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The effect of sclerotherapy and prolotherapy on chronic painful Achilles tendinopathy – a systematic review including meta-analysis

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Abstract

Chronic painful AT is a common disorder among athletes. Sclerotherapy (ST) and prolotherapy (AT) are two promising options among the numerous other conservative therapies. Since their efficacy and potential adverse effects (AE) are still unclear, we systematically searched, analysed, and synthesised the available literature on ST and PT for treatingAT. Electronic databases, GoogleScholar and articles' reference lists were searched according to PRISMA guidelines.

Eligibility criteria were set up according to the PICOS-scheme including human and animal studies. Three authors independently reviewed the results and evaluated methodological quality (Coleman Methodology Score and Cochrane Risk of Bias Assessment). The initial search yielded 1104 entries. After screening, 18 articles were available for qualitative synthesis, six of which were subjected to meta-analysis. The mean Coleman Score of the thirteen human studies was 50. Four RCTs were ranked as having a low risk of selection bias. Three of those reported a statistically significant drop in the VAS score, one a significant increase in the VISA-A Score. 12 of 13 human studies reported positive results in achieving pain relief and patient satisfaction, whereas only one study's finding differed. Meta-analysis revealed an unambiguous result in favour of the intervention (weighted mean difference D=-4.67cm, 95% CI -5.56 to –3.76 cm ($p<0.001$)). Only one serious AE and two minor AEs were reported in the entire literature. This SR suggests that ST and PT may be effective treatment options for AT and that they can be considered safe. Long-term studies and RCTs, are still needed to support their recommendation.

Introduction

Tendinopathy is defined as the triad of pain, swelling, and impaired performance (Maffulli, 1998). Chronic painful Achilles tendinopathy (AT) is the most common Achilles tendon disorder in athletic and sedentary individuals. Although there is ample research on various therapeutic modalities, there is no consensus on the most effective and least time-consuming therapy. Among the wide range of treatment options, heavy tendon loading has delivered the most convincing evidence. Additionally, shockwave therapy, nitrate oxide, cryotherapy, physiotherapy or injections may be of value (Andres and Murrell, 2008; Kearney et al., 2015; Sussmilch-Leitch et al., 2012; Maffulli et al., 2015). After discovering that the pain in chronic AT is rather due to the stimulation of free nerve endings accompanying neovessels alongside the tendon than to inflammation, sclerosing injections have been implemented to destroy the neovessels (Alfredson et al., 1999; Alfredson et al., 2003; Andersson et al., 2007). Sclerotherapy was originally approved for treating varicose veins or telangiectasia. Substances with sclerosing effect are polidocanol, a surface anaesthetic, sodium tetradecyl sulphate, and sodium morrhuate. All of those sclerosing substance cause endothelial damage, especially to the venous intimae layer. Detergent sclerosants such as polidocanol additionally act by reducing cell-surface tension and via several cell-matrix-interactions, eg, surface lipids and the denaturation of endothelial cell proteins (Duffy, 2010). Ohberg et al. (2002) first published on its use to treat chronic painful Achilles tendinopathy, their objective being to sclerose the neovessels and destroy the sensory nerves along them, leading to pain relief. They conducted a small non-controlled study that demonstrated pain reduction in eight of ten patients. In contrast to Ohberg's findings, other working groups maintain that neovessels may not be the source of pain by failing to observe any direct correlation between pain and neovessels (Tol et al.,2012; de Jonge et al., 2013).

Prolotherapy was first applied by the American surgeon George Hackett in the 1950s (Hackett, 1958). Injecting proliferants causes local damage and inflammation. The operating mechanism of often-used hypertonic dextrose solutions is claimed to cause damage by osmotic shock (dehydrating cells). A healing process is induced, while neovascularisation is (or neovessels are) presumably also destroyed (Banks, 1991; Yelland et al., 2011). Lyftogt and Maxwell obtained promising results in pilot studies treating Achilles tendinopathy for the first time: they injected hypertonic dextrose solution acting via osmotic shock (Lyftogt, 2005; Maxwell et al., 2007). As there have been various encouraging reports on the positive effect of those injecting sclerosing substances ever since, this systematic review was designed to systematically analyse the available literature on the effects and side effects of sclerotherapy and prolotherapy in patients with chronic Achilles tendinopathy. Since there is no recommendation to date regarding their specific clinical use, it was this review's aim to provide an overview of the most recent knowledge concerning the

specific benefits and harms of both therapies, the most effective way of injecting the substances, and the local effects observed after injecting the substances into the Achilles region. Given that the evidence from human studies is so limited, our aim was to comprehensively search and evaluate all the studies addressing sclerotherapy and prolotherapy in AT regardless of whether the subjects were human or animal.

Material and Methods

The systematic review was conducted in accordance with PRISMA guidelines (Moher et al., 2015).

Study protocol

The study protocol was established and registered on PROSPERO (International Prospective Register of Ongoing Systematic Reviews) on 11/27/15. The PROSPERO registration number is CRD42015029132 . Registration can be accessed via http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029132

Eligibility Criteria

The studies' eligibility criteria were set up according to the PICOS-scheme (population, intervention, control, outcome and study design). Athletes and non-athletes of every age and gender with chronic painful Achilles tendinopathy as well as animals were included, whereas patients suffering from systemic conditions (e.g., rheumatic diseases) were excluded. Further inclusion criteria were interventions describing injection treatments involving sclerosing agents (e.g., polidocanol) or prolotherapy (e.g., hyperosmolar glucose solution) targeting the Achilles region. Interventions involving the injection of substances with other effects or mechanisms on the tendon (e.g., corticosteroids, PRP) did not meet our inlusion criteria. Control treatments could be placebo, surgery, other injection therapies, conservative treatments or other injection therapies/different dosages of the same substance.

