NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of platelet-rich plasma injections for knee osteoarthritis

Osteoarthritis can develop in the knee when cartilage covering the ends of the bones becomes worn. This can cause pain, stiffness, swelling and difficulty walking. In this procedure, red blood cells are removed from a small amount of the person's own blood, leaving a liquid called plasma. This contains tiny cells called platelets, which can stimulate the natural healing process. This plasma is injected into the knee. The aim is to relieve symptoms.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the

medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2018.

Procedure name

- Platelet-rich plasma injections for knee osteoarthritis

Specialist societies

- British Association for Surgery of the Knee (BASK)
- British Society of Rheumatology
- Chartered Society of Physiotherapists (CSP)
- Royal College of General Practitioners (RCGP).

Description of the procedure

Indications and current treatment

Osteoarthritis of the knee is the result of progressive deterioration of the articular cartilage and menisci of the joint, usually because of trauma and wear and tear. This leads to exposure of the bone surface. Symptoms include pain, stiffness, swelling and difficulty walking.

Treatment depends on the severity of the symptoms. Conservative treatments include analgesics and corticosteroid injections to relieve pain and inflammation, and physiotherapy and prescribed exercise to improve function and mobility. When symptoms are severe, surgery may be indicated: options include upper tibial osteotomy and unicompartmental or total knee replacement.

What the procedure involves

Platelet-rich plasma is prepared by a clinician or technician. Blood is taken from the patient and centrifuged to obtain a concentrated suspension of platelets in plasma. It can be prepared by carrying out 2 spin cycles using a standard bench-top centrifuge, or by using commercially available single-step preparation systems. Different preparation methods may affect the concentrations of platelets. Agents such as calcium chloride may be added to activate the platelets.

The platelet-rich plasma is injected into the joint space in the knee, usually under ultrasound guidance. Platelets contain growth factors that are thought to stimulate chondrocyte proliferation, leading to cartilage repair. The aim is to relieve symptoms, potentially delaying the need for joint replacement surgery.

Osteoarthritis classification

Kellgren–Lawrence grading system

The Kellgren–Lawrence grading system employs radiographic images from X-rays to classify osteoarthritis according to the degree of joint space narrowing and the presence of osteophytes, which are small bony projections that form around joint margins that limit joint mobility and cause pain. The system consists of 5 categories:

- Grade 0: normal cartilage.
- Grade 1: possible osteophytes and unlikely joint space narrowing.
- Grade 2: small osteophytes and possible joint space narrowing.
- Grade 3: multiple, moderately sized osteophytes, definite joint space narrowing, some sclerotic areas, possible deformation of bone ends.
- Grade 4: multiple large osteophytes, severe joint space narrowing, marked sclerosis and definite bony end deformity.

Outerbridge classification system

The Outerbridge classification system is the most widely used grading system to describe the size and depth of cartilage defects. The system consists of 5 categories:

- Grade 0: normal cartilage.
- Grade 1: cartilage with softening and swelling.
- Grade 2: a partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter.
- Grade 3: fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm.
- Grade 4: exposed subchondral bone.

Outcome measures

International Knee Documentation Committee score

The International Knee Documentation Committee (IKDC) score is a joint-specific tool that can be used to evaluate a variety of knee conditions according to symptoms, activity of daily living and function in sports activities. The IKDC questionnaire consists of 18 questions, 90% (16/18) of which need to be completed before an evaluative score can be obtained. Scores range from 0 to 100 with higher scores indicating better outcomes. An increase in score of 11.5

units is needed for a patient to perceive a significant improvement in their condition.

Knee injury and Osteoarthritis Outcome Score

The Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire evaluates the functional status and quality of life of patients with any type of knee injury who are at increased risk of developing osteoarthritis. It consists of 5 subscales: pain, other symptoms, activities of daily living, sport and recreation function, and knee-related quality of life. Standardised answer options are given and each question is assigned a score from 0 to 4. A normalised score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

Tegner activity scale

The Tegner activity scale was designed as a score of activity level to complement other functional scores for patients with ligamentous injuries. Scores range from 0 (indicating the highest degree of disability relating to the knee joint) to 10 (indicating ability to participate in competitive sports).

Western Ontario and McMaster Universities Arthritis Index

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is an extensively used standardised questionnaire that is used to assess patients with osteoarthritis of the knee or hip. The questionnaire evaluates 3 domains: pain (score range 0–20); stiffness (score range 0–8) and physical function (score range 0–68). The total score ranges from 0 to 96 with lower scores indicating better outcomes.

Efficacy summary

WOMAC scores (total and sub-scores for knee pain and physical function)

Knee pain sub-score

PRP compared with all control groups

In a systematic review and meta-analysis of 14 randomised controlled trials (RCTs) including 1,423 patients, which compared the effect of PRP injections with other injections (including saline placebo, hyaluronic acid [HA], ozone, and corticosteroids) for the treatment of knee osteoarthritis [OA], PRP significantly improved WOMAC pain sub-scores compared with controls (placebo or HA) according to pooled analysis of the 3 studies that reported this outcome at 3-month follow-up (mean difference [MD], -3.69, 95% confidence interval [CI], -6.87 to -0.51, I^2=94%, p=0.02), the 5 studies that reported this outcome at 6 months (MD, -3.82, 95% CI, -6.40 to -1.25, I^2=96%, p=0.004) and the 4 studies that reported this outcome at 12 months (MD, -3.76, 95% CI, -5.36 to -2.16, I^2=86%, p<0.001) respectively.[1]

PRP compared with HA

In a systematic review and meta-analysis of 10 RCTs comparing PRP injections with HA or saline, pooled analysis of the 3 studies (n=339 patients) that reported pain at 6 months post injection showed that there was no significant difference between PRP and HA (MD -1.54, 95% CI -4.27 to 1.20, p=0.27, I^2=96%). At 12 months post injection, PRP was associated with significantly better pain relief (3 studies [n=302], MD -2.83, 95% CI -4.26 to -1.39, p=0.0001, I^2=79%). At 6 and 12-month follow-up the overall effect sizes exceeded the minimally clinically important differences (MCID, defined as smallest difference perceived as important and beneficial by the patient or clinician) (-0.83 at 6 months and -0.79 at 12 months).[2]

In a systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 3 studies (224 compared with 208 patients) reported lower WOMAC pain scores for PRP compared with HA, but this was not statistically significantly different (unstandardised mean difference [UMD] −1.95, 95 % CI −4.06 to 0.17, p =0.071, I^2=90.5%).[3]

PRP compared with saline

In the systematic review and meta-analysis of 10 RCTs comparing PRP injections with HA or saline, 1 study found that PRP statistically significantly improved the WOMAC pain score compared with saline at 6 months (MD-5.00, 95% CI -6.98 to-3.02, p<0.00001) and at 12 months (MD -6.00, 95% CI -8.32 to -3.68, p<0.00001) post injection. The overall effect sizes exceeded the MCID (-1.4 at 6 months and -1.6 at 12 months).[2]

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 2 studies (56 compared with 54 patients) reported lower WOMAC pain scores for PRP compared with saline, but this was not statistically significantly different (UMD −2.81 (95 % CI −6.47 to 0.84, p=0.132, I^2=85.5%).[3]

Leukocyte poor PRP (LP-PRP) compared with conventional pharmacological treatment

In an RCT of 65 patients comparing LP-PRP (n=33) with acetaminophen [AC] (n=32) in early knee OA (grade 1-2), significant differences in pain sub-scores were reported between the groups at 6 and 12 weeks follow-up (LP-PRP group scores 3.1 and 2.7 compared with AC group scores 5.8 and 5.7; p<0.05) respectively.[5]

PRP compared with prolotherapy (PRL)

In an RCT of PRP (n=21) compared with prolotherapy (n=21) in 42 patients with grade 1 or 2 knee OA, mean pain scores decreased significantly from baseline to

6 months in both groups. All pairwise comparisons of pain in different time periods for both groups were statistically significant. Comparison between the groups was statistically significant at 2 months (p=0.002) and 6 months follow-up (p=0.003).[6]

Physical function sub-score

PRP compared with all control groups

In the systematic review and meta-analysis of 14 RCTs (1,423 patients) that compared PRP injections with other injections (including saline placebo, hyaluronic acid, ozone, and corticosteroids) for the treatment of knee OA, PRP significantly improved WOMAC physical function sub-scores compared with control according to pooled analysis of 3 studies at 3 months follow-up (MD, -14.24, 95% CI, -23.43 to-5.05, I^2=91%, p=0.002), 5 studies at 6 months (MD, -13.51, 95% CI, -23.77 to -3.26, I^2=97%, p=0.01) and 4 studies at 12 months (MD, -13.96, 95% CI, -18.64 to -9.28, I^2=84%, p<0.001) respectively.[1]

PRP compared with HA

In the systematic review and meta-analysis of 10 RCTs comparing PRP injections with HA or saline, pooled analysis of 3 studies (339 patients) reported that at 6 months post injection, there was no significant difference between the PRP and HA groups (MD -4.39, 95% CI -10.51 to 1.74, p=0.16, I^2=87%). At 12 months post injection, PRP was associated with significantly better pain relief (3 studies [n=302], MD -12.53, 95% CI -14.58 to -10.47, p<0.00001, I^2=31%). At 6 and 12 months follow-up the overall effect sizes exceeded the MCID (-2.74 at 6 months and -2.85 at 12 months).[2]

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 3 studies (224 compared with 208 patients) reported lower WOMAC function scores for PRP compared with HA, but this was not statistically significantly different (UMD −8.02, 95% CI −17.45 to 1.41, p=0.096, I^2=95.8%).[3]

