Intervention protocol

Platelet-rich plasma versus other intra-articular injections for treatment of knee osteoarthritis

Abstract

This is the protocol for a non-Cochrane review and there is no abstract. The purpose of this review is to determine the efficacy and safety of intra-articular injections of autologous platelet-rich plasma for treatment of knee osteoarthritis compared with other injections.

Background

Description of the condition

Osteoarthritis (OA) is a leading joint disorder, most commonly affecting knee joints. Approximately one tenth of people aged over 55 suffered painful and disabling knee OA(1). This progressive and degenerative joint disease has a multi-factorial etiology and is deemed as the product of interplay between systemic and local factors(2). Knee OA is characterized by a cascade change of normal joint structures involving cartilage, subchondral bone, meniscus, ligaments and periarticular muscles. There is no cure for knee OA. Current treatment focuses on the improvement of OA symptoms, mainly reducing pain and restoring joint function.

Description of the intervention

Platelet-rich plasma (PRP) is a fraction of whole blood and prepared by the centrifugation of

autologous blood, thereby yielding a higher concentration of platelets than baseline values. Despite great variations in its makeup, PRP mainly contained concentrated platelets, a number of plasma proteins, leucocytes at a certain level and fibrinogen. As a concentrated source of autologous platelets, PRP contains several different growth factors and other cytokines that can stimulate healing of bone and soft tissue. It has since been applied to many different medical fields such as cosmetic surgery, dentistry, sports medicine and pain management.

How the intervention might work

Upon activation, the platelets in PRP can release a multitude of growth factors at concentrations significantly higher than the baseline blood levels, including transforming growth factor-β, platelet-derived growth factors, insulin-like growth factors, basic fibroblast growth factors, vascular endothelial growth factors, epidermal growth factors, and so on(3). In pre-clinical studies, PRP has been proved to be anabolic effect and chondro-protective(4). Moreover, PRP also contains a number of inflammatory mediator and modulators. Studies have found that PRP inhibit the inflammation in chondrocytes induced by interleukin-1β or excessive mechanical loading(5, 6). The regenerative effect and anti-inflammatory potential of PRP in the tissue healing process have led to extensive investigation of PRP as a potential treatment for a variety of musculoskeletal indications, including OA(7).

Why it is important to do this review

The efficacy of intra-articular PRP injections for treatment of knee OA remains inconclusive.

The updated clinical guidelines by American Association of Orthopaedic Surgeons demonstrated inconclusive evidence to recommend for or against PRP(8). The recommendation about PRP infiltration was based on 3 HA-controlled studies unable to be synthesized for a comparative analysis of clinical effectiveness. Recently, a number of randomized controlled trials (RCTs) were reported with favourable outcomes of PRP injections(9-15); however, unfavourable results compared with HA were also reported (16, 17). Due to the mixed results, several systemic reviews have been published (18-23), but most of them included non-RCTs for analysis (18, 19, 21, 22). Moreover, considerable heterogeneity among studies was common in the prior reviews (18-22), precluding a meta-analysis of those results. Consequently, the conclusion from previous systemic reviews was undermined. More recently, quite a few more RCTs have been published (24-30), which necessitates an updated systemic review to evaluate the efficacy of PRP with probably reduced heterogeneity among studies through subgroup analysis.

Objectives

To determine the efficacy and safety of intra-articular injections of autologous platelet-rich plasma for treatment of knee osteoarthritis compared with other injections.

Methods

Criteria for considering studies for this review

Types of studies

Human RCTs investigating the efficacy and/or safety of PRP for treatment of knee OA with at least a control group receiving intra-articular injections other than PRP.

Types of participants

At least 75% of participants with both clinically and radiologically confirmed osteoarthritis of the knee. We will not consider trials that included exclusively people with knee symptoms without radiologically osteoarthritic changes.

Types of interventions

The experimental intervention of interest is any type of PRP preparations, including but not limited to autologous platelet concentrate, autologous conditioned plasma and plasma rich in growth factors. The control group should receive other types of intra-articular injections, including but not limited to saline, hyaluronic acid, corticosteroids and ozone. The treatment in either group should not be used in combination with other types of treatment including surgery and prescribed treatment plans of physical therapy or non-steroid anti-inflammatory drugs.

Types of outcome measures

Primary outcomes

Western Ontario and McMaster Universities Arthritis Index (WOMAC) osteoarthritis index total scores.

Secondary outcomes

The number of patients with adverse events during follow-up; the number of patients satisfied with treatment at the end of follow-up.