Search

We conducted an electronic search of the following databases from the beginning of records to January 2017: Medline (Medline, Medline-In-Process, Medline Daily, Epub Ahead of Print), BIOSIS Previews and BIOSIS Previews Archive via Ovid, SPORTDiscus, CINAHL via EBSCOHost, CENTRAL (Cochrane Central Register of Controlled Trials)refined to Trials via Cochrane Library, Embase and Web of Science. The very last database searches were conducted on 19/01/2017, respectively Embase on 06/02/17. A GoogleScholar search targeting the term "achilles tendinopathy sclerotherapy prolotherapy" was also conducted. The reference lists of potentially suitable articles were also screened for further yields. Our search strategy was decided upon by OM after consulting with AH, JT, and SB. The entire strategy of the MEDLINE Ovid search is stated in the appendix. The other strategies can be provided on request.

Study Selection

Three authors independently reviewed the studies (OM, AH, EJK).Titles and abstracts were screened once duplicates had been removed. When they met our inclusion criteria, the entire text was assessed for eligibility. Disagreements among the reviewers were discussed and resolved by consensus. If the eligibility determination was unclear after screening the title and abstract, we read the entire article to clarify eligibility.

Data Collection

The level of pain or dysfunction measured by the Visual Analogue Scale (VAS) or the Victorian Institute of Sport Assessment-Achilles score (VISA-A) was defined as the primary outcome measure. The VAS is a single-item instrument measuring pain on a 100mm line (0 the best, 100 the worst). The VISA-A score is a multi-item questionnaire on pain and dysfunction of the Achilles tendon and a valid instrument for assessing the clinical severity of Achilles tendinopathy (Robinson et al., 2001). Secondary outcome measures were the results of further pain rating scales and subjective patient evaluation measures as well as return to activity/sport. Furthermore, possible adverse effects including tendon ruptures, infections or neural lesions as well as histological or ultrasonographical tendon remodelling were assessed. Initially, all study types, both human and animal studies were included to detect any adverse effects. There were no restrictions in language, setting, or date of publication. Individual study data was extracted using the full text by OM and confirmed by AH. We extracted title, author, study type, year, sample size, type of intervention, mean number of interventions, mean pre- and post-intervention outcome values (e.g. VAS or VISA-A scores) and their corresponding variability measures and adverse events. Two investigators (Hakan Alfredson and Michael Ryan) were contacted for additional information. Ryan clarified that the subjects included in the congress abstract (Ryan et al 2009) were identical to the full text article (Ryan et al 2010). We did not receive an answer from HA.

Quality and Risk of Bias

The studies' quality was independently evaluated by three reviewers (OM, AH and EJK) referring to the Coleman Methodology Score (Coleman et al., 2000). Disagreements were discussed and resolved by consensus. Since there is no strong agreement on how to interpret the Coleman Score, we defined a Coleman score of 0-25 as poor, 26-50 as fair, 51-75 as good and 76-100 as excellent quality, which we believe is a reasonable classification. The Coleman Methodology Score was determined for all included human studies to obtain a comparable overview thereof. We also applied the Cochrane Risk of Bias Assessment Tool to analyse the RCTs as recommended by the Cochrane Collaboration (Higgins et al., 2011). We did not refer to the Cochrane Risk of Bias Assessment for the non-RCTs, since it is not readily applicable to non-RCTs.

Statistical Analysis

The authors found that six studies that reported on effect sizes in terms of pain (expressed as VAS) were combinable. All VAS scores in the studies were assessed in the same way. The VAS score reflects pain during tendon-loading activity on a 100mm scale. Two of those studies compared the same intervention in conjunction with different doses or at different anatomical sites. We treated each intervention arm in those two studies therefore as an individual pre-post study. Accordingly, eight studies were analysed. Because all studies reported effect sizes via the same metric (i.e., VAS), we calculated the raw mean difference (D) and corresponding 95% CI of the each study. A random-effect model with an inversed-variance method to calculate study weights was chosen a priori to pool the individual studies' effect sizes. The heterogeneity statistic Q and its corresponding (df) and p- value as well as Higgins' I2 as a measure of heterogeneity were calculated. A subgroup analysis was performed to try to explain any apparent heterogeneity. Several calculations were conducted using Comprehensive Meta-Analysis - 2 software (CMA-2, Biostat Inc., Englewood, NJ 07631 USA).

