followed a standard systematic review protocol, according to the guidelines described in the Cochrane Handbook and recommendations listed in the PRISMA statement.[10] The following databases were searched for articles published until April 2015: MEDLINE, EMBASE, PubMed, CINAHL, Web of Science, Scopus, and Cochrane CENTRAL. The search was conducted combining the following subject heading terms: "tennis elbow", "lateral epicondylitis", "tendinosis", "tendinitis", "corticosteroid", "autologous blood", "injection". English language restriction was applied. Moreover, manual search of published studies was also conducted and retrieved study reference list were screened. In order to obtain reliable evidence, the analysis has been limited to randomized controlled trials, and accordingly has not included observational studies, case reports and other studies of lower methodological rigor.

Study selection

The titles and abstracts of the articles identified in literature search were screened by three independent researchers to assess their eligibility for the analysis. Full texts of the articles describing randomized controlled trials were obtained. Studies were considered eligible for qualitative and quantitative analysis based on the following inclusion criteria: human (adults >18 years old), clinical and/or instrumental diagnosis of lateral epicondylitis, randomized controlled trials comparing corticosteroids *versus* autologous blood injections (studies with more complex design were also considered and only data regarding corticosteroids and autologous blood injection groups were taken into consideration for quantitative analysis), pain assessment. Exclusion criteria were previous surgery for lateral epicondylitis or for other elbow disorders, concurrent treatment with drugs or physiotherapy, diagnosis of musculoskeletal systemic disorders.

Data extraction and assessment of risk of bias

The following data were extracted from each study: sample size, age, sex, number of patients in each treatment arm, follow-up period, and year of publication. Measurement of pain treatment outcome by spontaneous pain description on Visual Analog Scale (VAS) was recorded. Complex evaluation scales combining different items regarding function, strength and pain in a single score were not considered, unless it was feasible to extract only pain domain assessment value.

The studies included in the analysis were assessed for risk of bias using Cochrane tools.[11] The following potential sources of bias were considered: sequence generation, allocation concealment, blinding of partici-

pants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Following Cochrane guidelines, each item was judged as "low risk", high risk" or "unclear risk" of bias. Due to the subjectivity of pain perception, the blinding of participants and personnel was considered a factor with the highest impact on a study's risk of bias.

Statistical analysis

The extracted data were analyzed using STATA software (StataCorp. v.12, College Station, TX, USA). Effect sizes and 95% confidence intervals were calculated for each study according to data types, using METAN routine. Based on the characteristics of included studies, summary estimates of effect were calculated with a fixed-effects or random-effects model. In random-effects model, the presence of heterogeneity was assessed using Q statistics. P values less than 0.05 (two-tailed) were considered significant to reject null hypothesis. P values >0.05 were evaluated according to the power of the test used. T^2 and T were measured. I^2 was used to express heterogeneity as percentage. Significant heterogeneity was considered if P<0.05 and I^2>60%. When necessary, meta regression and subgroup analysis were performed.

Sensitivity analysis was used to assess consistency of the results. Impact of each study on estimate of summary effect was investigated using the METANINF command.