PRP compared with saline

In the systematic review and meta-analysis of 10 RCTs comparing PRP injections with HA or saline, 1 study found that PRP statistically significantly improved the WOMAC function score compared with saline at 6 months (MD-24.00, 95% CI -31.30 to-16.70, p<0.00001) and 12 months (MD -24.00, 95% CI -30.01 to -17.99, p<0.00001) post injection. The overall effect sizes exceeded the MCID (-4.8 at 6 months and -5 at 12 months).[2]

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 2 studies (56 compared with 54 patients) reported lower WOMAC function scores for PRP compared with saline, but this

was not statistically significantly different (UMD −8.02, 95 % CI −17.45 to 1.41, p=0.327, I^2=94.2%).[3]

LP-PRP compared with conventional pharmacological treatment

In the RCT of 65 patients comparing LP-PRP (n=33) with acetaminophen [AC] (n=32) in early knee OA (grade 1-2), significant differences in knee function sub-scores were reported between the groups at 6,12 and 24 weeks follow-up (LP-PRP group scores 8.7, 8.3 and 7.9 compared with AC group scores 18.2,18.3 and 16.7 respectively; p<0.05).[5]

PRP compared with prolotherapy (PRL)

In the RCT of PRP (n=21) compared with prolotherapy (n=21) in 42 patients with grade 1 or 2 knee OA, mean knee function scores decreased significantly from baseline to 6 months in both groups. All pairwise comparisons of knee function in different time periods for both groups were statistically significant. Comparisons between the groups were statistically significant at 2 months (p=0.009) and 6 months follow-up (p=0.02).[6]

Stiffness sub-score

PRP compared with HA

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 3 studies (224 compared with 208 patients) reported lower WOMAC stiffness scores for PRP compared with HA, but this was not statistically significantly different (UMD −0.99 (95% CI −2.09 to 0.11, p=0.077, I^2=92.9%).[3]

PRP compared with saline

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 2 studies (56 compared with 54 patients) reported lower WOMAC stiffness score for PRP compared with HA, but this was not statistically significantly different (3 studies, UMD −0.09, 95 % CI −0.70 to 0.53, p=0.781, I^2=0).[3]

PRP compared with prolotherapy (PRL)

In the RCT of PRP (n=21) compared with prolotherapy (n=21) in 42 patients with grade 1 or 2 knee OA, mean articular stiffness scores decreased significantly from baseline to 6 months in both groups (PRP from baseline 5.4±1.2 to 2.5±0.8 at 6 months; PRL from baseline 5.2±1.3 to 3.0±0.7 at 6 months). All pairwise comparisons between the 2 groups showed that all differences were not statistically significant.[6]

WOMAC total score, IKDC score and Lequesne score

PRP compared with all control groups

In the systematic review and meta-analysis of 14 RCTs (1,423 patients) that compared the effect of PRP injections with other injections for the treatment of knee OA, PRP significantly improved total WOMAC scores compared with control according to pooled analysis of 6 studies at 3 months follow-up (MD, -14.53, 95% CI, -21.97 to-7.09, I^2=90%, p<0.001), 8 studies at 6 months (MD, -18.21, 95% CI, -27.84 to -8.59, I^2=97%, p<0.001) and 4 studies at 12 months (MD, -19.45, 95% CI, -26.09 to -1^2.82, I^2=85%, p<0.001) respectively.[1]

PRP compared with HA

In the systematic review and meta-analysis of 10 RCTs comparing PRP injections with HA or saline, pooled analysis of 8 studies at 6 months follow-up reported that there was no significant difference between the PRP and HA groups for WOMAC total score, International Knee Documentation Committee [IKDC] score and Lequesne score (standardized mean difference [SMD] 0.68, 95% CI -0.04 to 1.41, p=0.06, I^2=95%). Analysis was based on 4 studies (459 patients) with data on WOMAC total score, 2 studies [n=261 patients] with data on IKDC score and 2 studies (272 patients) with data on Lequesne scores. However at 12 months follow-up, PRP was associated with significantly better WOMAC total score, IKDC score, Lequesne scores, (SMD1.05, 95% CI 0.21-1.89, P = 0.01, I^2=94%) than HA (analysis based on 3 studies [n=302 patients] with data on WOMAC score, 1 study [n=183 patients] with data on IKDC score and 1 study [n=96 patients] with data on Lequesne score). [2]

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 4 studies (284 compared with 268 patients) reported statistically significantly improved WOMAC total scores for PRP compared with HA at a mean less than 1 year follow-up (UMD −15.4, 95 % CI −28.6 to −2.3, p=0.021, I^2=96.6%). The minimal clinically significant improvement was by 12%. PRP was also associated with significantly better IKDC subjective scores (UMD 8.83, 95 % CI 5.88 to 11.78, p<0.001, I^2=90.7%; analysis based on 2 studies [133 compared with 128 patients]). Pooled analysis of 2 studies (137 compared with 135 patients) reported no significant difference in Lequesne scores between PRP and HA (UMD −2.82, 95 % CI −8.01 to 2.38, p=not significant, I^2=97%).[3]

PRP compared with saline

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 2 studies (56 compared with 54 patients) reported lower WOMAC total score for PRP compared with saline placebo but this was not statistically significantly different (UMD -11.44, 95 % CI −32.81 to 9.94, p=0.294, I^2=93.6%).[3]

LP-PRP compared with conventional pharmacological treatment

In the RCT of 65 patients comparing LP-PRP (n=33) with acetaminophen [AC] (n=32) in early knee OA (grade 1-2), the total WOMAC scores significantly reduced in both groups at all follow-up time points (6, 12 and 24 weeks) compared with baseline (LP-PRP group $p<0.001$ and AC group $p<0.05$). The difference between the 2 groups was also statistically significant (total scores at 6, 12 and 24 weeks: LP-PRP group 26.2, 26.3, and 24.0, AC group 12.8, 12.0 and 11.7; all $p<0.05$).[5]

PRP compared with prolotherapy (PRL)

In the RCT of PRP (n=21) compared with prolotherapy (n=21) in 42 patients with grade 1 or 2 knee OA, overall mean WOMAC scores decreased significantly from baseline to 6 months in both groups. All pairwise comparisons in different time periods for both groups were statistically significant. Comparison between the 2 groups showed that differences were statistically significant at 2 months ($p=0.004$) and 6 months follow-up ($p=0.009$).[6]

KOOS score

PRP compared with transcutaneous electric nerve stimulation (TENS) plus exercise

In an RCT comparing PRP with transcutaneous electrical nerve stimulation (TENS) and exercise therapy, mean Knee injury and Osteoarthritis Outcome Scores (KOOS) symptom score improved significantly from baseline to 4 weeks follow-up ($p=0.010$) for PRP compared with TENS, but did not change significantly from week 4 to week 8 between the groups ($p=0.060$). No significant changes were observed in other KOOS subscales (pain, activities of daily living, sports and recreation and quality of life) at 8 weeks follow-up between the groups.[4]

LP-PRP compared with corticosteroid

In an RCT comparing LP-PRP (n=34) with corticosteroid (n=30), improvements between baseline and subsequent follow-ups tended to be greater for PRP for each of the KOSS sub-scales, but these differences were not statistically significant. The differences in the KOOS quality of life sub-score between baseline and 3 and 6 months increased significantly more for PRP compared with the control (mean 17.77 compared with 4.91 at 3 months, and 16.88 compared with 3.56 at 6 months; $p<0.05$ and 0.03 respectively)[7].

Quality of life (QOL assessed using EuroQol-VAS, SF-12)

PRP compared with all control groups

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 2 studies (133 and 128 patients) reported statistically significantly better quality of life for PRP compared with HA (assessed using EuroQol-VAS scores, range from 0 to 100; UMD 7.37, 95% CI 4.43 to 10.05, p = 0.021, I^2=79.9%).[3]

PRP compared with TENS plus exercise

In the RCT comparing PRP with transcutaneous electrical nerve stimulation (TENS) plus exercise therapy, VAS scores for pain improved in both groups at 4 weeks follow-up (p<0.0001) but no significant improvement was reported from week 4 to 8. The pattern of change of VAS scores was not statistically significantly different from baseline to follow-up between the 2 groups (p=0.900). The mean time to feel intolerable pain during treadmill workout increased significantly from baseline to 4 weeks follow-up and remained unchanged till week 8 in the PRP group (p<0.001) but no significant change was found in the TENS group from baseline to end of study (13.9 minutes compared with 12.72 minutes). However, the mean time to feel pain was statistically significantly different between the groups at 4 weeks follow-up (p=0.04).[4]

LP-PRP compared with conventional pharmacological treatment

In the RCT of 65 patients comparing LP-PRP (n=33) with acetaminophen [AC] (n=32) in early knee OA (grade 1-2), significant improvement in quality of life scores (higher SF-12 score) were reported for LP-PRP at 6, 12, and 24 weeks follow-up (p<0.01) in 2 major physical and mental domains. Only mean physical component summary (PCS) scores were significantly different between the LP-PRP group and conventional pharmacological treatment group (p<0.05). The decrease in VAS pain level score in the LP-PRP group was greater than in the pharmacological treatment group (LP-PRP <0.001 compared with AC p<0.01); the most significant difference was reported at 12 weeks (1.9 compared with 4.1, p<0.01).[5]

PRP compared with corticosteroid

In an RCT comparing LP-PRP (n=34) with corticosteroid (n=30), SF-36 scores for various dimensions improved more from baseline to 6 months follow-up in the PRP group than the control group, but the differences were not statistically significant. General health perception score between baseline and 6 months was greater in the PRP than the control group (4.25 compared with 4.92; p = .018)[7].