Results

Our database search delivered 1103 records. One additional entry was identified by screening articles' references, resulting in a total of 1104 entries. After removing 236 duplicates, 868 articles were screened. We excluded 844 records

and assessed the remaining 24 full-text articles for eligibility. Six of those 24 articles were excluded. Three of them reported a different therapy (Choy et al., 2005; Shah et al., 2013; Solchaga et al., 2014) , one case report was excluded due to diverse injections and substances (including corticosteroids) (Hamilton et al., 2008) and two provided no study data (Alfredson, 2007; Alfredson, 2011). The main author was contacted by E-Mail for more information but did not reply. Hence 18 articles were available for qualitative synthesis and six of those were included in the meta-analysis. Figure 1 illustrates the entire selection process in a flow chart

. All studies were analysed as full texts. To make the information more easily accessible, we categorised the studies in three units consisting of sclerotherapy, prolotherapy, and animal studies. We identified nine studies assessing sclerosing agents (Öhberg et al., 2002; Öhberg and Alfredson, 2003; Alfredson and Öhberg, 2005; Alfredson et al., 2007; Lind et al., 2006; Clementson et al., 2008; Willberg et al., 2008; van Sterkenburg et al., 2010; Humphries, 2013), five dealing with prolotherapy (Lyftogt, 2005; Lyftogt, 2007; Maxwell et al., 2007; Ryan et al., 2010; Yelland et al., 2011) and four investigating one of the two interventions in animals (Bumpus et al., 1964; Maynard et al., 1985; Boesen et al., 2007; Martins et al., 2012). Regarding the study type we obtained four randomised controlled trials comparing the injection intervention to placebo (Alfredson and Öhberg, 2005), alternative dosages (Wilberg et al., 2008), surgery (Alfredson et al., 2007) or eccentric loading (Yelland et al., 2011), seven non-controlled prospective studies (Öhberg et al., 2002; Öhberg and Alfredson, 2003; Lyftogt, 2005; Lind et al., 2006; Lyftogt, 2007; Maxwell et al., 2007; Ryan et al. 2010), two retrospective studies (Clementson et al., 2008; van Sterkenburg et al., 2010) and one case report (Humphries, 2013). A summary of findings highlights the main characteristics of the included studies (Tables 1 and 2).

Characteristics

Overall, there were 610 human tendons included in the studies receiving different injections. 235 tendons were targeted via sclerosing interventions, whereas 375 tendons were included in the prolotherapy studies. Nine of 13 human studies focussed on mid-portion tendinopathy, one on insertional tendinopathy, and three on both entities. Among the studies reporting gender, there were 321 men and 228 women corresponding to 58.5% men in the study population. As the mean age was 49.5 years, the study population can be considered middle-aged. Mean follow-up terms ranged from three months (Alfredson and Öhberg, 2005) to 3.9 years (van Sterkenburg et al., 2010); mean duration of symptoms ranged from 14 to 33 months. The mean number of injections (when reported) averaged 2.6 in the sclerotherapy versus 4.2 injections in the prolotherapy studies. All except two studies made use of Doppler-sonography to confirm the diagnosis of Achilles tendinopathy (Lyftogt, 2005; Lyftogt, 2007). All the studies addressing sclerotherapy used polidocanol as the sclerosing agent. The concentration (when reported) was 5mg/ml or 10mg/ml. One study used both concentrations to compare their effectiveness (Willberg et al., 2008). In another study the control group was treated with a placebo solution containing adrenaline 5µg/ml + lidocaine hydrochlorid 5mg/ml (Alfredson and Öhberg, 2005). The substances used for prolotherapy were mainly 20% or 25% dextrose solution.

In the animal studies, 41 rabbits, 4 horses and 60 rats were the objects of investigation. Several agents were deployed in those studies. Bumpus et al. 1964 investigated eight different solutions (10% quinine and urea hydrochloride; 10% quinine and urea hydrochloride, 1% silica, 1% procaine; 7% quinine and urea hydrochloride, tannic glucoside; 5% quinine and urea hydrochloride; Sylnasol one part in six parts diluent, sylnasol two parts in six parts diluent; zinc sulfate-phenol solution; 1% asbestos and 10% quinine and urea hydrochloride; all in diluted in a long-lasting quinine hydrobromide local anaesthetic) Maynard injected 5% sodium morrhuate solution, Boesen and colleagues (2007) examined the effect of polidocanol 10mg/ml and Martins et al. 2011 administered a 12.5% dextrose solution, comparing it to the effect of saline solution, corticosteroids, or no injection.

Quality Assessment

The mean Coleman Score for the 13 studies was 50 points (ranging from 27 to 73). Seven studies were rated as having fair quality (26-50 points) and six studies were considered to be of good quality (51-75 points). No study was classified as having poor (0-25) or excellent (76-100) quality. A detailed overview of the Coleman Methodology Score is outlined in Table 3.

Our risk of bias analysis revealed that the four RCTs revealed a low risk of selection bias. Öhberg 2007 and Yelland et al. 2011 were classified as having a high risk of bias concerning the blinding of participants and investigators. However, blinding appeared to be infeasible in the two latter studies due to the two obviously different interventions (surgery vs. injection, or eccentric loading vs. injection). It was not addressed in the studies whether the outcome assessor was blinded for the treatment arm. We therefore classified the item "blinding of outcome assessment" in the Cochrane risk of bias assessment with "unclear risk". As with the Coleman Score, the risk of bias assessment is summarised in Figure 2.

Individual Results

RCTs on Sclerotherapy and Prolotherapy

Our search yielded only four randomised controlled trials (RCT) (Alfredson and Öhberg, 2005; Alfredson et al., 2007; Willberg et al., 2008; Yelland et al., 2011). Of those four trials, only one was double-blinded and randomised controlled where the intervention is compared to a placebo intervention (Alfredson and Öhberg, 2005). Another double-blinded study compared two different dosages of polidocanol (5 mg/ml vs.10mg/ml) (Willberg et al., 2008)] without a placebo group. In the other two RCT studies, the investigator and patients could not be blinded due to the different nature of the interventions (injection vs. surgery; injection vs. eccentric training) (Alfredson et al, 2007; Yelland et al., 2011).