Search methods for identification of studies

Electronic searches

Database: Pubmed, Embase, Scopus and Cochrane library. The search strategy is as follows: (platelet[text word] OR plasma[text word]) AND (knee[text word] OR tibiofemoral[text word] OR patellofemoral[text word]) AND (*arthritis[text word] OR *arthritic[text word] OR cartilage[text word] OR *arthrosis[text word] OR gonarthrosis[text word]) AND random*[text word]. If no [text word] field is available, the field [TITLE-ABS-KEY] will be used. Limit to human will be applied if more than 200 items are searched in 1 database. No language or publication year exclusion will be applied.

Searching other resources

We will retrieve and screen the reference lists of the systematic reviews and narrative reviews published since January 2012 that evaluated the effects and/or safety of PRP injections for knee osteoarthritis, degenerative pathology or cartilage injuries.

Data collection and analysis

Selection of studies

Two investigators will independently review the search results and identify studies that appear to meet our inclusion criteria. All articles selected by either investigator will be retrieved for closer examination. Any disagreement about inclusion or exclusion of individual studies will be resolved by panel discussion with a third investigator.

Data extraction and management

Two investigators will extract the following data from the included trials and resolve any differences by panel discussion with a third investigator:

1. Trial characteristics including sample size, location of the trial, study design and conflict of interest;

2. Characteristics of the study population including age, the percentage of female patients, body mass index and the dropout rate;

3. Characteristics of the knee OA including the number of participants at different stages of knee degeneration;

4. Characteristics of PRP injection therapy including the preparation methods, components, injection dose and frequency and total number of treatment sessions;

5. Characteristics of the control interventions including the types of control, injection dose and frequency and times in total;

6. Outcome measures: the measurement scale, and direction of the scale, and the mean and standard deviation, and number of participants per treatment group for continuous outcomes (such as mean pain, function, quality of life), and number of events and number of participants per treatment group for dichotomous outcomes (such as proportion with 30% or more pain relief, withdrawals due to adverse events, adverse events and satisfaction rates).

7. Conclusion: the inclination of the authors in each study.

In multi-arm trials including more than 1 PRP treatment groups, only the group treated with at least twice PRP injections was considered as the intervention group, as the regimen of multiple PRP injections was more common and reported to be more efficacious than a single injection (31, 32). Although data concerning the patients treated with single PRP injection in

those trials were also extracted, they were not used for quantitative synthesis.

Assessment of risk of bias in included studies

Two investigators will assess the bias of the included studies in following methodological domains, as recommended by the Cochrane Collaboration Group(33). The differences will be resolved by consult with a third investigator.

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants (performance bias);
4. blinding of personnel (performance bias);
5. blinding of outcome assessment (detection bias);
6. incomplete outcome data (attrition bias);
7. selective reporting (reporting bias);
8. other bias.

The risk of bias for each domain was graded as either low (+), high (−), or unclear (?). We will present figures generated by the risk of bias tool to provide a summary assessment of the risk of bias.

Measures of treatment effect

For the continuous variables, the mean difference (MD) with 95% confidence interval (CI) was used, while the relative risk (RR) with 95% CI was adopted for dichotomous variables to

express intervention effects. Where different scales are used to measure the same outcome, standardized mean differences (SMDs) will be used.

Dealing with missing data

When data is missing or incomplete, the following measures will be taken.

1. Personal correspondence will be attempted to obtain missing data or clarify ambiguous information.
2. Missing data may be calculated from other statistics according to the methods recommended in the Handbook for Systematic Reviews of Interventions (33).
3. Published reviews or articles containing these information or data will be screened and extracted.

Assessment of heterogeneity

We assumed the presence of heterogeneity a priori and used the random-effects model in all pooled analysis. The I^2 was used to test heterogeneity. As defined previously, a value less than 40% means the heterogeneity might not be important, whereas the value more than 75% means considerable heterogeneity (33). In case of considerable heterogeneity, we will plan subgroup analysis to test the difference in PRP components and controls. Alternatively, the results were displayed in descriptive tables.

Assessment of reporting biases

In order to determine whether reporting bias is present, we will determine whether the protocol of the trial was published before. We will evaluate whether selective reporting of outcomes is present (outcome reporting bias). The random-effects model will be adopted in all pooled analysis in order to minimize the effect of potential reporting bias on the final results. The potential for small-study effects in the main outcomes of the review will be further explored using funnel plots if at least 10 studies reporting pain are included in a meta-analysis.

Data synthesis

For studies with similar participant and intervention characteristics and a common comparator, we will pool outcomes in a meta-analysis using the random-effects model as a default. Any *p* value less than 0.05 will be considered to be statistically significant. All analysis will be undertaken using Review Manager 5.3.

Sensitivity analysis

The robustness of results will be assessed by excluding each included trial from the pooled analysis.

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