Safety summary

PRP compared with all control groups

In the systematic review and meta-analysis of 14 RCTs (1,423 patients) that compared the effect of PRP injections with other injections (including saline placebo, hyaluronic acid, ozone, and corticosteroids), pooled analysis of 9 RCTs reported that there was no statistically significant difference in the number of patients with adverse events between PRP and HA (risk ratio [RR] 1.40, 95% CI 0.80 to 2.45, I^2=59%, p=0.24). All adverse events were non-specific, the symptoms including pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia. No severe complications were reported and all the events self-resolved in days.[1]

PRP compared with HA

In the systematic review and meta-analysis of 10 RCTs comparing PRP injections with HA or saline, pooled analysis from 4 studies showed no significant difference in adverse events between PRP and HA (RR 0.63, 95% CI 0.20 to 1.98, I^2=66%, p=0.43).[2]

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 5 studies (290 compared with 289 patients) showed no significant difference between PRP and HA (RR 0.85, 95% CI 0.57 to 1.28, I^2=0%, p=0.91) in adverse events (composite outcomes of injected site pain, infection and other local complications) at a mean follow-up of less than 1 year.[3]

PRP compared with saline

In the systematic review and meta-analysis of 10 RCTs comparing PRP injections with HA or saline, pooled analysis of 2 studies showed no significant difference in adverse events between PRP and saline groups (RR 2.63, 95% CI 0.04 to 158.93, I^2=73%, p=0.64).[2]

In the systematic review and meta-analysis of 9 RCTs comparing PRP injections with HA or saline, pooled analysis of 2 studies (56 compared with 54 patients) showed no significant difference between PRP and saline placebo (RR 6.30, 95% CI 0.34 to 117.48, I^2=36%, p=0.21) in adverse events (composite outcomes of injected site pain, infection and other local complications) at a mean follow-up of less than 1 year.[3]

PRP compared with TENS plus exercise therapy

Mild complications such as swelling and pain was reported in 11% (3/26) of patients in the PRP group and 4% (1/24) of patients in the TENS plus exercise group in the RCT of 54 patients.[4]

LP-PRP compared with conventional pharmacological treatment

Mild pain at injection site that resolved spontaneously after 3 days was reported in the LP-PRP group in the RCT of 65 patients.[5]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed no anecdotal adverse events. They considered that the following were theoretical adverse event: potential risk of infection.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to platelet-rich plasma injections for knee osteoarthritis. The following databases were searched, covering the period from their start to 26.02.2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with osteoarthritis of the knee.
Intervention/test	Platelet-rich plasma injections.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 2,717 patients from 3 systematic reviews[1-3] and meta-analyses and 4 randomised controlled trials (RCTs)[4-7].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are in the appendix.

Table 2 Summary of key efficacy and safety findings on platelet-rich plasma injections for knee osteoarthritis

Study 1 Shen L (2017)

Details

Study type	Systematic review and meta-analysis
Country	China
Search period	Inception to November 2016; Databases searched: PubMed, Embase, Cochrane library, and Scopus. References of prior systematic reviews were also reviewed.
Study population and number	n=**14 Randomised controlled trials (RCTs from 2011-16) (n=1423)** **Platelet Rich Plasma [PRP] injections compared with other injections (including saline placebo, hyaluronic acid[HA], ozone, and corticosteroids) for early or mid-stage knee osteoarthritis [OA]**
Age and sex	Mean age range in studies: PRP group 27.9 to 66 years, control group: 27.5 to 66 years % female: PRP group range 27% to 97%, control group: 30% to 97%
Study selection criteria	Inclusion criteria: all published RCTs comparing the efficacy and/or safety of PRP (or preparations including autologous platelet concentrate, autologous conditioned plasma, and plasma rich in growth factors) in the treatment of knee OA in human compared with control group treated by other intra-articular injections; studies that included patients aged 18 years or older with symptomatic knee OA and had a minimum follow-up of 12 weeks. Exclusion criteria: studies that PRP was used in combination with operations, published abstracts of RCTs without complete data for analysis.
Technique	Intervention: Platelet-rich plasma (PRP) for treatment of knee osteoarthritis (OA) PRP treatment protocols varied among studies in terms of preparation devices, centrifugations, the use of exogenous activators, and the injection regimen of dose, times, and intervals. Control: included saline placebo, HA, ozone, and corticosteroids. Protocols varied.
Follow-up	**Ranged from 12 weeks to 12 months**
Conflict of interest/source of funding	Study was funded by the National Natural Science Foundation of China and Shanghai Youth Science and Technology Start-up. The authors declare that they have no competing interests.

Analysis

Follow-up issues: Follow-up intervals and length varied among studies (12 weeks to 12 months)

Study design issues: this systematic review is comprehensive, based on a large number of RCTs and was performed following PRISMA guidelines. 2 reviewers screened and selected studies and extracted data using a pre-developed data extraction table. In multi-arm trials with more than one PRP treatment group, only the group treated with at least two 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. Although data concerning the patients treated with single-PRP injection in those trials were also extracted, they were not used for quantitative synthesis.

Quality assessment was done using Review Manager 5.3 to determine the risk of bias. 4 studies were considered as moderate risk of bias and 10 as high risk of bias. Nearly half of the studies have performed blinding of participants. Any discrepancy was resolved through panel discussion with a third investigator and correspondence with authors. For studies reporting primary and secondary outcomes (Western Ontario and McMaster Universities Arthritis Index (WOMAC) or adverse events), a random-effects model was used for data synthesis. High heterogeneity among studies was reported.

Study population issues: 2 different radiographic OA grading systems were used: the Kellgren Lawrence grading (0–IV) [40] in 12 studies and the Ahlback scale (I–V) in 2 studies. According to these scales, most participants receiving PRP treatment were at the early or mid-stage of knee OA. The sample size of both PRP and control groups ranged from 12 to 96 patients.

Other issues: authors pooled data on all other types of injections as one control group. There is an overlap of studies with other 2 meta-analysis included in table 2.

Key efficacy and safety findings

Efficacy and Safety
Number of studies analysed: **14 RCTs** (only RCTs that measured WOMAC scores and adverse events were pooled together in this analysis). **Knee pain (forest plots comparing the effect of PRP with control at 3, 6 and 12 months)** PRP treatment was found to improve WOMAC pain sub-scores significantly compared with control [HA or placebo] according to pooled analysis of 3 studies at 3 months follow-up (MD, -3.69, [95% CI, -6.87 to-0.51], I^2=94%, p=0.02), 5 studies at 6 months (MD, -3.82 [95% CI, -6.40 to -1.25], I^2=96%, p=0.004) and 4 studies at 12 months (MD, -3.76, 95% CI, -5.36 to -2.16], I^2=86%, p<0.001) respectively. **Physical function (forest plots comparing the effect of PRP with control at 3, 6 and 12 months)** PRP treatment was found to improve WOMAC physical function sub-scores significantly compared with control according to pooled analysis of 3 studies at 3 months follow-up (MD, -14.24, [95% CI, -23.43 to-5.05], I^2=91%, p=0.002), 5 studies at 6 months (MD, -13.51 [95% CI, -23.77 to -3.26], I^2=97%, p=0.01) and 4 studies at 12 months (MD, -13.96, 95% CI, -18.64 to -9.28], I^2=84%, p<0.001) respectively. **Total WOMAC scores (forest plots comparing the effect of PRP with control at 3, 6 and 12 months)** PRP treatment was found to improve total WOMAC scores significantly compared with control according to pooled analysis of 6 studies at 3 months follow-up (MD, -14.53, [05% CI, -21.97 to-7.09], I^2=90%, p<0.001), 8 studies at 6 months (MD, -18.21 [95% CI, -27.84 to -8.59], I^2=97%, p<0.001) and 4 studies at 12 months (MD, -19.45, 95% CI, -26.09 to -12.82], I2=85%, p<0.001) respectively. **Adverse events (forest plots comparing the effect of PRP with control) (n=9 studies)** There was no statistically significant difference in the number of patients with adverse events between PRP and HA groups (RR 1.40, [95% CI 0.80 to 2.45], I^2=59%, p=0.24). All adverse events were non-specific, the symptoms including pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia. No severe complications were recorded and all the events were self-resolved in days.
Abbreviations used: CI, confidence interval; HA, hyaluronic acid; IV, inverse variance; M-H, Mantel-Haenszel; MD, mean difference; PRP, platelet-rich plasma; RCTs, randomised controlled trials; RR, risk ratio; SD, standard deviation; WOMAC scores, Western Ontario and McMaster Universities Arthritis Index.

Study 2 Dai WL (2017)

Details

Study type	Systematic review and meta-analysis
Country	China
Search period	Inception to April 2016; Databases searched: PubMed, Embase, Cochrane database, and Scopus. Manual check of references of identified articles was also done.
Study population and number	n=**10 randomised controlled trials (RCTs from 2011-16) (with 1069 patients)** **PRP injections [n=562 [612 knees]) compared with HA (n=429 [429 knees]) (8 studies); or saline (n=78 [101 knees]) (3 studies) for early or mid-stage knee osteoarthritis [OA]** sample size ranged from 21 to 183 patients
Age and sex	Mean age range in studies: PRP group 51 to 66 years, control group: 52 to 66 years Percentage of male compared with female patients varied among studies
Study selection criteria	All published RCTs comparing PRP injections with control group (HA or saline); English language studies that included patients aged 18 years or older with symptomatic knee OA and had a minimum follow-up of 12 weeks.
Technique	Intervention: Platelet-rich plasma (PRP) injections. PRP treatment protocols (preparation [use of single compared with double spinning techniques, speed and length of centrifugation, use of an activator] and administration [frequency of injections, volume of injections] varied among studies; 2 studies included more than 1 PRP groups. Control: included saline placebo and HA. Protocols were heterogeneous.
Follow-up	**12 months (in 5 studies), 6 months (in 4 studies) and 3 months (in 1 study)**
Conflict of interest/source of funding	The authors report that they have no conflicts of interest.