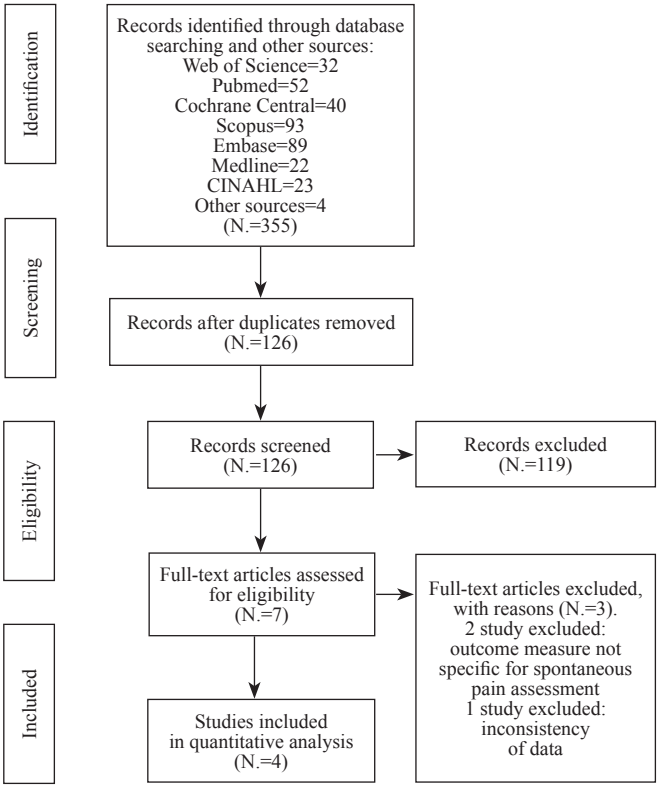

Figure 1.—The outcome of study search and selection.

Evidence synthesis

Out of 355 articles initially identified, after removal of duplicates, titles and abstracts of 126 studies were screened. Based on inclusion/exclusion criteria specified above, seven studies comparing corticosteroid and autologous blood injections were considered for a detailed evaluation and their full texts were retrieved. Among them, five [12-16] had a double-arm design and allocated patients in CI or ABI group, while two [17, 18] had a more complex design, with three treatment arms (comparing CI, ABI and extracorporeal shockwave therapy [17] or CI, ABI and saline injections).[18]

After detailed evaluation of the full texts, three out of seven studies were excluded for the following reasons: Ozturan *et al.*[17] reported a 0-100 pain assessment scale recorded during Thomsen test and not the spontaneous assessment of pain perception; Singh *et al.*[16] used an outcome measure reporting a summary score ranging from 0 to 100 to assess pain and function of the affected arm (Patient-rated Tennis Elbow Evaluation), hence it was impossible to consider only the pain assessment score; Dojode *et al.*[13] had inconsistency across outcome measures. As a result, only four studies were included in our quantitative analysis. The outcome of study search and selection is reported in Figure 1.

The trials included in the analysis enrolled total of 218 patients (139 females and 79 males) with a mean age of 44.8 years (range 38 to 49 years). In the study by Wolf *et al*.,[18] 9 patients were enrolled in the saline injections group; hence, in overall analysis, 104 patients were enrolled in CI group and 105 in ABI group. All patients included in our meta-analysis were treated with a single injection of corticosteroids or autologous blood. Arik *et al.*[12] and Jindal *et al.*[14] used 40 mg of methylprednisolone, Wolf *et al.*[18] used 40 mg of triamcinolone and Kazemi *et al.*[15] used 20 mg of methylprednisolone

in CI group. In ABI group, the treatment consisted in one injection of 2 mL of autologous blood in all the studies included in the analysis. Both groups received 1 mL of local anesthetic (lidocaine, lignocaine or prilocaine) in addition to autologous blood or corticosteroid in the same injection. In all studies, injection was done with a single-needle percutaneous access and none reported the use of the peppered injection technique. None of the studies reported complications or side effects of the treatments, other than short-lived pain after ABI.[12]

The outcome measurements were reported at 2 weeks,[12, 14, 18] 4 weeks,[12, 15] 6 weeks,[14] 8 weeks,[15, 18] 12 weeks,[12] and 24 weeks.[12, 18] To assess spontaneous pain, VAS ranging from 0 (no pain) to 10 (worst pain) was adopted in all included studies and was considered in quantitative analysis. At baseline, VAS score was 6.17±1.5 in the CI group and 6.07±1.95 in the ABI group. As specified earlier, and motivated in the following section, function and strength measurements, including Nirschl Scale, the Disabilities of the Arm, Shoulder and Hand (DASH) Questionnaire, maximum grip strength and pressure pain threshold, were not taken into consideration in this meta-analysis, even if reported in some of the studies. Characteristics of included studies are summarized in Table I.