All RCTs reported positive results from the injecting intervention, superior to other established treatments in two cases (surgery and eccentric training, Alfredson et al, 2007; Yelland et al., 2011).

Alfredson and colleagues (2005) compared polidocanol to a placebo solution (adrenaline + lidocaine) in a RCT and showed a drop in the VAS score of approximately 60 points (77.1 to 16.5, $p < 0.05$) in the intervention group, whereas there was no significant difference in VAS in the placebo group ($p < 0.878$). After crossing-over to polidocanol, the mean VAS dropped by almost 50 points in the initial control group (64 to 16, $p < 0.005$). The difference in VAS, before and after treatment, in the group that received sclerosing injections (polidocanol), was significantly larger ($p < 0.005$) than the difference in the VAS, before and after treatment, in the group that received non-sclerosing injections (lidocaine + adrenaline).In a subsequent study, the same research group compared sclerosing injections to Achilles tendon surgery (Alfredson et al., 2007) and reported positive results similar to their first study's in the sclerosing intervention group, namely a significant decrease in VAS in six out of nine patients (VAS change from 76 to 24 in the satisfied patients, $p < 0.005$, the mean VAS in the unsatisfied patients was 81, no p-value stated). Eight out of ten patients in the surgery group were also satisfied at follow-up (VAS from 75 to 21 in the satisfied patients, $p < 0.05$). Therefore sclerotherapy and surgery seemed to be equally effective in alleviating chronic AT pain.

Willberg et al. (2008) compared two different doses of polidocanol (5mg/ml vs. 10mg/ml) in their RCT study: both dosages attained good results yielding significant improvements in VAS scores in both groups (Group 5mg/ml: 66 to 25; Group 10mg/ml: 66 to 24; $p < 0.05$). However, they observed no statistically significant differences between the two groups. Because of the lack of a control or placebo group, no further conclusions are possible on their intervention's overall efficacy . Nevertheless the study indicates that there might be no clear dose-response relationship.

We identified only one RCT investigating prolotherapy: Yelland et al (2011) compared the effect of prolotherapy to the effect of heavy load eccentric training and as well as a combined therapy scheme. They documented faster improvement in the prolotherapy therapy and the combined scheme group than in the eccentric group. Nevertheless, they detected no statistically significant differences in VISA-A scores in long-term follow-up (12 months). Their mean gain in VISA-A score after 12 months was 23.7 points for eccentric loading, 27.5 points for prolotherapy and 41.1 for the combined therapy.

Results of non-controlled sclerosing studies

All other included 13 studies were non-controlled studies investigating solely the effect of sclerotherapy or prolotherapy in an one-arm design. They thus provide little solid evidence. Even so, nearly all of these 13 studies reported favourable outcomes. Most of those referring to sclerotherapy used the VAS scale to measure outcome. Öhberg's pilot study from 2002 assessing the injection of polidocanol to the ventral site of the tendon revealed a reduction in the mean VAS value from 73.6 to 20.9 resulting in 8/10 satisfied patients at follow-up. The same researchers in 2003 confirmed their findings treating insertional Achilles tendinopathy as well: in that trial, mean VAS values dropped from 83.2 to 28.5 with 8/11 satisfied patients.

Lind et al. (2006) also delivered good long-term outcomes (mean 23 months) with the VAS dropping from 75.7 to 7.4.

Clementson et al. (2008) conducted a retrospective study yielding 19/25 good and excellent results 6 to 12 months after sclerosing neovascularisation. There was only one study whose results were not positive: Van Sterkenburg's (2010) retrospective study reported no improvement in 56% of their patients at the 6-week follow-up. At the time of long-term follow-up (mean 3.9 years), >50% had undergone additional therapies.

Results of non-controlled prolotherapy studies

Regarding prolotherapy, Lyfogt (2005) reported 14/16 satisfied patients after injecting 20% dextrose solution in a pilot study, with 13 of the 16 tendinopathic tendons in the 14 satisfied patients being completely pain-free (VAS 0). In his second study he injected different local dextrose- -anaesthetic solutions in over 169 tendons over a four-year period achieving a mean VAS at follow-up of 4 points starting with an initial VAS of 64 (Lyftogt, 2007). Maxwell et al. (2007) used prolotherapy and demonstrated a mean change in activity VAS score of 83.2% in patients with mid-portion and 64.7% in those with insertional tendinopathy. In a 12-month telephone follow-up, 20 out of 32 patients still had no symptoms. Later, Ryan et al. (2010) conducted a similar study, documenting a drop in the VAS score from 70.7 pre-intervention to 36.7 post-intervention and 16.7 at follow-up (28 months) for the mid-portion group. VAS scores of patients suffering from insertional tendinopathy fell from 69.6 to 39.8 and 17.7 at follow-up, respectively.

Adverse effects

Considering that three studies made no clear statements on investigating adverse events (Lyftogt, 2005; Ryan et al., 2010; van Sterkenburg et al., 2010) there were only one serious and two minor adverse events reported other than discomfort during the injection. Clementson et al. described one *nervus suralis* lesion and Maxwell reported a partial tear of the Achilles tendon that was only detected after the therapy although it had existed before the first injection.

The sole serious adverse event was reported from Humphries (2013) in a case report, where a 51-year-old woman suffered from embolia cutis medicamentosa after receiving one injection of a 1% polidocanol solution.