Analysis

Follow-up issues: Follow-up intervals and length varied among studies (3 months to 12 months).

Study design issues: the systematic review is based on RCTs and was performed following PRISMA guidelines and Cochrane handbook of systematic reviews for interventions. 2 reviewers screened and selected studies and extracted data using a standardised data extraction form. Any discrepancies were resolved through discussion with a third reviewer and correspondence with authors for missing data. In multi-arm trials with more than one PRP treatment groups, only the group treated with at least two PRP injections was considered as the intervention group. Quality assessment was done using Cochrane risk of bias tool to determine the risk of bias. 2 studies were considered as low risk of bias and 8 as high risk of bias. Nearly half of the studies have performed blinding of participants. For primary and secondary outcomes (Western Ontario and McMaster Universities Arthritis Index (WOMAC) or IKDC score, Lequesne score), the treatment effect was calculated from the difference between the pre-intervention and post-intervention changes in the treatment and control groups. The pooled effect sizes of primary outcomes were compared with their minimum clinically important differences (set at 20% for pain and function scores). Depending on the heterogeneity a fixed effects or random effects model was used. The effect of various factors on the primary outcomes were done in a subgroup analysis.

Study population issues: 2 different radiographic OA grading systems were used: the Kellgren Lawrence grading (0–IV) in 8 studies and the Ahlback scale (I–V) in 2 studies. Substantial heterogeneity (in age, sex, activity level, BMI, and OA grade) was noted among patients included in the meta-analysis.

Other issues: authors pooled data on controls (HA and saline) separately. Majority of the analyses are based on 1 to 3 studies only. There is an overlap of studies with other 2 meta-analysis included in table 2.

Key efficacy and safety findings

Efficacy and Safety

Number of studies analysed: **10 RCTs**

PRP compared with HA

WOMAC pain score (forest plots comparing the effect of PRP with HA at 6 and 12 months) (3 studies)

Pooled analysis of 3 studies (n=339 patients) at 6 months follow-up reported that there was no significant difference between the PRP and HA groups (MD -1.54, 95% CI -4.27 to 1.20, p=0.27, I^2=96%).

Pooled analysis of 3 studies (n=302 patients) at 12 months follow-up reported that PRP was significantly more efficacious in pain relief compared with HA (MD -2.83, 95% CI -4.26 to -1.39, p=0.0001, I^2=79%).

At 6 and 12 months follow-up the overall effect sizes exceeded the MCID [defined as smallest difference perceived as important and beneficial by the patient or clinician) (-0.83 for pain score at 6 months and -0.79 at 12 months).

WOMAC function score (forest plots comparing the effect of PRP with HA at 6 and 12 months) (3 studies)

Pooled analysis of 3 studies (n=339 patients) at 6 months follow-up reported that there was no significant difference between the PRP and HA groups (MD -4.39, 95% CI -10.51 to 1.74, p=0.16, I^2=87%).

Pooled analysis of 3 studies (n=302 patients) at 12 months follow-up reported that PRP was significantly more efficacious in functional improvement compared with HA (MD -12.53, 95% CI -14.58 to -10.47, p<0.00001, I^2=31%).

At 6 and 12 months follow-up the overall effect sizes exceeded the MCID (-02.74 at 6 months and -2.85 at 12 months).

WOMAC total score, IKDC score, and Lequesne score (forest plots comparing the effect of PRP with control at 6 and 12 months)

Pooled analysis of 8 studies (4 studies [n=459 patients] with data on WOMAC total score, 2 studies [n=261 patients] with data on IKDC score and 2 studies [n=272 patients] with data on Lequesne scores) at 6 months follow-up reported that there was no significant difference between the PRP and HA groups (SMD 0.68, 95% CI -0.04 to 1.41, p=0.06, I^2=95%).

Pooled analysis of 6 studies (3 studies [n=302 patients] with data on WOMAC score, 1 study [n=183 patients] with data on IKDC score and 1 study [n=96 patients] with data on Lequesne score) at 12 months follow-up reported that PRP was associated with significantly better outcome compared with HA (SMD -1.05, 95% CI 0.21 to 1.89, p=0.01, I^2=94%).

Adverse events (forest plots comparing the effect of PRP with HA) (n=4 studies)

Pooled analysis showed that there was no significant difference between PRP and HA group (RR 0.63, [95% CI 0.20 to 1.98], I^2=66%, p=0.43).

PRP compared with Saline

WOMAC pain score (forest plots comparing the effect of PRP with saline at 6 and 12 months) (1 study)

1 study (Smith) found a statistically significant difference in the WOMAC pain score in favour of PRP compared with saline at 6 months (MD-5.00, 95% CI -6.98 to-3.02, p<0.00001) and 12 months (MD -6.00, 95% CI -8.32 to -3.68, p<0.00001) post injection. The overall effect sizes exceeded the MCID (-1.4 at 6 months and -1.6 at 12 months).

WOMAC function score (forest plots comparing the effect of PRP with saline at 6 and 12 months) (1 study)

1 study (Smith) found a statistically significant difference in the WOMAC function score in favour of PRP compared with saline at 6 months (MD-24.00, 95% CI -31.30 to-16.70, p<0.00001) and 12 months (MD -24.00, 95% CI -30.01 to -17.99, p<0.00001) post injection. The overall effect sizes exceeded the MCID (-4.8 at 6 months and -5 at 12 months).

Adverse events (forest plots comparing the effect of PRP with saline) (n=2 studies)

Pooled analysis showed that there was no significant difference between PRP and saline groups (RR 2.63, [95% CI 0.04 to 158.93], I^2=73%, p=0.64).
Abbreviations used: CI, confidence interval; HA, hyaluronic acid; IV, inverse variance; IKDC, International Knee Documentation Committee score; MCID, minimally clinically important differences; M-H, Mantel-Haenszel; NA, not applicable PRP, platelet-rich plasma; RCTs, randomised controlled trials; RR, risk ratio; WOMAC scores, Western Ontario and McMaster Universities Arthritis Index.

Study 3 Kanchanatawan W (2016)

Details

Study type	Systematic review and meta-analysis
Country	Thailand
Search period	Inception to August 2015; Databases searched: PubMed, Medline, and Scopus. Manual check of references of identified articles and previous systematic reviews was also done.
Study population and number	n=**9 randomised controlled trials (RCTs)** **PRP injections compared with HA (7 studies); or saline placebo (2 studies) for early or mid-stage knee osteoarthritis [OA]**
Age and sex	Mean age range: 52.7 to 66.4 years; female gender range 37.6 to 93.5 %; BMI range 26 to 30.9 kg/cm^2
Study selection criteria	All published RCTs or quasi experimental designs comparing clinical outcomes between PRP injections with control group (HA or saline or placebo) for primary OA of knee; English language studies, compared at least one of following outcomes: range of motion, adverse events, function score, osteoarthritis indices including WOMAC total score, sub-scores Lequesne scores, IKDC subjective score and EQ-VAS; and had sufficient data to pool and analyse.
Technique	Intervention: Platelet-rich plasma (PRP) injections. PRP treatment protocols ((platelet concentration, leucocytes, activation method and injective protocol)] varied among studies; In all studies mean platelet counts were more than 150,000/microlitre. 4 studies used leucocyte-poor (LP) PRP and 5 studies used leucocyte-rich (LR) PRP. Single spinning was used in 4 studies and double spinning in 5 studies. PRP was injected twice in 3 studies, 3 times in 5 studies and 4 times in 1 study. One study compared single injection and double injection with placebo injection. Control: included saline placebo and HA. Protocols were heterogeneous.
Follow-up	**Mean follow-up varied from 6 to 12 months**
Conflict of interest/source of funding	The authors report that they have no conflicts of interest.

Analysis

Follow-up issues: varied among studies (6 to 12 months).

Study design issues: the systematic review is based on RCTs and was performed following PRISMA guidelines. 2 reviewers screened and selected studies and extracted data using a standardised data extraction form. Any discrepancies were resolved through discussion with a third reviewer. Quality assessment was done to determine the risk of bias. Nearly half of the studies have performed blinding of participants. Relevant clinical outcomes (Western Ontario and McMaster Universities Arthritis Index (WOMAC) or IKDC scores, Lequesne score, EQ-VAS score and adverse events) of PRP injection compared with HA injection or placebo were pooled using an unstandardized mean difference (UMD). Possible causes of heterogeneity and publication bias were explored.

Study population issues: Percentages of patients with osteoarthritis graded by Kellgren–Lawrence (KL) I–II ranged from 50 to 90%.

Other issues: authors pooled data controls (HA and saline) separately. Majority of the analyses are based on only 2 to 3 studies. There is an overlap of studies with the other 2 meta-analysis included in table 2.