To begin with, risk of bias of each included study was evaluated. Only Wolf *et al.*[18] used an adequate method to generate randomization sequence and conceal allocation, and reported the use of aluminum foil on the syringe during injection in order to blind participants. In two studies,[14, 15] the methods of randomization and allocation concealment were considered at high risk of bias, while in the study of Arik *et al.*,[12] the risk of bias was defined as unclear in this regard. In both Jindal *et al.*[14] and Kazemi *et al.*[15] studies, blinding of outcome assessment was at low risk of bias, while in the other two studies this risk was unclear. Attrition bias was detected only in Jindal *et al*.[14] No relevant reporting bias or other sources of bias were detected. The risks of bias according to the Cochrane tool are graphically reported in Figure 2.

VAS scores were used to estimate summary effect. Based on the time of follow-up and VAS score evaluation, three different subgroups were defined, namely short term (VAS score recorded at 2 weeks), medium term (VAS score recorded between 4 and 12 weeks), and long term (VAS score recorded at 24 weeks). Results are summarized in figure 3. In short-, medium- and long-term follow-up, there were no statistically significant differences in VAS scores between CI and ABI group. Nevertheless, in short term (2 weeks), our analysis showed positive trend in favor of CI, with a mean reduction of VAS score 2 points larger than ABI (WMD=-2.12 [95% CI: -4.38 to 0.14]; comparison: P=0.07; heterogeneity: χ^2=37.07, P<0.05, I^2=94.6%, τ^2=3.55, random-effects model). In medium-term follow-up (4-12 weeks), the overall effect recorded analyzing all included studies did not show significant differences in VAS scores between CI and ABI (WMD=0.85 [95% CI: -0.44 to 2.15]; comparison: P=0.19; heterogeneity: χ^2=72.53, P<0.05, I^2=93.1%, τ^2=2.28, random-effects model). Similarly, the results of sensitivity analysis in medium-term follow-up were not statistically significant (WMD=0.19 [95 CI: -1.34 to 1.71]; comparison: P=0.81, heterogeneity: χ^2=44.73, P<0.05, I^2=93.3%, τ^2=2.06, random-effects model). Only Wolf *et al.*[18] and Arik *et al.*[12] studies reported data at 24 weeks and, as such, were included in the long-term follow-up subgroup. As with the previous analysis, the overall effect was not significant (WMD=0.63 [95% CI: -2.40 to 3.66]; comparison: *P*=0.68, heterogeneity: χ^2=9.62,

TABLE I.—*Summary of studies included in meta-analysis.*

Study	Design	N. (M/F ratio)	Mean age (years)	Intervention groups	Follow-up (weeks)
Arik *et al*.[8]	RCT	80 (21/59)	45.2	CSI (N.=40): methylprednisolone acetate 40 mg with 2% prilocaine hydrochloride 1 mL ABI (N.=40): venous blood 2 mL with 2% prilocaine hydrochloride 1 mL	2, 4, 12, 24
Jindal *et al*.[10]	RCT	50 (31/19)	38.1	CSI (N.=25): methylprednisolone acetate 40 mg with 2% lignocaine 1 mL ABI (N.=25): venous blood 2 mL with 2% lignocaine 1 mL	2, 6
Kazemi *et al*.[11]	RCT	60 (11/49)	47.1	CSI (N.=30): methylprednisolone 20 mg with 2% lidocaine 1 mL ABI (N.=30): venous blood 2 mL with 2% lidocaine 1 mL	4, 8
Wolf *et al*.[14]	RCT	28 (16/12)	49.0	CSI (9): triamcinolone 40 mg with lidocaine 1 mL ABI (N.=10): venous blood 2 mL with lidocaine 1 mL SI (N.=9): saline 2 mL with lidocaine 1 mL	2, 8, 24

RCT: randomized control trial; CSI: corticosteroid injection; ABI: autologous blood injection; SI: saline injection.

