Physical Therapy in Sport 17 (2016) 87–94

Contents lists available at ScienceDirect

Physical Therapy in Sport

journal homepage: www.elsevier.com/ptsp

Literature review

The clinical impact of platelet-rich plasma on tendinopathy compared to placebo or dry needling injections: A meta-analysis

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ARTICLE INFO

Article history:
Received 30 December 2014
Received in revised form
14 April 2015
Accepted 9 June 2015

Keywords:
Platelet-rich plasma
Tendinopathy
Meta-analysis

ABSTRACT

Objective: The purpose of this meta-analysis was to compare the impact of platelet-rich plasma with that of placebo or dry needling injections on tendinopathy.
Methods: The databases of PubMed, CENTRAL, Scopus, Web of Science, and trial registries, reference lists, and conference abstract books were searched up to December 2014. Adults with tendinopathy in randomized controlled trials were enrolled. The trials compared effect of platelet-rich plasma with that of placebo or dry needling. We used subgroup analysis linked to the anatomical location of the tendinopathy. The primary outcome was pain intensity at two or three and six months after intervention. The secondary outcome was functional disability at three months after treatment.
Results: Five trials were included. There was a statistically significant difference in favor of the platelet-rich plasma intervention at the second primary outcome time point (SMD −0.48, 95%CIs −0.86 to −0.10, $I^2 = 0\%$, $p = 0.01$) and at the secondary outcome time point (SMD −0.47, 95%CIs −0.85 to −0.09, $I^2 = 0\%$, $p=0.01$).
Conclusions: Platelet-rich plasma did not provide significantly greater clinical benefit versus placebo or dry needling for the treatment of tendinopathy at a six-month follow-up. However, there was a marginal clinical difference in favor of platelet-rich plasma injections on rotator cuff tendinopathy.

1. Introduction

Tendinopathy is a common orthopaedic problem that includes tendinitis, paratenonitis and tendinosis (Khan, Cook, Bonar, Harcourt, & Astrom, 1999). It is characterized by chronic pain, functional deterioration and tendon thickening. Both intrinsic and extrinsic factors have been implicated in the etiology of tendinopathy (Riley, 2004). The histopathology of tendinopathy reveals the absence or minimal presence of inflammatory cells, which has been confirmed by gene array studies (Alfredson, Lorentzon, Bäckman, Bäckman, & Lerner, 2003; Ireland et al., 2001). Tendinopathy is characterized by increased mucoid substance, intratendinous degeneration, and collagen disorganization (Khan et al., 1999). In some cases, a 10- to 20-fold increase in calcium concentration may be detected (Kannus, 2000).

There are a variety of approaches for treating tendinopathy, with traditional methods (i.e., non-steroidal anti-inflammatory drugs and activity modification) still advocated as first-line management (Andres & Murrell, 2008). In cases where conservative treatments fail, surgical consultation is suggested.

In addition to the well-established conservative therapies, many investigational injectable treatments have been developed. Ultrasound- (US) guided dry needling intervention, and US-guided platelet-rich plasma (PRP) injections are two injectable treatments. PRP is defined as the volume of autologous plasma that has a platelet concentration above baseline (Marx, 2001). The dry needling technique, also known as peppering, consists of multiple tendon perforations without injecting any substances.

PRP, placebo and dry needling injections cause bleeding in the tendon, which can increase inflammation and induce the release of

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http://dx.doi.org/10.1016/j.ptsp.2015.06.003
1466-853X/

beneficial growth factors. This stimulates tendon healing (Filardo, Kon, Della Villa, Vincentelli, Fornasari, & Marcacci, 2010; Mishra, Harmon, Woodall, & Vieira, 2012). Consequently, it is thought that the needling of a tendon, with or without injecting any substances, exerts a positive clinical impact on rehabilitation (Dommerholt, 2011; Krey, Borchers, & McCamey, 2015; Nagraba, Tuchalska, Mitek, Stolarczyk, & Deszczyński, 2013). The use of high platelet concentrations in PRP, results in the release of significantly greater amounts of beneficial growth factors than that released by any type of needling. Moreover, the concentration of growth factors increases linearly with increasing platelet number (Eppley, Woodell, & Higgins, 2004; Marx, 2001). Nevertheless, it is evident that PRP with significantly high platelet concentrations does not further increase tendon rehabilitation (Marx, 2001; Rughetti et al., 2008). Considering this, we hypothesized that the clinical effect of PRP on tendinopathy would be greater than that of placebo or dry needling.