Key efficacy and safety findings

Efficacy and Safety
Number of studies analysed: **9 RCTs** **PRP compared with HA** **WOMAC total score** (range 0-96) **(forest plots comparing the effect of PRP with HA) (4 studies [284 compared with 268 patients])** Pooled analysis of 4 studies reported that the PRP group had statistically significantly improved OA symptoms when compared to the HA group. (UMD −15.4, 95 % CI −28.6, −2.3, p = 0.021, I^2=96.6%). The PRP group had a minimal clinically significant improvement in WOMAC total score by 12%. **WOMAC sub-scores for pain stiffness and function score (forest plots comparing the effect of PRP with HA) (3 studies[224 compared with 208 patients])** *(sub-scores for pain 0-20, stiffness 0-8, function 0-68)* Pooled analysis of studies reported lower WOMAC pain (3 studies UMD −1.95, 95 % CI −4.06 to 0.17, p =0.071, I^2 = 90.5%), stiffness (3 studies, UMD −0.99, 95% CI −2.09 to 0.11, p=0.077, I^2 = 92.9%) and function scores (UMD −8.02, 95% CI −17.45 to 1.41, p=0.096, I^2 = 95.8%) in PRP group when compared to HA group, but with no statistically significant difference. **Lequesne score (n=2 studies [137 compared with 135 patients])** *(score for pain 0-10, maximum distance walked 0-6, and activities of daily living 0-8, with total score range 0-24)* Pooled analysis of 2 studies reported that there was no significant difference between PRP and HA group (UMD −2.82, 95 % CI −8.01 to 2.38, p=ns, I^2=97%). **IKDC subjective scores (n=2 studies [133 compared with 128 patients])** *(IKDC form has 3 domains: knee symptoms with 10 items, sports and daily activities with 10 items and knee function with 1 item, score range at 0-100, where 100 means absence of symptoms and limitation for daily activities)* Pooled analysis of 2 studies reported an UMD 8.83, (95 % CI 5.88, 11.78, p < 0.001, I^2 = 90.7 %), indicating that the PRP group had statistically significantly improved activity post-treatment when compared to the HA group. **EuroQol-VAS scores** *(VAS pain intensity scale range from 0 to 100)* **(n=2 studies [133 and 128 patients])** Pooled analysis of 2 studies reported an UMD 7.37 (95 % CI 4.43 to 10.05, p = 0.021, I^2=79.9%) indicating that the PRP group had statistically significantly better quality of life than the HA group. **Adverse events (composite outcomes of injected site pain, infection and other local complications) (forest plots comparing the effect of PRP with HA) (n=5 studies [290 compared with 289 patients])** Pooled analysis showed that there was no significant difference between PRP and HA group (RR 0.85, [95% CI 0.57 to 1.28], I^2=0%, p=0.91). **PRP compared with Saline** **WOMAC total score (forest plots comparing the effect of PRP with saline placebo) (2 studies [56 compared with 54 patients]** Pooled analysis of 2 studies reported lower WOMAC score in PRP group when compared to saline placebo group but not statistically significant different (UMD -11.44, 95 % CI −32.81 to 9.94, p=0.294, I^2 = 93.6 %). **WOMAC sub-scores for pain, stiffness and function (forest plots comparing the effect of PRP with saline placebo) (2 studies [56 compared with 54 patients])** *(sub-scores for pain 0-20, stiffness 0-8, function 0-68)* Pooled analysis of studies reported lower WOMAC pain (3 studies UMD −2.81 (95 % CI −6.47 to 0.84, p=0.132, I2 = 85.5%), stiffness (3 studies, UMD −0.09, 95 % CI −0.70 to 0.53, p=0.781, I^2=0) and function scores (UMD −−8.02, 95 % CI −17.45 to 1.41, p=0.327, I2 = 94.2%) in PRP group when compared to HA group, but with no statistically significant difference. **Adverse events (forest plots comparing the effect of PRP with saline placebo) (n=2 studies [56 compared with 54 patients])**

Pooled analysis showed that there was no significant difference between PRP and saline groups (RR 6.30, [95% CI 0.34 to 117.48], I^2=36%, p=0.21).
Abbreviations used: CI, confidence interval; EuroQol-VAS, EuroQol visual analogue scale; HA, hyaluronic acid; IKDC, International Knee Documentation Committee score; UMD, unstandardized mean difference; MCID, minimally clinically important differences; PRP, platelet-rich plasma; RCTs, randomised controlled trials; RR, risk ratio; WOMAC scores, Western Ontario and McMaster Universities Arthritis Index; WMD, weighted mean difference.

Study 4 Angoorani H (2015)

Details

Study type	Randomised controlled trial
Country	Iran
Recruitment period	Not reported
Study population and number	**n=54 patients with knee osteoarthritis** **Group A (n=26) PRP injections compared with group B (n=24) Transcutaneous electric nerve stimulation [TENS] +exercise therapy**
Age and sex	Mean age PRP 61.59 compared with TENS 62.15 years; female % PRP 92.6% compared with TENS 81.5%
Patient selection criteria	Inclusion criteria: grade 1, 2 and 3 knee osteoarthritis based on Kellgren and Lawrence radiographic scoring system, no history of corticosteroid injection or consumption within past 6 months, no history of peripheral vascular disease, spinal stenosis, severe disabilities, inflammatory and metabolic diseases and lack of history of anti-coagulative drugs consumption or coagulopathies. Exclusion criteria: consumption or intra-articular injection of corticosteroids, anti-coagulative drugs during study and patient request for leaving the study.
Technique	Group A: 2 PRP injections given 4 weeks apart. PRP was prepared by the clinic using PRP kit (Tubex tube) and injected inside the knee and discharged after 30 minutes. NSAIDs and antiplatelet drugs were not allowed before and after 72 hours of injection and paracetamol was given 3 times daily for 72 hours. Group B 10 sessions of TENS (twice a week with a frequency of 100 hertz for 30 minutes in each session) plus specialised exercise program (daily knee resistance and flexibility exercises in 3 sets of 10 repetitions and 1 set of 5 repetitions) given on a CD and in a guide booklet.
Follow-up	**8 weeks**
Conflict of interest/source of funding	No conflicts of interests declared. Study funded by Iran University of Medical Sciences.

Analysis

Follow-up issues: very short-term follow-up.

Study design issues: small randomised clinical trial, randomisation done using a computer derived random chart. Lack of blinding. Clinical outcomes were evaluated using subjective and objective tools (Knee injury and Osteoarthritis Outcome Scores [KOOS] questionnaire, visual analogue scale [VAS] for pain, time to feel intolerable knee pain during workout, and adverse effects) before treatment and at 4 weeks and 8 weeks after treatment. Generalized Estimating Equation (GEE) models were done to examine the associations between type of therapy and change in the KOOS scores, VAS pain scores and time to feel knee pain over time. These models included two main effects (type of therapy and time) and the interaction of these effects.

Study population issues: The baseline characteristics of the two groups were similar. Knee OA was diagnosed by American College of Rheumatology criteria and graded as per Kellgren and Lawrence radiographic scoring system.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **26 PRP compared with 24 TENS + exercise therapy**

KOOS scores*

Variable	Baseline (mean±SD)	Week 4 (mean±SD)	Week 8 (mean±SD)	p value^^
Pain				
PRP	44.9 (3.56)	54.4 (4.15)^	50.7 (3.24)	0.59
TENS + exercise	41.3 (3.43)	46.7 (3.14)^	44.2 (3.88)	
Symptoms				
PRP	51.5 (4.47)	63.6 (4.23)^	61.5 (3.86)	0.047
TENS + exercise	50.3 (3.87)	51.7 (3.56)	52.0 (3.96)	
Activities of daily living				
PRP	48.3 (3.81)	58.7 (4.08)^	54.4 (3.35)	0.44
TENS + exercise	42.4 (4.09)	46.9 (3.68)	44.2 (4.36)	
Sports and recreation				
PRP	23.8 (4.87)	22.9 (4.68)	21.3 (4.33)	0.99
TENS + exercise	28.4 (6.16)	27.6 (6.11)	25.4 (5.31)	
Quality of life				
PRP	17.1 (2.62)	23.0 (3.14)	22.6 (2.49)	0.12
TENS + exercise	20.6 (3.65)	18.4 (2.68)	17.6 (2.58)	

**KOOS consists of five subscales; pain, other symptoms, function in sport and recreation and knee related quality of life. A normalized score (range 0 to 100 with 0 indicating extreme problems and 100 indicating no problem) is calculated for each subscale*. ^p<0.05 for statistical difference from baseline to week 4 within the group. ^^p is for group × time interaction.

VAS pain scores between groups

In both groups significant reductions were observed in VAS pain scores from baseline to 8 weeks follow-up but these were not significantly different (p=0.900). Pain relief was observed in the first month in both groups (both p<0.0001). However, no significant improvement was seen from week 4 to end of follow-up.

Time to feel intolerable pain during workout (walking on a treadmill with a speed of 3km/h and grade 0 till felt intolerable to pain)

	Baseline, mean time (SD)	4 weeks mean time (SD)	8 weeks mean time (SD)
PRP group	10.07 (1.52)	15.86 (1.41) (p<0.001)	17.06 (1.51)
TENS + exercise group	13.09 (2.52)	13.05 (1.84)	12.72 (1.74)

The PRP group in comparison with the TENS group had an additional 5.8 minutes increase in the meantime to feel pain from baseline to week 4 (group × time interaction, p=0.04).

Safety

Pain 11% (3/26) in PRP group and 4% (1/24) in TENS plus exercise group.

Abbreviations used: PRP, platelet rich plasma; SD, standard deviation; TENS, transcutaneous electric nerve stimulation; VAS, visual analogue scale.