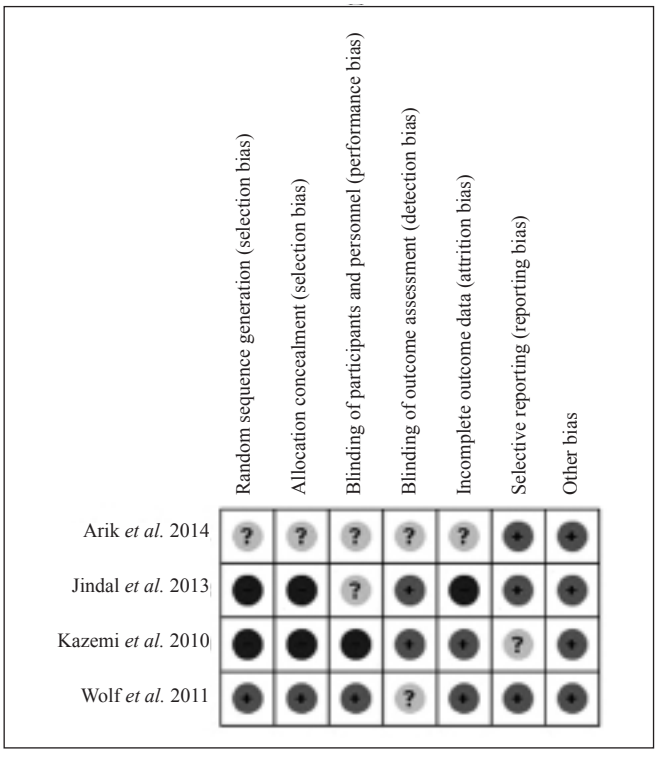

Figure 2.—Risk of bias as per the Cochrane tool for the studies included in this meta-analysis.

P≤0.05, I^2=89.6%, τ^2=4.30, random-effects model). Due to the small number of studies included in the analysis and differences in effect size, a high degree of heterogeneity was detected in each group. For the same reason, meta regression and evaluation of publication bias using the funnel plot were not performed.

While all the studies applied the same ABI protocol, in CI group, Kazemi *et al*.[15] used 20 mg of steroid, instead of 40 mg as in all other cases, recording the outcome at 4 and 8 weeks. To reduce heterogeneity, we performed the sensitivity analysis with exclusion of Kazemi's results (Figure 4). Yet the fact remains that this study had the major influence on the summary effect estimate in favor of ABI in medium-term follow-up, as revealed by the assessment of the impact of this study using METANINF command in STATA.

Discussion

Local CI represents a common approach to the treatment of several musculoskeletal disorders. It is a simple and not expensive procedure, aimed at reducing pain and other symptoms associated with inflammatory process. Several biological hypotheses have been proposed to justify the effect of corticosteroids on pain control, such as suppression of prostaglandins, modification of connective tissue and extracellular matrix, regulation of nociceptive receptors and chemical mediators, modification of the relationship between tendon structures and paratendinous tissues.[19, 20] Although none of these hypotheses has been definitely confirmed, the effectiveness of corticosteroids on pain reduction is clinically demonstrated. As a matter of fact, existing evidence [21, 22] indicates that CI is more useful than other therapies in short term pain reduction. Currently, however, no data support corticosteroid use on the long term.

Notwithstanding the potential benefits, CI can cause moderate side effects, such as skin atrophy, tendon rupture, cutaneous rash, pain after injection and, in a specific group of patients, serious and systemic effects, which could preclude its use. Moreover, based on new insights into pathophysiology of tendon disorders, the re-evaluation of the role of inflammation is mandatory. Indeed, a growing body of evidence demonstrates that a degenerative process and a failure in healing responses of tendon are the key features in many such disorders, including lateral epicondylitis.[3] For these reasons, new approaches to therapy, aimed at modifying degenerative and regenerative mechanisms, have been proposed, among them ABI. The rationale of this treatment is to provide cellular and humoral mediators able to stimulate healing cascade.