Animal study results

The animal studies delivered the following findings: Bumpus et al. (1964) showed that of the eight tested solutions, the one containing 3% quinine and urea hydrochloride was best suited to provoke a sclerosing reaction. Maynard and colleagues' (1985) main finding was that injecting a 5% sodium morrhuate agent enlarges the tendon's diameter and increases both the number of cells and their variety (e.g., fibroblasts, neutrophils, lymphocytes,
and plasma cells). Furthermore, Boesen et al. (2007) reported that after applying polidocanol to the peritendineum of horses' lower limb flexor tendons, colour Doppler ultrasound revealed neither blood flow nor visible vessels. The horses continued to prosper without revealing any signs of suffering during the post-injection period until veterinary euthanasia. The most important finding from the controlled trial by Martins et al. (2012) was that administering a dextrose solution did not weaken tendons or alter their characteristics.

Meta-Analysis

Our meta-analysis demonstrated an overall weighted mean pro-intervention difference of D = - 4.67 cm (95% CI -5.56 to – 3.76 cm ($p<0.001$)). The Q test revealed significant heterogeneity (Q = 54.7, (df)=7, $p<0.0001$). The amount of heterogeneity was high (I2 = 87%). A subgroup analysis based on the original study design (RCT versus non-RCT) was conducted, grouping the Lind (2006) and the Öhberg (2002,2003,2005) studies and the Ryan (2010) and Willberg (2008) studies. The overall weighted mean difference (D) in the RCT-derived studies was – 3.60 cm (95%CI: -4.00 to -3.20 cm), while D was – 5.81 cm (95%CI: -6.28 to -5.34 cm) in the other subgroup. The between studies-heterogeneity among groups decreased to I2 = 0% and I2 = 27%, respectively.

Discussion

The aim of this systematic review with meta-analysis was to comprehensively search and evaluate all studies dealing with sclerotherapy or prolotherapy for the therapy of chronic painful Achilles tendinopathy.

All four RCTs delivered generally positive results achieving pain relief and patient satisfaction with the treatment. Alfredson et al. compared polidocanol injections to placebo injections in a randomised controlled trial and showed statistically significant superior results in the intervention group compared to the placebo group. Moreover, eight out of the nine non-randomised studies investigating sclerotherapy or prolotherapy in humans confirmed these favourable outcomes and none of the other RCTs contradicted it. Our methodological-quality analysis of the included studies revealed fair quality with a mean Coleman Score of 50 points highlighting the need for additional high quality studies in this field. Most of the studies were not randomised or blinded, the main factors that compromised their quality considerably. No study was ranked as having poor or excellent quality, respectively. Despite the high number of non-randomised trials, the mean Coleman score of 50 points, nevertheless, demonstrates sound methodological quality that enables us to draw conclusions regarding the effect of sclerotherapy and prolotherapy..Meta-analysis was possible on the effect of sclerosing agents on VAS scale in AT patients. Although analysed as pre-post studies, the overall weighted mean suggests that sclerotherapy and prolotherapy may be effective options for treating chronic painful Achilles tendinopathy, reducing pain on average by about four VAS units on a 0-10 scale. This is obviously a clinically highly relevant effect size. In contrast to our findings, there are two recent systematic reviews addressing multiple injection therapies for Achilles tendinopathy. The two systematic reviews concluded that the use of polidocanol or prolotherapy cannot be strongly recommend but that both substances are well tolerated. Both reported on sclerotherapy and on prolotherapy (Coombes et al., 2010; Kearney et al., 2015). Coombes (2010) assessed the use of corticosteroid injections, as well as polidocanol, prolotherapy and other substances in randomised trials. Kearney's results resemble

those of Coombes: they could not recommend the use of sclerotherapy or prolotherapy in clinical practice, calling for further research (Kearney et al., 2015). Since we rated the quality of the studies included in our meta-analysis as good (mean 56.5 points) and its result unambiguously favours the intervention, we believe that sclerosing neovascularisation can be recommended. Bearing in mind that several of the available studies were conducted by the same research groups, which might be a source of bias, we are in line with Coombes et al. and Kearney et al., highlighting the need for more high-quality studies of randomised controlled design to defend the recommendation of these therapies.

Animal studies

Three of the four included animal studies investigated the effect of sclerotherapy and one of prolotherapy. The significance of the work by Bumpus and Maynard is questionable since their trials date back to 1964 and 1985, respectively, and the substances they applied are not longer in clinical use. However, a statement regarding the principal mechanism can be made, namely that as hypothesised, the injections initiate a healing process (increased number of fibroblasts, neutrophils, lymphocytes) in the tendon. Boesen's study from 2007 enables no conclusion regarding a local effect on the tendon except that no blood flow on colour Doppler ultrasound was visible after the injection. Their sample size (four horses) was very small, and the impression that the horses did not suffer after injection is a subjective rather than objective parameter. The controlled study by Martins et al. in 2011 demonstrated good methodology and tested dextrose solution injections into rats' Achilles tendon. Beside their main assertion of causing no harm to the tendon, they demonstrated a higher incidence of immature collagen in the prolotherapy group, supporting the finding of Maynard et al. that a healing process starts after the injection. Nevertheless, it is difficult to draw a clear conclusion at that point and more research with larger sample sizes, longer follow-up periods and precise outcome measures are required.