Study 5 Simental-Mendia M H (2016)

Details

Study type	Randomised controlled trial
Country	Mexico
Recruitment period	Not reported
Study population and number	**n=65 patients with mild [grade 1-2] knee osteoarthritis [OA]** **Leukocyte poor PRP [LP-PRP] injections (n=33) compared with conventional pharmacological treatment (with acetaminophen [AC]) (n=32)**
Age and sex	Mean age LP-PRP 57.2 years, AC 55.6 years; female LP-PRP 67%, AC 62%
Patient selection criteria	Inclusion criteria: All patients diagnosed with degenerative OA based on clinical and radiological examination, more than 18 years old, pain symptoms or inflammation related to knee OA lasting for at least 3 months, no use of non-steroidal anti-inflammatory drugs [NSAIDS] and radiological signs of grade 1 or 2 knee OA according to the Kellgren-Lawrence classification system. Exclusion criteria: any surgical intervention of the knee, pregnancy, rheumatic disease, herpetological disease, liver disease, severe cardiovascular disease, diabetes coagulopathy, infection, immunodepression, anticoagulant therapy and an Hb value<11 g/dL and platelet value <150,000/mL.
Technique	LP-PRP injections were injected under local anaesthesia and sterile condition using a 22-G needle through the inferolateral approach (45 degree angle) over 6 weeks with 2 injections every 6 weeks. Patients were advised to flex and extend knees after injection for adequate distribution of LP-PRP, use cold therapy for 15 minutes 3 times per day, take adequate rest for 24-48 hours and use of 500 mg of acetaminophen if pain and inflammation develops. Pharmacological treatment group received acetaminophen with a dosage of 500 mg every 8 hours for 6 weeks. No other medication was allowed during this period.
Follow-up	**24 weeks**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: short-term follow-up.

Study design issues: small randomised clinical trial with adequate sample size, method of randomisation not described. Clinical outcomes pain, knee function, stiffness and quality of life were assessed using VAS, WOMAC and Spanish version of the Short-Form [SF] 12.

Study population issues: The baseline demographic characteristics of the two groups were similar. Knee OA was graded as per Kellgren and Lawrence radiographic scoring system. 23 patients had grade I and 42 had grade II knee OA. In patients with bilateral knee OA only the knee that had more significant symptoms was considered.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **33 LP-PRP compared with 32 conventional pharmacological treatment with AC**

VAS score (mean±SD)

	LP-PRP	AC	P value
Baseline	4.9±2.4	5.9±2.2	>0.05
6 weeks	1.9 (p<0.01)	3.9 (p<0.01)	<0.05
12 weeks	1.9±1.6 (p<0.001)	4.1±2.6 (p<0.05)	<0.01
24 weeks	2.1 (p<0.001)	3.9 (p<0.01)	NR

WOMAC score (mean±SD)

	LP-PRP	AC	P value
Mean total WOMAC score			
Baseline	37	37	
6 weeks	12.8±11.0 (p<0.001)	26.2±16.0 (p<0.05)	<0.01
12 weeks	12.0±10.6 (p<0.001)	26.3±17.8 (p<0.05)	<0.01
24 weeks	11.7±10.0 (p<0.001)	24.0±18.6 (p<0.05)	<0.01
Pain sub-score			
Baseline	8	8	
6 weeks	3.1±2.6	5.8±2.9	<0.05
12 weeks	2.7±2.4	5.7±3.9	<0.05
Stiffness			
Baseline	3	3	
6 weeks	NS	1 (p<0.001)	NS
12 weeks	NS	1 (p<0.001)	NS
24 weeks	NS	1 (<0.001)	NS
Functional capacity sub-score			
Baseline	26	26	
6 weeks	8.7±8.0	18.2±12.0	<0.05
12 weeks	8.3±7.3	18.3±12.7	<0.05
24 weeks	7.9±7.7	16.7±13.3	<0.01

Quality of life (assessed using SF-12) (mean±SD)

	LP-PRP	AC	P value
Mental component summary			
Baseline	44.2±11.8	50	
6 weeks	55.4±8.7 (p<0.001)	49	NS
12 weeks	55.9±7.9 (p<0.001)	50	NS
24 weeks	54.3±7.6 (p<0.001)	51	NS
Physical component summary			
Baseline	38.0±8.0	39	
6 weeks	47.6±7.9 (p<0.001)	40	<0.05
12 weeks	48.8±7.9 (p<0.001)	41	<0.05
24 weeks	49.9±8.1 (p<0.001)	41	<0.05

In the LP-PRP group all components of quality of life score except for general health improved at 24 week follow-up compared with baseline values (at least p<0.05).

Safety

Mild pain in the injection site for 3 days, resolved spontaneously.

Abbreviations used: AC, acetaminophen; LP-PRP, leukocyte poor-platelet rich plasma; NR, not reported; NS, not significant; SF-12, short-form 12.

Study 6 Rahimzadeh P (2018)

Details

Study type	Randomised controlled trial
Country	Iran
Recruitment period	Not reported
Study population and number	**n=42 patients with mild [grade 1-2] knee osteoarthritis [OA]** **PRP injections (n=21) compared with prolotherapy [PRL] (n=21)**
Age and sex	Mean age LP-PRP 57.2 years, AC 55.6 years; female LP-PRP 67%, AC 62%
Patient selection criteria	Inclusion criteria: age range 40–70 and stage 1 or 2 OA (based on the Kellgren–Lawrence scale of the Radiological Society of America). Exclusion criteria: rheumatoid arthritis or haemophilia, previous history of knee surgery, drug or alcohol addiction, and use of anticoagulant or nonsteroidal anti-inflammatory drugs (NSAIDs) in the previous 7 days.
Technique	PRP group: ultrasound-guided knee injection (7 mL PRP solution prepared using Standard kit) PRL group: ultrasound-guided knee injection of an irritant solution into a damaged zone (7 mL 25% hypertonic dextrose) Both injections were done under local anaesthesia and sterile condition using 22 G needle via the in-plane technique. Patients were discharged after an hour and the same procedures were repeated 1 month later for all. Paracetamol was given for post-procedural pain.
Follow-up	**24 weeks**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: short-term follow-up.

Study design issues: small randomised double blind clinical trial, block randomisation (block size of 4) was used to assign patients to groups. Clinical outcomes pain, knee function, were assessed using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) immediately after injection, at 1 month, 2 months and 6 months.

Study population issues: The baseline demographic and baseline characteristics of the two groups were similar. Knee OA was graded as per Kellgren and Lawrence radiographic scoring system.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 21 PRP compared with 21 PRL
WOMAC scores (mean±SD)
<table>
<tr><th>WOMAC scores</th><th>Group</th><th>Baseline</th><th>1 month</th><th>2 months</th><th>6 months</th></tr>
<tr><td>Pain sub-score</td><td>PRP</td><td>14.8±1.5</td><td>9.2±2.7</td><td>5.4±1.8</td><td>6.2±2.1</td></tr>
<tr><td></td><td>PRL</td><td>14.6±1.4</td><td>9.5±2.3</td><td>7.1±1.7</td><td>8±1.6</td></tr>
<tr><td>P value between group</td><td></td><td>0.76</td><td>0.71</td><td>0.002</td><td>0.003</td></tr>
<tr><td>Function sub-score</td><td>PRP</td><td>47.8±4.7</td><td>30.3±7.6</td><td>19.6±7.2</td><td>22.8±7.9</td></tr>
<tr><td></td><td>PRL</td><td>47.3±6.7</td><td>31±6.3</td><td>25±5.5</td><td>27.8±5.2</td></tr>
<tr><td>P value between group</td><td></td><td>0.81</td><td>0.74</td><td>0.009</td><td>0.021</td></tr>
<tr><td>Stiffness</td><td>PRP</td><td>5.4±1.2</td><td>3.3±1.1</td><td>2.1±0.7</td><td>2.5±0.8</td></tr>
<tr><td></td><td>PRL</td><td>5.2±1.3</td><td>3.2±1.1</td><td>2.6±0.7</td><td>3±0.7</td></tr>
<tr><td>P value between group</td><td></td><td>0.73</td><td>0.65</td><td>0.055</td><td>0.091</td></tr>
<tr><td>Total WOMAC score</td><td>PRP</td><td>67.9±7.3</td><td>42.9±10.85</td><td>27.1±9.1</td><td>31.4±10.2</td></tr>
<tr><td></td><td>PRL</td><td>67.1±7.9</td><td>43.8±8.2</td><td>34.8±6.9</td><td>38.7±6.6</td></tr>
<tr><td>P value between group</td><td></td><td>0.74</td><td>0.77</td><td>0.004</td><td>0.009</td></tr>
</table>
All pairwise comparisons for WOMAC and its subscales in different time periods for both groups were statistically significant. In addition the mixed model ANOVA and the main effect of time and interaction of time with treatment group was statistically significant.</td><td>No significant side effects were observed.</td></tr>
<tr><td colspan="2">Abbreviations used: PRP, platelet rich plasma; PRL, prolotherapy.</td></tr>
</table>

Study 7 Jubert JN (2017)

Details

Study type	Randomised controlled trial
Country	Spain
Recruitment period	2013-14
Study population and number	**n=64 patients with symptomatic knee osteoarthritis [OA] (Kellgren-Lawrence grade 3 to 4)** **Leukocyte reduced PRP [LR-PRP] injections (n=34) compared with corticosteroid [CS] (n=30)**
Age and sex	Mean age LR-PRP 65 years, CS 68 years; female LR-PRP 66%, CS 67%
Patient selection criteria	Inclusion criteria: Age 40-80 years, knee osteoarthritis as diagnosed by American College of Rheumatology, eligibility for total knee arthroplasty, walking ability with or without external support, visual analog scale baseline value more than 60. Exclusion criteria: received intra-articular injections of steroids, anaesthetics, or hyaluronic acid in the past year, underwent arthroscopic surgery in the past 3 months ,received open surgery, compromised bone metabolism, fibromyalgia, chronic fatigue syndrome, liver disease, clotting deficiency, thrombocytopenia (<150,000 platelets per mm^3, haemoglobin (<11 g/dL), treated with anticoagulants, infection, cancer, rheumatoid arthritis, limited knee range of movement, ligamentous instability of the knee joint, damage to hip or knee, deformity, allergic to steroids or blood products, neuromuscular disease, cardiovascular disease, inflammatory diseases of the connective tissue.
Technique	PRP group: single LR-PRP injection of 4 mL autologous PRP prepared using double spinning method) Exogenous factors were not used for activation process. CS group: single shot of corticosteroid injection (2 mL betamethasone: 6 mg betamethasone sodium phosphate and betamethasone acetate 6 mg [Merck] and 2 mL bupivacaine 0.25% [B.Braun]). Injected under aseptic conditions into the medial compartment with an intramuscular needle without local anaesthetic, with knees hanging at 90 degrees of flexion. All patients were allowed to use painkillers and nonsteroidal anti-inflammatory drugs during the study period.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: short-term follow-up.