Previous studies have compared CI with other conservative treatment options for lateral epicondylitis, concluding in favor of the former as regards short-term pain reduction.[6] In addition, other studies concluded that CI is useful in pain reduction within 4 weeks [22] or 6 weeks.[21, 23] When a longer follow-up was taken into consideration, Krogh *et al*.[6] observed that there were no differences between CI and placebo in terms of pain reduction beyond 8 weeks. In the same analysis, results in favor of ABI were reported (including Kazemi *et al.*[15] at 8 weeks, Creaney *et al*.[24] at 26 weeks, and Ozturan *et al.*[17] at 52 weeks); however, no data about role of ABI on the short term were considered.

Considering the high prevalence of this disorder in the active middle-aged population and the negative impact of pain on function, daily activities and quality of life, the choice of the treatment providing fast

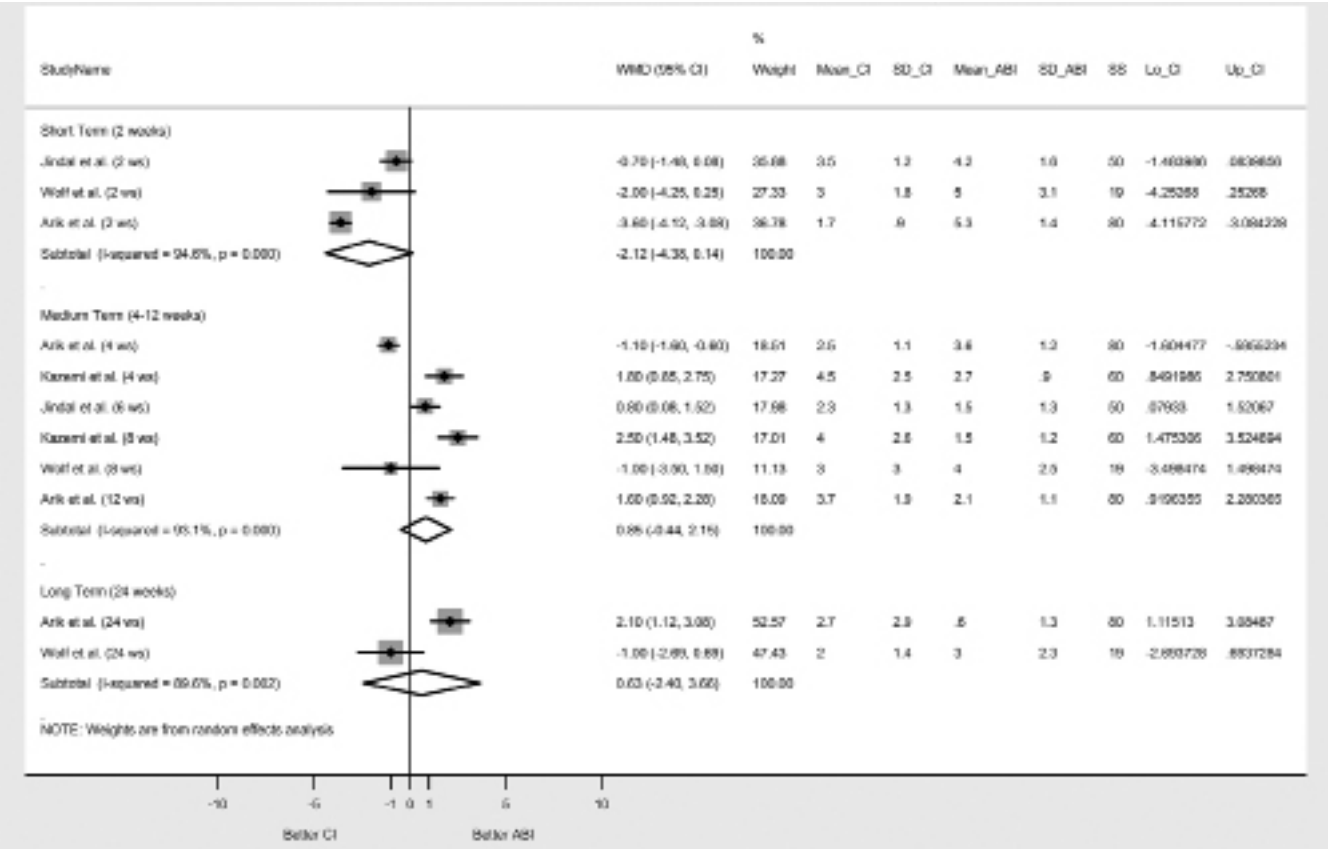

Figure 3.—VAS score in the short, medium, and long term.

