SHORT REPORT

The Efficacy of Platelet-Rich Plasma Injection in the Management of Hip Osteoarthritis: A Systematic Review Protocol

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Background

Osteoarthritis (OA) is a progressively debilitating condition that is associated with pain and morbidity. It is associated with ageing and most often affects the joints of the knees, hips, fingers and lower spine region (Hochberg et al., 2013). It is estimated that about 10% of men and 18% of women aged over 60 years have symptomatic OA. Eighty per cent of those with OA will have limitations in movement, and 25% cannot perform major daily activities of life (Murray and Lopez, 1997). According to the World Health Organization, OA is commonly regarded as the most frequent cause of functional disability, and about 80% of people over the age of 65 years show radiological symptoms of OA (World Health Organization, 2007). This condition has an adverse impact on patient mobility and quality of life. Researchers have reported that the hip is the second most common weight-bearing joint – after the knee – to be affected by OA, affecting approximately 5% of adults aged 60 years or older (Scott, 2010), and there is an upward trend in the incidence of hip osteoarthritis (HOA).

The current main objectives of HOA management are to relieve pain, educate the patients about their disease, restore function, minimize the progression of the disease and maintain health-related quality of life (Zhang et al., 2010). Currently, there is no known cure for HOA, so the main therapeutic strategy is symptomatic. Several treatment modalities are available, involving both conservative and operative approaches. Non-operative management includes analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase-2 inhibitors, glucocorticoids, opioids (Hitzeman and Athale, 2010), cartilage protective agents (e.g. diacerin, glucosamine and chondroitin) (Bruyere and Reginster, 2007) as well as physiotherapy (Bennell et al., 2014), exercise (Fransen et al., 2014; Iversen, 2010), intra-articular injections (Caglar-Yagci et al., 2005) and joint denervation (Gupta et al., 2014). Although these treatments have been beneficial in the short term, there is a lack of evidence that such interventions alter the natural history or progression of OA. Therefore, innovative methods are needed to treat HOA more effectively, especially if the disease process itself can be altered.

Recently, platelet-rich plasma (PRP) has been used in the management of OA (Cerza et al., 2012; Kon et al., 2011). PRP is an autologous blood product produced by the centrifugation of whole blood, yielding a concentration of platelets above baseline levels. The OA disease process involves the whole joint, including bone, ligament, muscle and cartilage, with changes such as joint space narrowing, bony osteophytes and sclerosis seen on X-ray. Chondrocytes stimulated with PRP *in vitro* have been shown to increase their synthesis of proteoglycans and collagen (Akeda et al., 2006), with the repair tissue generated after PRP treatment demonstrating similar histological and biomechanical characteristics to the original tissue. Because the administration of PRP is relatively simple to perform, minimally invasive and pain-free, with a fair cost–effectiveness ratio, it has generated substantial

interest in the treatment of HOA in recent years. The treatment schedule for HOA involves three consecutive intra-articular ultrasound-guided injections of 5–8 mL autologous PRP, with an interval between injections ranging from one to two weeks (Battaglia et al., 2013; Sánchez et al., 2012).

Multiple systematic and narrative reviews on the use of PRP injections for muscle (Hamid, et al., 2014), tendon (Di Matteo et al., 2014; Mautner and Kneer, 2014), ligament (Taylor et al., 2011) and cartilage healing have shown conflicting evidence. High-quality studies have shown no significant benefit of PRP at the final follow-up measurement in pathologies such as epicondylar tendinopathy (Krogh et al., 2013), rotator cuff injury (Rodeo et al., 2012) and ankle sprain (Rowden et al., 2015). To our knowledge, no previous study has systematically reviewed and critiqued the efficacy of PRP in the treatment of HOA. There is, therefore, a clear gap in the existing literature, necessitating the proposed review.

The overall aim of the present study is to conduct a systematic review of the recent literature to determine the effectiveness of PRP as a primary or adjuvant treatment of HOA. More specifically, we aim to: describe the key research questions; document our systematic literature search strategy; describe the criteria for inclusion or exclusion of studies and other data sources identified by the review; and describe data categorizations and study quality measures.

Methods

The present systematic review protocol was developed using guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009). The review protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/prospero) (Registration number CRD 42014010210) to reduce the variability in the review process and increase the validity of the results (Straus and Moher, 2010). PROSPERO is a database of prospectively registered systematic reviews for health and social topics. The study was registered after a pilot search and prior to an updated data search and extraction.

Literature search

Electronic databases will be searched using a strategy developed by the researchers using the Medical Subject Headings (MeSH) pertaining to each database. MeSH terms represent a very detailed taxonomy of keywords developed by the National Library of Medicine to describe anything in biomedicine. Under the supervision of a professional librarian, a primary search (in five electronic databases: Pubmed, ProQuest Health & Medical Complete, CINAHL, E-journals and SPORTdiscus) to retrieve primary studies published prior to December 2014 will be performed. Key terms used in our search strategy will be 'platelet-rich plasma', 'hip' and 'osteoarthritis'. A secondary search will include trial databases (ClinicalTrials.gov, European Trials Register, Controlled-trials.com) for unpublished trials and the screening of citing and cited references in the relevant articles previously identified. Systematic reviews and other review articles will be scanned to ensure that no eligible studies are missed. In addition, a recognized expert in this field will be consulted in an attempt to identify any further published or unpublished studies.