Study design issues: small prospective randomized, double-blind (both treatments were given by same person and opaque syringes were used), parallel group, active-controlled study, sample size was calculated. Primary outcome was visual analog scale assessment at 1 month. Secondary outcomes were the Knee injury and Osteoarthritis Outcome Score (KOOS) and Short Form–36 (SF-36) at 1, 3, and 6 months after treatment.

Study population issues: The baseline demographic characteristics of the two groups were similar. The 2 groups did not differ in any of the qualitative variables collected at baseline except for OA grade and SF-36 general health perception subscale, which were worse for the PRP group. Patients had late stage of OA and were waiting for knee replacement.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **34 PRP compared with 30 CS**

No differences were found in the use of painkillers and nonsteroidal anti-inflammatories or dose or frequency between groups at any time point.

Patient satisfaction at 6 months

Patient satisfaction	PRP group %	Control (CS) group %
Very good	52.94	46.67
Good	20.59	10
Regular	8.82	16.67
Poor	17.65	26.67

VAS score

	PRP group (mean ±SD)	Control (CS) group (mean ±SD)	P value
Baseline	75.14±10.11	75.00±9.38	0.95
1 month	35.88±24.63	31.67±22.14	0.50
3 months	33.38±22.59	41.00±26.95	0.22
6 months	38.24±24.80	46.33±29.88	0.29

KOOS outcomes

KOOS subscale	PRP group (mean ±SD)	Control (CS) group (mean ±SD)	P value
Pain			
Baseline	35.11±17.94	38.80±18.99	0.43
1 month	48.28 ± 21.61	54.21 ± 24.94	0.31
3 months	55.63 ± 23.71	55.14 ± 21.06	0.93
6 months	53.09 ± 22.15	49.52 ± 23.70	0.55
Symptoms			
Baseline	45.41 ± 12.45	47.98 ± 15.35	0.46
1 month	50.17 ± 11.19	52.17 ± 14.22	0.21
3 months	53.49 ± 14.06	55.30 ± 15.31	0.62
6 months	50.92 ± 12.81	54.86 ± 12.08	0.23
Activities of daily living			
Baseline	36.05 ± 18.58	37.22 ± 17.83	0.80
1 month	48.86 ± 21.39	51.90 ± 23.86	0.59
3 months	55.21 ± 26.02	52.32 ± 20.05	0.62
6 months	56.14 ± 21.70	46.75 ± 24.90	0.12
Sport and recreation			
Baseline	10.16 ± 14.89	15.62 ± 14.10	0.07
1 month	18.75 ± 21.84	29.61 ± 24.36	0.04
3 months	24.72 ± 24.54	25.19 ± 23.10	0.83
6 months	25.78 ± 24.23	22.92 ± 22.20	0.68
Quality of life			
Baseline	16.36 ± 15.00	20.91 ± 17.30	0.30
1 month	25.61 ± 17.59	29.65 ± 21.90	0.45

Safety

No patient had adverse effects at injection or follow-up.

3 months	33.52 ± 24.93	24.35 ± 16.31	0.21
6 months	33.96 ± 23.37	23.92 ± 23.73	0.08

SF-36 scores

SF-36 subscale	**PRP group (mean ±SD)**	**Control (CS) group (mean ±SD)**	P value
Physical functioning			
Baseline	32.91 ± 19.38	30.15 ± 20.65	0.58
3 months	42.37 ± 24.30	39.03 ± 20.88	0.56
6 months	41.27 ± 22.47	34.17 ± 21.01	0.21
Physical role functioning			
Baseline	17.83 ± 10.22	18.10 ± 9.50	0.97
3 months	16.10 ± 10.83	15.95 ± 11.28	0.96
6 months	17.29 ± 8.94	17.08 ± 9.56	0.97
Bodily pain			
Baseline	30.65 ± 17.76	34.87 ± 27.65	0.85
3 months	39.68 ± 25.65	39.04 ± 23.08	0.92
6 months	38.10 ± 19.40	34.10 ± 23.79	0.47
General health perception			
Baseline	37.12 ± 15.12	46.35 ± 18.58	0.03
3 months	39.04 ± 13.41	45.71 ± 20.12	0.12
6 months	41.37 ± 14.66	41.43 ± 21.27	0.99
Vitality			
Baseline	38.97 ± 23.86	40.69 ± 23.37	0.41
3 months	42.71 ± 21.89	41.96 ± 23.82	0.90
6 months	41.04 ± 19.27	36.67 ± 26.62	0.47
Social role functioning			
Baseline	66.67 ± 25.90	61.25 ± 26.94	0.42
3 months	66.91 ± 34.53	68.97 ± 26.65	0.83
6 months	61.29 ± 33.60	57.50 ± 33.41	0.66
Emotional role functioning			
Baseline	11.87 ± 11.42	12.22 ± 11.93	0.90
3 months	12.50 ± 12.01	13.69 ± 12.26	0.70
6 months	13.98 ± 11.86	13.89 ± 12.44	0.98
Mental health			
Baseline	54.43 ± 20.50	52.85 ± 19.05	0.76
3 months	55.32 ± 23.49	55.77 ± 22.29	0.94
6 months	52.23 ± 22.52	45.63 ± 5.41	0.31
Physical health component			
Baseline	-1.88 ± 0.40	-1.82 ± 0.66	0.76
3 months	-1.66 ± 0.58	-1.55 ± 0.62	0.51
6 months	-1.56 ± 0.53	-1.65 ± 0.58	0.53
Mental health component			
Baseline	-1.59 ± 0.69	-1.60 ± 0.79	0.95
3 months	-1.62 ± 0.83	-1.51 ± 0.92	0.64
6 months	-1.75 ± 0.79	-1.98 ± 1.04	0.37

Abbreviations used: PRP, platelet rich plasma; CS, corticosteroid; KOOS, Knee injury and Osteoarthritis Outcome Score; SF-36, short form-36; SD, standard deviation; VAS, visual analog scale.

Validity and generalisability of the studies

- Large systematic reviews and meta-analysis (with small number of randomised controlled trials [RCTs] and non-RCTs) included in this overview have concluded that intra-articular knee injection of PRP is safe and effective but more high quality RCTs are still needed. Evidence was mainly by pooling the results of 2 to 5 RCTs which reported WOMAC scores.
- Majority of the comparative studies included in the analyses compared the efficacy of PRP injections with hyaluronic acid (NICE clinical guideline 177 has stated that hyaluronic acid should not be used to treat OA).
- Control interventions in other randomised controlled trials consisted primarily of corticosteroids, saline placebo, TENS combined with exercise therapy, prolotherapy and conventional pharmacological treatment.
- Few RCTs reported favourable outcomes of PRP injections for treatment of Knee OA in terms of pain relief and self-reported functional improvement in the short-term (at 3 to 12 months follow-up) compared with other injections. Long term clinical effectiveness is unknown.
- Outcomes measures of self-reported pain relief and knee function are subjective and may be confounded by various factors.
- All studies were limited to patients who were at the early or mid-stage of knee OA and had no previous intra-articular therapy.
- There was high heterogeneity across studies in terms of PRP treatment protocols (harvesting and preparation [use of single compared with double spinning techniques, speed and length of centrifugation, use of an activator] and administration [frequency/number of injections, volume of injections, interval between injections]).

Existing assessments of this procedure

The Australian Health Policy Advisory Committee on Technology (HealthPACT) published a technology brief on platelet-rich plasma for the treatment of knee osteoarthritis, in August 2013. This document summarised platelet-rich plasma preparation methods and outlined the efficacy and safety profile of the procedure.

HealthPACT stated that there was insufficient evidence to support the use of platelet-rich plasma injections for patients with osteoarthritis of the knee in routine clinical practice. Furthermore, they recommended that further research was desirable, particularly assessing pain, mobility and pharmaceutical usage in patients who had received repeat platelet-rich plasma injections over longer follow-up periods[8].