pain relief should be preferred. Incidentally, summary effect measured in our analysis indicates that there is a positive trend towards CI, with a reduction in VAS score 2 points larger than ABI at 2 weeks. In the analyses performed in the medium-term subgroup (follow-up of 4-12 weeks), no significant differences between two injection therapies in terms of pain reduction were revealed. Only two studies [12, 18] reported data at 24 weeks and were included in the long-term subgroup. Conclusions from these studies are contradictory, although, in a random-effects model, more weight has been assigned to Arik *et al.* (reporting higher efficacy of ABI in long-term pain relief),[12] probably due to a lower sample size in the study by Wolf *et al*.[18] Nevertheless, as revealed by the present analysis, summary effect remains not significant.

Interestingly, Coombes *et al.*[5] performed a meta-analysis of several randomized trials assessing efficacy of different types of injections for tendinopathy treatment. However, their results should not be generalized because of variation in effect between sites of tendinopathy. In fact, given the emerging complexity of pathogenesis and outcomes of tendinopathies, we could argue that, for instance, rotator cuff tendinopathy should be considered a clinical entity different from lateral epicondylalgia. As for the latter diagnosis, only one of the studies included in that meta-analysis directly compared the effects of corticosteroid injection *versus* platelet-rich plasma. Of note, our meta-analysis included four trials comparing the effects of corticosteroid versus autologous blood injection. Again, these two treatments (*i.e*., platelet-rich plasma and autologous blood injection) are not equivalent and may have different clinical effects. In particular, considerable controversy remains about the effectiveness of local platelet-rich plasma injection, due to differences in preparation, method of platelet activation, and experimental design.[25] Such variability was not an issue in our meta-analysis, as all the included