Study selection

Studies examining a well-described intervention in the form of an injection with PRP or equivalent products [i.e. platelet–leucocyte gel, platelet concentrate, platelet gel or Plasma Rich in Growth Factors–Endoret (PRGF–Endoret)] in patients with HOA, published after January 1973, will be considered. In a first selection phase, two review authors (IM, PA) will independently screen the title and abstract of all identified studies for inclusion against the eligibility criteria (Table1).

In a second selection phase, two independent reviewers (PA, IM) will confirm the eligibility of the studies by reviewing the full text of the selected studies. Any discrepancies will be settled by further discussion and consensus. A kappa statistic and the percentage agreement will be used to calculate inter-rater agreement in both selection phases.

A PRISMA diagram will be developed based on the search strategy and eligibility assessment to show the flow of included and excluded studies.

Data extraction

A qualitative synthesis will be conducted comparing the results of the different articles. Two reviewers (IM, PA) will independently extract data from the studies regarding: 1) general information (authors and year of

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Languages: English and Spanish. • Publication types: experimental and epidemiological study designs, including randomized controlled trials; non-randomized controlled trials; quasi-experimental before-and-after studies; prospective and retrospective cohort studies; case control studies and analytical cross-sectional studies; and case reports. Qualitative and observational studies will also be taken into consideration. • Study population: patients (>18 years) diagnosed with mild, moderate or severe hip OA. • Use of an injection of PRP. • Intervention setting: public and private practice.	• Publication types: editorial, anecdotal report and letters published in abstract form, studies using platelet-poor plasma in combination with PRP, and studies using a recombinant or single growth factor. • Study population: studies involving animal subjects, non-OA injuries, OA affecting other joints, children only. • Intervention setting: acute rehabilitation, outpatient rehabilitation and community integration setting.

OA, osteoarthritis; PRP, platelet-rich plasma

publication); 2) participants' characteristics; 3) the main intervention – PRP injection; 4) outcomes and 5) related results, and any other important aspect related to each research question of interest, using a standardized form. Summary tables will be created showing key study characteristics. Disagreements between the reviewers will be resolved by discussion and consensus.

Risk of bias assessment

The risk of bias in randomized studies included will be undertaken independently by two reviewers (IM, PA) using the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003). The PEDro scale scores ten items: random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, >85% follow-up for at least one key outcome, intent-to- treat analysis, between-group statistical comparison for at least one key outcome, and point and variability measures for at least one key outcome (de Morton, 2009). Each item will be rated as either present (1) or absent (0), and a score out of 10 is obtained by summation. High-quality scores will be defined as a PEDro score ≥6 and low- quality scores will be defined as a PEDro score <6 (de Morton, 2009). If in some cases the information is unclear, then attempts to contact the specific authors will be made to clarify any methodological issues. In the event of any disagreement, a third reviewer will be consulted. The Transparent Reporting of Evaluations with Nonrandomized Design (TREND) grid will be used to assess risks of bias in non-randomized studies (Des Jarlais et al., 2004). A risk of bias table will be generated with the principal biases and the methodological quality of the studies. The results of the quality assessments of the individual trials will be used to classify the level of evidence (van Tulder et al., 2003). This qualitative analysis will be performed with five levels of evidence based upon the quality and results of clinical studies:

I. Strong evidence: provided by generally consistent findings in multiple high-quality randomized clinical trials (RCTs);
II. Moderate evidence: provided by generally consistent findings in one high-quality RCT and one or more lower-quality RCTs, or by generally consistent findings in multiple low-quality RCTs;
III. Limited evidence: provided by only one RCT (either of high or low quality) or generally consistent findings in non-randomized clinical trial (nRCTs);
IV. Conflicting evidence: inconsistent findings in multiple RCTs or nRCTs;
V. No evidence: no RCTs or nRCTs.

Discussion

The study protocol was designed to meet PRISMA standards (Liberati et al., 2009) and is being disclosed so that our methods can be retrieved and evaluated against the final analyses and interpretation of findings.

The use of PRP is also an area of controversy and challenge in orthopaedics and sports medicine.

Methodological limitations of current PRP research in OA hamper conclusions and progress. However, there are currently important gaps in our knowledge on the effectiveness of PRP injections for HOA patients. The present systematic review aims to provide reliable and trustworthy data regarding the effectiveness of PRP injections for the conservative management of HOA in comparison with other possible options, so that decision makers can come to their own conclusions about the value of this treatment strategy. The results of the present systematic review could be included in a clinical guideline or be used to develop performance indicators for institutions and professionals treating patients with HOA. We expect this review to fill the gap in knowledge in PRP injections on HOA.

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