Adverse effects

The present review also revealed that prolotherapy and sclerotherapy can be considered safe, as only three adverse events following all interventions were reported. Although there is no clear cut-off value to define an intervention as safe, we are of the opinion that multiple injections per tendon in more than 600 tendons compared to three adverse events can be considered safe. Humphries reported the occurrence of embolia cutis medicamentosa in one patient after injecting 2ml of 1% polidocanol. The *nervus suralis* lesion is probably attributable to an injection on the lateral side in the proximal third of the Achilles tendon, where the nerve is very close to the lateral tendon border. The injection should be made in the upper parts of the tendon from the medial side to minimise this risk (Öhberg and Alfredson, 2002; Clementson et al., 2008). The second reported minor adverse event, a partial Achilles-tendon tear , is unlikely to have been caused by the injection itself, even though it became apparent thereafter. Therefore, it is questionable whether the partial tear should be classified as an adverse event (Maxwell et al., 2007). Beside these three adverse events, we should draw attention to other reports on adverse events reported in the investigations we had to exclude from our systematic review: another case of embolia cutis medicamentosa was reported after sclerosing varicosis (Geukens et al., 1999). There are also several reports of triceps-surae lesions after sclerosing the external saphenous vein (Natali, 1987). It is assumed that accidental injections in the arterial system may cause this damage, but this remains unclearan. Willberg (2008) reported (unpublished) data that injecting high volumes of polidocanol might cause thrombosis in the lower limb. As none of the studies in our review was a double-blind randomised-controlled trial entailing a low risk of missing adverse effects, further research is necessary. No side effect or harm was reported in the included animal studies addressing the local effect of the sclerosing substances.

Limitations

Our systematic review has some methodological limitations. Our electronic search strategy cannot claim to be complete,, which might bias our results due to incomplete retrieval. We included all study types to obtain a clearer perspective of the entire topic and to be able to give practical recommendations regarding the clinical use of these substances. Thus, the methodological quality of the included studies is lower than if we had only included randomised controlled trials or quasi randomised controlled trials from the beginning. Only a few studies qualified for our meta-analysis. Furthermore, some failed to provide valuable data. There was often no information on the post-interventional rehabilitation regimen or on compliance, nor was there any detailed information on how the treatment is applied most effectively. There is thus a potential bias, since one cannot definitively attribute the positive outcome solely to sclerotherapy and/or prolotherapy. Nevertheless most authors commented on side therapies and did not start eccentric exercises after the injections. Important questions need to be answered, i.e., whether polidocanol is superior to dextrose, whether the application of polidocanol is more effective as foam or in liquid form, or at which intervals the injections should be made. Concerning the latter: most of included studies report an interval of four weeks, but why not shorten this interval to cure the patient faster? As recovery-time is very important in high-level athletes, the intervals between the injections are often much shorter, despite the current lack of solid evidence from the literature. Shortening the interval between two interventions may also raise the risk of side effects, but this remains speculative as no study reported on that factor. Furthermore, the question as to how much of the sclerosing substance should be injected to achieve the best effect with the least side effects remains unanswered. The Willberg study (2010) might support the assumption that there is no clear dose-related response, however it is difficult to draw a conclusion based on that small study. There is no information in the literature we reviewed on local effects or histological changes in the tendon and surrounding soft tissue following injections. Lastly, we do not know which post-interventional rehabilitation program is ideal. Most of published studies describe full tendon loading after 14 days and light activities such as walking, and bicycling the day after injection. Faster rehabilitation programs are conceivable, but none have been reported on or investigated. Future research should additionally focus on combined treatments, such as needling the tendon, high-volume injections versus sclerosing alone, or substances tested against each other in randomised controlled trials (ideally with a double-blind design), as well as foamed polidocanol examined against not-foamed polidocanol to clarify the differences and benefits of these modalities. Animal studies could facilitate the analysis of substances' local effect (e.g., inflammation, vessel destruction, collagen proliferation). New animal models should be established to get to the bottom of the mechanism and effect. As suggested in the introduction, neovessels as the source of pain are actively discussed in the literature. As there is still no clear agreement on the origin of pain, the mechanism of action of sclerotherapy and prolotherapy must be questioned too. Future research should keep this fact in mind as well.

Perspectives

This systematic review with meta-analysis suggests that prolotherapy and sclerotherapy may be effective treatment options for chronic painful Achilles tendinopathy and that they can be considered safe. Due to the shortage of high quality, long-term data, additional randomised controlled trials are needed to enable strong recommendations and clarify the value of sclerotherapy or prolotherapy in the daily clinical routine as well as the long-term effect of these promising treatments.