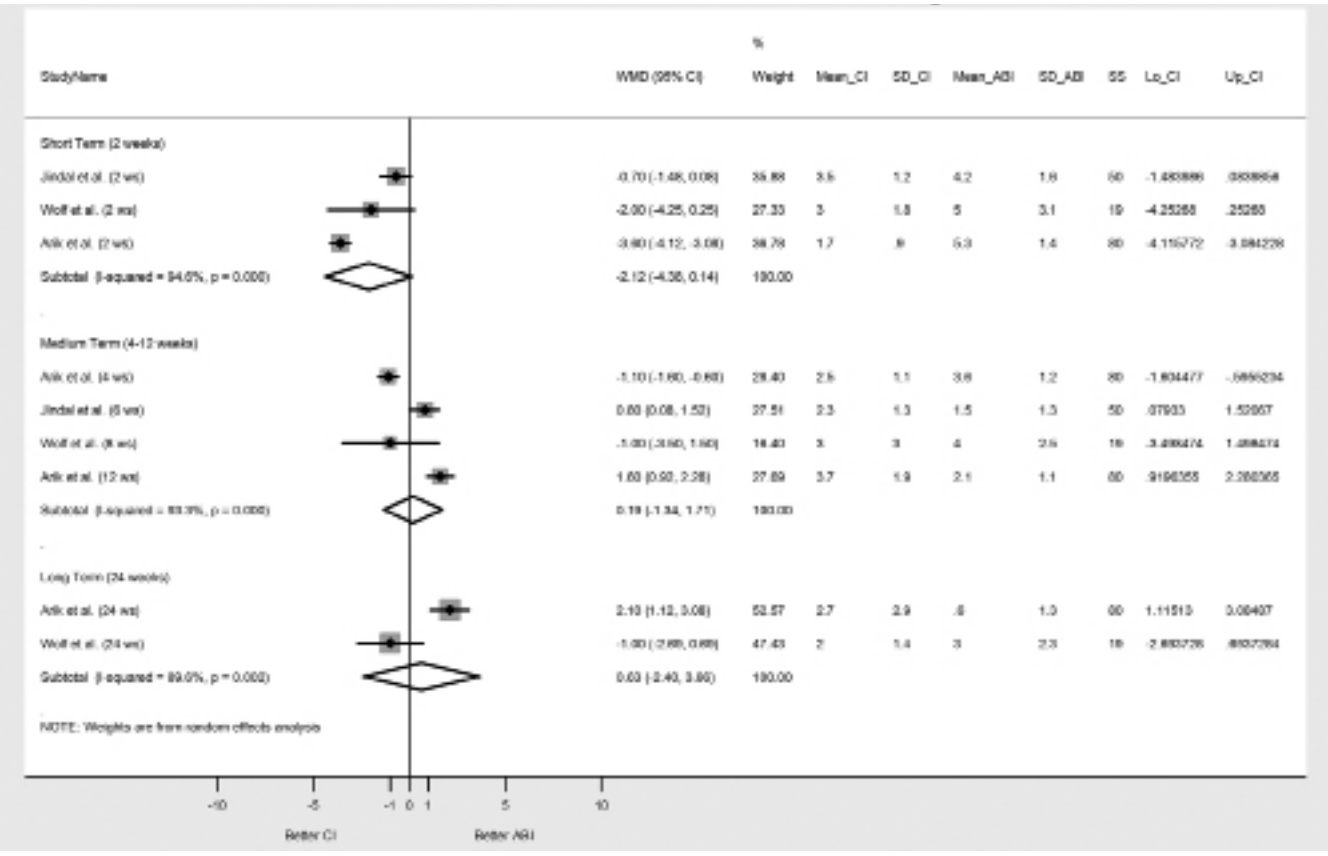

Figure 4.—Sensitivity analysis.

studies used venous blood injection in a homogenous groups of patients and comparable protocols.

A recent study by Qian *et al*.[7] compared ABPs with CSI, where ABPs meant both ABI and PRP injections. Arguably, such grouping could influence the results, as these treatments can have different mechanisms of action, thus different effects on pain in lateral epicondylitis. Of note, the study by Qian *et al*. has allowed different methods of the evaluation of treatment effects to be considered, including the VAS and the Patient-rated Forearm Evaluation Questionnaire or other pain scores. As for pain evaluation, it is possible that the method of measurement profoundly influences the results and different methods of measurement do not give corresponding results. Hence, it is not advisable to extrapolate data from results obtained through different measures. To overcome this problem and guarantee the validity of pain measurement, only the studies using and reporting the VAS score were included in our meta-analysis and VAS scores were used to estimate summary effect. Similarly, Ozturan *et al*.[17] was excluded, as they used Thomsen provocative testing, upper extremity functional scores and maximal grip strength for outcome evaluation. As for their pain evaluation, spontaneous pain score, as in VAS, could not be extrapolated from the provocative testing for purpose of our meta-analysis. Second, the work by Dojode *et al*.[13] was excluded due to inconsistencies in reporting the VAS score. Third, in the study conducted by Singh *et al*.[16] the primary outcome was Patient-rated Tennis Elbow Evaluation (PRTEE), which consists of 15 items. In that study, the authors themselves underline the differences between the PRTEE and VAS scoring systems; the same differences are the reason why their work could not be included in the present meta-analysis.

Since VAS is a meaningful and widely accepted scale to assess pain, raw mean difference was adequate to calculate effect size. This statistical approach represents

an advantage in reporting results, allowing to avoid log data transformation and interpret results immediately. Considering characteristics of the included studies and reported differences in study population, design and outcome measures, a fixed-effect model was not appropriate to define a summary effect.[26] For this reason, a random-effects model was used in our analysis.