The purpose of this meta-analysis was to compare the clinical impact of PRP with that of placebo or dry needling on adults with tendinopathy. The primary outcome measure was pain intensity at two or three and six months after the initial intervention. The secondary outcome was functional disability at three months after the initial treatment.

2. Methods

The review was registered with PROSPERO (CRD42014010003) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Liberati et al., 2009).

2.1. Eligibility criteria

Randomized controlled clinical trials (RCTs) that compared the effects of PRP and placebo or dry needling injections on patients with tendinopathy were enrolled. Adults who suffered from tendinopathy for more than six weeks were included in the meta-analysis. Moreover, the diagnosis had to have been confirmed with the use of either Magnetic Resonance Imaging (MRI) or US. In each included study, a randomized group of patients was treated with US-guided PRP intervention and another group with US-guided placebo or dry needling injections. Placebo in the present meta-analysis contained either normal saline or local anesthetic. Furthermore, the minimum length of follow-up in the enrolled trials was six months. Experimental animal studies and full-thickness tendon tears were excluded. The primary outcome measure in this meta-analysis was pain intensity at two or three and six months after the initial intervention. The secondary outcome measure was functional disability at three months after the initial intervention.

2.2. Literature search

A comprehensive literature search was performed using the PubMed, CENTRAL, Web of Science, and Scopus databases, as well as conference abstract books and reference lists of relevant studies without language restrictions up to December 16, 2014. The following clinical trial registries were also searched up to the same date for the identification of completed unpublished studies: ClinicalTrials.gov; Australian New Zealand Clinical Trials Registry (ANZCTR); and the International Standard Randomized Controlled Trial Number (ISRCTN) Register. The search strategy included the use of the terms: “Platelet-Rich Plasma”, “platelet concentrate”, “autologous blood”, “platelet rich transfusion”, “tend*”, “plantar fasciitis”, “patellar”, “jumper's knee”, “golfer's elbow”, “tennis arm”, “epicondyl*”, “Achilles”, “rotator cuff”, “shoulder”. This search was adapted for each database, and the terms that were used were not combined with specific database filters. The corresponding authors of the completed unpublished trials were contacted to request their data.

2.3. Study selection

Two authors (KT and ES) searched for records independently. The titles and abstracts of the retrieved studies were screened. Then, full-text articles were obtained and assessed for eligibility. If an identified study fulfilled the eligibility criteria but contained insufficient data for quantitative synthesis, the corresponding author of the article was contacted twice (with a three-week interval) in order to request additional information. If there was no reply or the data were still insufficient the study was excluded from the quantitative synthesis.

2.4. Data extraction

Information was extracted independently by two reviewers (KT and ES). Details that were abstracted from each enrolled trial included the year of publication, comparators in the control group, and the number and demographics of patients in the included intervention groups. Moreover, Information about the duration of symptoms, intervention characteristics, study outcomes, follow-up and side effects were also extracted. In cases with more than two intervention groups in an included RCT, data were abstracted from the PRP and either the placebo or the dry needling group.

The data that were used in the quantitative synthesis were abstracted from questionnaires that evaluated pain intensity, functional disability, or both. Information from composite questionnaires was used only in cases where pain and function subscores were available. Additional required information was obtained by contacting the corresponding authors. There were few discrepancies during abstracting and these were resolved through consensus.

2.5. Risk of bias assessment

The quality of the included RCTs was independently assessed by two investigators (KT and ES) using the Cochrane collaboration's risk of bias tool (Higgins & Green, 2011). Thus, the following domains were assessed: randomization; concealment of the allocation; masking of patients, study personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential sources of bias.

The risk of selection bias across studies was assessed using both the results of the randomization and that of allocation concealment. In addition, the risk of detection bias (also known as observer bias) was assessed using the results of the blinding of the outcome assessors (Bello, Krogsbøll, Gruber, Zhao, Fischer, & Hróbjartsson, 2014; Higgins & Green, 2011). The decision to use funnel plots for the assessment of publication bias in this meta-analysis was depended on the number of the included studies (Higgins & Green, 2011). Discrepancies between the review authors' opinion about the risk of bias were resolved through discussion.

2.6. Statistical analysis

Review Manager Software (version 5.3) was used in this meta-analysis with random-effects models. Ninety-five percent confidence intervals (CIs) were calculated according to the inverse variance method for all study outcomes. The use of final values was preferred for both primary and secondary outcomes because