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Tables and Figures

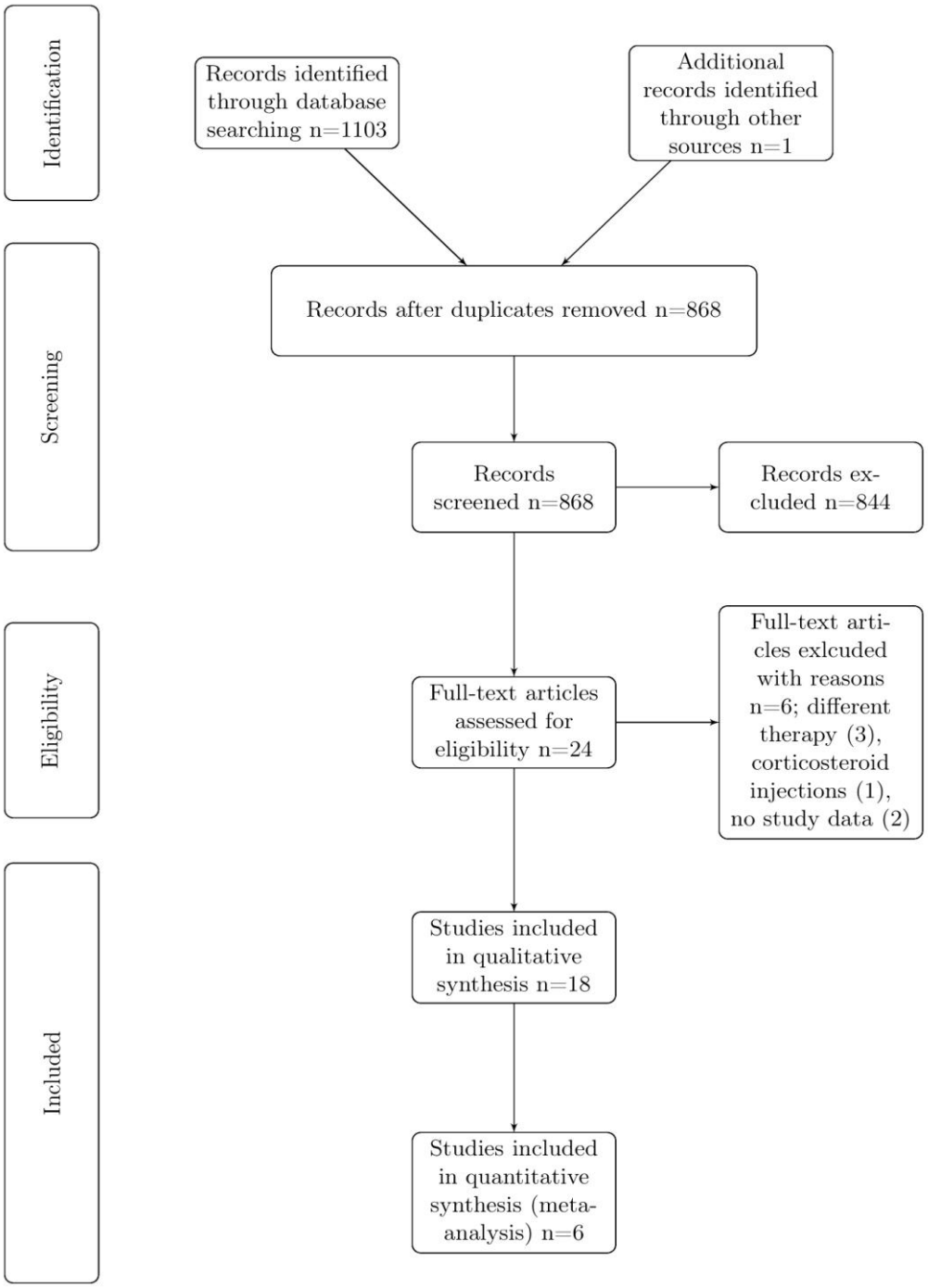

Figure 1: Flow Chart of the entire selection process according to PRISMA (Moher et al. 2015)