Arirachakaran *et al*.[8] have recently performed a network meta-analysis, *i.e*. multiple treatment comparison meta-analysis of randomized controlled trials, comparing clinical outcomes between the PRP, ABI, and CSI. That methodology combines direct evidence obtained within randomized clinical trials and indirect evidence obtained across trials through a common comparator. Notwithstanding its attractiveness, such approach has not yet been validated and implemented in clinical decision making, and it should be based on high number of carefully selected and assessed clinical randomized trials. In this respect, it is worth noting that, among ten studies included in the network meta-analysis by Arirachakaran *et al*., only three have compared directly ABI and CSI. Importantly, we argue that the results of PRP injections should not be included in a meta-analysis (and even more importantly, in a network meta-analysis) until the procedure becomes standardized from the methodological and technical point of view, as both the preparation and intratendinous injection technique of PRP appear to be of great clinical significance.[25]

Interestingly, Dong *et al*.[9] have attempted an evaluation of the effects of different treatments in lateral epicondylitis at 6 months. Based on their network meta-analysis, the authors conclude that hyaluronate injection and prolotherapy are the most effective treatments. Other commonly used injection therapies, including PRP and ABI can be considered as treatment candidates, while corticosteroid injection is not recommended. The recommendations of the authors regarding the use of hyaluronate, however, are based on a single study and should be supported by more clinical data. Moreover, other important limitations of that analysis should be noted, as the differences in pain scoring systems, treatment schedules and dosages, and follow-up period have been ignored. Even though the conclusions reached by Dong *et al.* and our conclusions partially overlap (ABI may be a better choice than CI in the long term), in our analysis more stringent inclusion criteria for trial selection have been applied and those limitations have been completely resolved.

Limitations of the study

A major limitation of the present meta-analysis remains the small number of included studies; however, this is due to the scarcity of high quality studies that compare effects of CI and ABI. Another limitation consists in the fact that the studies are often at high or unclear risk of bias, assessed using Cochrane tool. For these reasons, further well-designed studies are mandatory to compare these two treatment options. Notwithstanding these limitations, the available data, cumulatively and quantitatively evaluated in this meta-analysis, point to the positive effects of CI in the short-term and ABI in the long-term pain relief. These findings seem to be justified also from the etiological point of view, since the corticosteroids could provide an immediate control of inflammatory response able to modify pain perception, while the autologous blood could stimulate tendon healing process able to obtain stable results in the long term. However, current data are not sufficient to confirm this hypothesis statistically.

Based on the above discussion, the present meta-analysis could have important implications on research and current clinical practice. Unquestionably, the results underline the lack of studies comparing CI and ABI, as the available evidence is not sufficient to conclude in favor of one or the other. Although some studies have encouraged the use of ABI in the long-term control of pain, statistics do not support this recommendation. In this connection, it is important to emphasize that clinical trials mostly applied only a single injection protocol and a short follow-up period. Hence, to assess the promising long term effects of ABI on pain control, studies with an adequate follow-up are mandatory. Moreover, studies with complex treatment protocol including multiple injections of CI and ABI may be necessary in order to develop new treatment strategy that could guarantee the best pain control and clinical management of lateral epicondylitis. A better knowledge of possible treatment outcomes should determine a more conscious application of different therapeutic injections in course of the disorder. If future findings are able to confirm the short-term

effectiveness of CI and the hypothesized advantage of ABI in long-term follow-up, a multiple injection protocol of treatment could be proposed.

Conclusions

In conclusion, the present meta-analysis compared CI and ABI treatment for pain control in lateral epicondylitis. Only few published studies met the inclusion criteria. In the included studies, a high risk of bias in some aspects and a high degree of heterogeneity in results have been reported. Even though the present data are not statistically significant, CI tends to reduce VAS score more than ABI in short-term follow-up. No differences have been recorded between two treatment options in medium and long term and, importantly, no evidence is available to support the use of ABI in long-term pain management. Therefore, further well-designed studies are necessary to establish the effectiveness of CI and ABI in the management of pain in lateral epicondylitis.

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