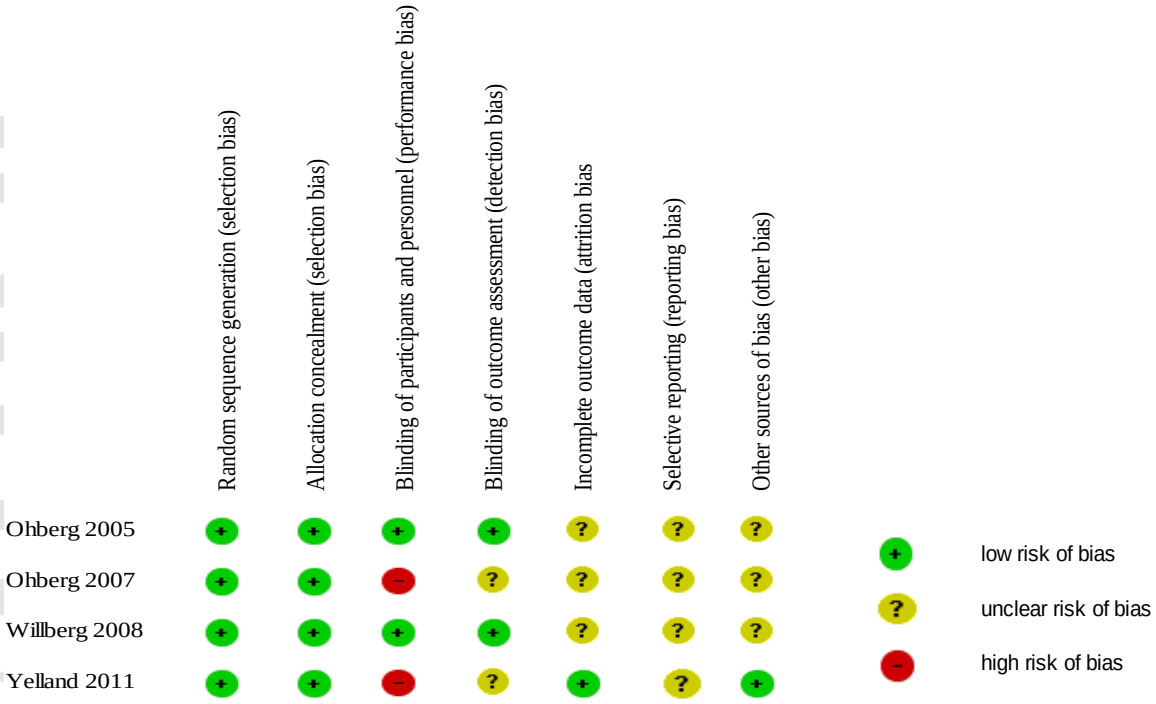

Figure 2: Summary of the Risk of Bias Assessment

Table 1: Demographic

Author	Year	Study Type	Patients		no of tendons	mean age	mean follow-up	mean duration of symptoms
			m	f		years		
Sclerotherapy								
Öhberg and Alfredson	2002	prospective	7	3		55	na	16.5 months
Öhberg and Alfredson	2003	prospective	9	2		44	8 months	29 months
Öhberg and Alfredson	2005	RCT	9	11		50.3	3 months	33 months
Lind	2006	prospective	23	19		53	23 months	33 months
Öhberg and Alfredson	2007	RCT	9	11		46	6 months	28 months
Clementson	2008	retrospective	14	11	26	49.6	6-12 months	na
Willberg	2008	RCT	35	17		49.6	14 months	26.8 months
van Sterkenburg	2010	retrospective	28	20	53	45	3.9 years	23 months
Humphries	2013	case report	0	1	1	51	na	18 months
Prolotherapy								
Lyftogt	2005	prospective	12	4	19	48	na	14 months
Lyftogt	2007	prospective	92	77		47.7	20 months	25 months
Maxwell	2007	prospective	25	11		52.6	12 months	28.6 months
Ryan	2010	prospective	58	41	108	54	28 months	21 months
Yelland	2011	RCT	43			46.6	12 months	17.1 months

49.5

Animal studies				
Author	Year		Animal	sample size
Bumpus	1964	animal	rabbit	32
Maynard	1985	animal	rabbit	9
Boesen	2007	animal	horse	4
Martins	2011	animal	Wistar rats	60

Table 2: Intervention

Author	Year	Study Type	Site of Tendinopathy	Substance	Control	mean VAS			mean no of injections	Adverse Events
						pre	post	FU		
Sclerotherapy										
Öhberg and Alfredson	2002	prospective	mid-portion	polidocanol 5mg/ml	na	73.6	20.9		2.6 ± 1.02	none
Öhberg and Alfredson	2003	prospective	insertion	polidocanol 5mg/ml	na	83.2	28.5		2.7 ± 1.48	none
Öhberg and Alfredson	2005	RCT	mid-portion	polidocanol 5mg/ml	adrenaline 5µg/ml+ lidocaine hcl 5mg/ml	77.1	16.5		2.7 ± 1.1	none
Lind	2006	prospective	mid-portion	polidocanol 5mg/ml	na	75.7	16.2	7.4	na	none
Öhberg and Alfredson	2007	RCT	mid-portion	polidocanol 5mg/ml	surgery				na	none
Clementson	2008	retrospective	mid-portion	polidocanol 10mg/ml	na				2.46 ± 1.25	lesion of nervus suralis (1)
Willberg	2008	RCT	mid-portion	polidocanol 5mg/ml	na	66.3	25.0		2.6	none
				polidocanol 10mg/ml	na	66.0	24.0		2.5	none
van Sterkenburg	2010	retrospective	mid-portion	polidocanol	na				2.67 ± 1.42	not reported
Humphries	2013	case report	not stated	1% polidocanol solution	na				1	Embolia cutis medicamentosa
Prolotherapy										
Lyftogt	2005	prospective	both	20% dextrose solution	na				na	not reported
Lyftogt	2007	prospective	mid-portion	different dextrose/LA	na	64		4	na	none
Maxwell	2007	prospective	mid-portion	25% dextrose solution	na	73.9	12.4		4.0	partial tear after injection (1)
			insertion			66.4	23.4			
Ryan	2010	prospective	mid-portion	25% dextrose solution	na	70.7	36.7	16.7	median 5	not reported
			insertion			69.6	39.8	17.7		
Yelland	2011	RCT	mid-portion	20% dextrose solution	eccentric loading				4.4 ± 1.7	none

Animal studies

Author	Year		Substance	Primary Outcome	Control
Bumpus	1964	animal	8 different sclerosing solutions	effect on tendon	na
Maynard	1985	animal	5% sodium morrhuate	effect on tendon	Ethanol
Boesen	2007	animal	polidocanol 10mg/ml	immediate effect	na
Martins	2011	animal	12.5% dextrose solution	effect on tendon	no injection. saline solution, corticosteroids

Table 3: Summary of the Coleman Methodology Score

Author	Study Type	Coleman Score	Rating
Öhberg and Alfredson 2002	prospective	44	fair
Öhberg and Alfredson 2003	*prospective*	50	fair
Öhberg and Alfredson 2005	*RCT*	59	good
Lind 2006	*prospective*	60	good
Öhberg and Alfredson 2007	*RCT*	57	good
Clementson 2008	*retrospective*	32	fair
Willberg 2008	*RCT*	66	good
van Sterkenburg 2010	*retrospective*	50	fair
Lyftogt 2005	*prospective*	28	fair
Lyftogt 2007	*prospective*	27	fair
Maxwell 2007	*prospective*	44	fair
Ryan 2010	*prospective*	60	good
Yelland 2011	*RCT*	73	good
overall		50	fair