NICE clinical guideline on Osteoarthritis: the care and management of osteoarthritis in adults recommends that

Intra-articular injections

1.5.12 Intra-articular corticosteroid injections should be considered as an adjunct to core treatments for the relief of moderate to severe pain in people with osteoarthritis. **[2008][9]**

1.5.13 Do not offer intra-articular hyaluronan injections for the management of osteoarthritis. **[2014][10].**

There are no recommendations on PRP injections in this guideline.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Autologous blood injection for tendinopathy. NICE interventional procedure guidance 438 (2013). Available from http://guidance.nice.org.uk/IPG438
- Autologous blood injection for plantar fasciitis. NICE interventional procedure guidance 437 (2013). Available from http://guidance.nice.org.uk/IPG437

NICE guidelines

- Osteoarthritis: the care and management of osteoarthritis in adults. NICE clinical guideline 177 (2014). Available from http://guidance.nice.org.uk/cg177

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public

consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Specialist Advisor Questionnaires for platelet-rich plasma injections for osteoarthritis of the knee were submitted and can be found on the NICE website

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Ongoing studies
  - ChiCTR-TRC-14004351 Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma for knee osteoarthritis: a randomized controlled trial (recruiting)
  - ChiCTR-OIC-17010625: Intra-articular and extra-articular Platelet Rich Plasma injections for knee osteoarthritis: a pilot single arm feasibility study (recruiting)
  - IRCT2015070210599N4: Comparison of intra-articular injection of platelet rich plasma (PRP) compared with combined PRP/somatropin on pain and joint range of motion in patients with knee osteoarthritis (recruiting)
  - EUCTR2015-004738-90-ES Efficacy, safety and systemic effect of intra-articular and intraosseous infiltrations of Platelet Rich Plasma in patients with knee osteoarthritis: Randomized Clinical Trial (authorised recruitment)
  - JPRN-UMIN000016585:The Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: a double-blind randomized trial (enrolling)

- JPRN-UMIN000028688: Clinical study on the tissue repair ability and pain improvement effect of PRP on osteoarthritis (not yet recruiting)
- ACTRN12617001162303: Assessment of blood injections (Platelet Rich Plasma) on symptomatic early worn out knees. (not yet recruiting)
- ACTRN12617000853347: Platelet rich plasma for knee osteoarthritis - the RESTORE trial (recruiting)
- CTRI/2017/04/008406: EFFECTIVENESS OF SINGLE DOSE COMPARED WITH MULTIDOSE INTRA ARTICULAR INJECTION OF PLATELET RICH PLASMA IN EARLY OSTEOARTHRITIS OF KNEE - A RANDOMISED CONTROL SINGLE BLIND TRIAL (not yet recruiting)
- NCT02923310: Evaluation of Two Types of PRP in Knee Osteoarthritis (recruiting).
- NCT02135367: Platelet-rich Plasma (PRP) vs Viscosupplementation for the Treatment of Early Knee Articular Degenerative Pathology: a Randomized Double-blind Controlled Trial (ongoing)
- NCT02964143: Prospective, Randomized, Controlled Clinical Investigation to Compare the Safety and Performance of a Combination of Autologous Platelet-rich Plasma (PRP) and Hyaluronic Acid Prepared With Cellular MatrixTM to Those of Ostenil® Plus and to Those of PRP Alone in the Treatment of Mild to Moderate Osteoarthritis of the Knee (recruiting)
- NCT03117608: A SINGLE-BLIND, RANDOMIZED, CONTROLLED STUDY OF A SINGLE, INTRA-ARTICULAR INJECTION OF AUTOLOGOUS MICRO-FRAGMENTED ADIPOSE TISSUE (aMAT) COMPARED WITH (VS) PRP IN PATIENTS WITH OSTEOARTHRITIS (OA) OF THE KNEE (recruiting)
- NCT02776514: Intraarticular Injections of Steroids, Hyaluronic Acid or Platelet Rich Plasma Compared with Placebo for the Knee Osteoarthritis (recruiting)

- NCT02370420: Intra-Articular Injections of Platelet-Rich Plasma in Knee Osteoarthritis: Unique Application Compared with Triple Application (unknown)
- NCT03290365: The Combination Long-term Effect of Platelet-rich Plasma and Hyaluronic Acid in Patients With Knee Osteoarthritis: a Prospective Randomized Double-blind Controlled Trial (recruiting)
- NCT03197441: Intraoperative Platelet Rich Plasma Injection in Arthroscopic Surgery for Osteoarthritis of the Knee (recruiting)
- NCT03271229: A Randomized, Single-Blinded, Controlled Trial Comparing Conventional Platelet Rich Plasma (PRP) to Concentrated Bone Marrow Aspirate (BMAC) for Osteoarthritis of the Knee (recruiting)
- NCT03289416: Efficacy of Bone Marrow Aspirate Concentrate Compared With Platelet Rich Plasma for the Treatment of Symptomatic Knee Osteoarthritis: A Randomized, Controlled Clinical Trial (recruiting)
- NCT03326544: Ultra-sound Guided Saphenous Nerve Block Compared with Platelet Rich Plasma for Chronic Knee Joint Osteoarthritis (enrolling participants)
- NCT03211650: Efficacy of Intra-articular Injection of Combined Hyaluronic Acid and Platelet-rich Plasma in Knee Degenerative Joint Disease (recruiting)
- NCT01697423: Comparative Assessment of Intra-articular Knee Injections of Platelet-rich Plasma (PRP) and Hyaluronic Acid in the Treatment of Knee Osteoarthritis (recruiting)

References

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3. Kanchanatawan W, Arirachakaran A et al (2016). Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 24: 1665-1677.
4. Angoorani H, Mazaherinezhad et al (2015). Treatment of knee osteoarthritis with platelet-rich plasma in comparison with transcutaneous electrical nerve stimulation plus exercise: a randomized clinical trial. Medical Journal of the Islamic Republic of Iran (MJIRI). 29:223.
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10. Osteoarthritis: the care and management of osteoarthritis in adults. NICE clinical guideline 177 (2014). Available from http://guidance.nice.org.uk/cg177

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Aydogan NH, Gul D et al (2016). The Clinical Effect of Platelet–Rich Plasma Prepared Through Different Activation Methods on Patients with Knee Osteoarthritis. Clin Anal Med;7(6): 767-71	Comparative study N=51 (76 knees) randomly selected to 2 groups Group 1, PRP activated by adding calcium chloride. Group 2, PRP activated by keeping the solution at -70° for 24 hours and immersed in water at 37o C for 5 minutes for complete dissolution. Then PRP was applied.	VAS and WOMAC pain scores were significantly higher at baseline compared to the results obtained at the 2nd, 6th and 12th months (p=0.06). A gradual downward tendency was seen in both scores, even though no significant difference was found between the groups after 2nd, 6th and 12th months. Patients received some clinical benefits from both activation methods. There is no significant difference between activating PRP by CaCl or -70°C which com-pared in terms of clinical benefits. Therefore, blood storage at -70ºC may be preferred primary due to no need for additional material such as CaCl.	Different activation methods of Platelet Rich Plasma.
Bennell KL, Hunter DJ et al (2017). Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. Current Rheumatology Reports 19:24.	Narrative review With focus on RCT evidence. 15 RCTs in knee OA, and 3 RCTs in hip OA.	All studies are of low to moderate methodological quality and use variable PRP protocols. Results showed that PRP is a safe treatment with potential to provide symptomatic benefit for OA at least in the short term (up to 12 months). Younger patients with less severe disease may be more responsive. There are no RCTs investigating the effects of PRP on OA structural changes. No definitive conclusions can be made about the effects of PRP in OA given methodological concerns and considerable heterogeneity between studies. Further high-quality research is needed to establish the clinical and cost-effectiveness of PRP, the patients most likely to benefit and the optimal PRP protocol.	More comprehensive systematic reviews included in table 2.
Bottegoni C, Dei Giudici L et al (2016). Homologous platelet-rich plasma for the treatment of knee osteoarthritis in selected elderly patients: an open-label, uncontrolled, pilot study. Ther Adv Musculoskel Dis 8(2) 35–41	N=60 elderly patients with early or moderate knee osteoarthritis injected with 5ml homologous PRP intraarticular injections every 14 days for a total of three injections. Follow-up: 6 months	No severe complications were noted during the treatment and the follow-up period. A statistically significant improvement from basal evaluation to the 2-month follow-up visit was observed, whereas a statistically significant worsening from the 2-month to the 6-month follow-up visit was showed. The overall worst results were observed in patients aged 80 years or over and in those affected by minor bone attrition. It was found that 90% of patients were satisfied at the 6-month evaluation.	Pilot study on homologous PRP.

Campbell KA, Erickson BJ et al (2015). Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 31 (10): 2036-45	14 meta-analyses (n=20,049) comparing treatment of knee osteoarthritis (OA) with intra-articular viscosupplementation (intra-articular hyaluronic acid [IA-HA, n=13,698]) compared with NSAIDs (n=355), IA-corticosteroids (n=294), intra-articular platelet-rich plasma (IA-PRP), or IA-placebo(n=5702)	Regarding IA-HA compared with IA-PRP, IA-HA improved knee function at 2 and 6 months after injection but the effects were less robust than those of IA-PRP. This systematic review of overlapping meta-analyses comparing IA-HA with other nonoperative treatment modalities for knee OA shows that the current highest level of evidence suggests that IA-HA is a viable option for knee OA. Its use results in improvements in knee pain and function that can persist for up to 26 weeks. IA-HA has a good safety profile, and its use should be considered in patients with early knee OA.	More comprehensive reviews on PRP included in table 2.
Campbell KA, Saltzman BM et al (2015). Does Intra-articular PRP Injection Provide Clinically Superior Outcomes Compared With Other Therapies in the Treatment of Knee Osteoarthritis? A Systematic Review of Overlapping Meta-analyses.	Systematic review of meta-analyses on PRP for treatment of knee joint cartilage degenerative pathology. 3 meta-analyses included (Khoshbin 2013, Chang 2014, Laudy 2015) PRP compared with control HA or placebo	Use of PRP led to significant improvements in patient outcomes at 6 months after injection, and these improvements were seen starting at 2 months and were maintained for up to 12 months. It is unclear if the use of multiple PRP injections, the double-spinning technique, or activating agents leads to better outcomes. Patients with less radiographic evidence of arthritis benefit more from PRP treatment. The use of multiple PRP injections may increase the risk of self-limited local adverse reactions. After application of the Jadad algorithm, 3 concordant high-quality meta-analyses were selected and all showed that IA-PRP provided clinically relevant improvements in pain and function compared with the control treatment.	More recent and comprehensive systematic reviews included in table 2.
Calis HT, Tomruk Sutbeyaz S et al (2015). Efficacy of Intra-Articular Autologous Platelet Rich Plasma Application in Knee Osteoarthritis. Arch Rheumatol 30(3):198-205.	Case series N=82 patients with grade 3-4 knee OA IA-PRP injections Follow-up: 6 months	Compared to values before treatment, patients' visual analog scale values were significantly decreased at third and sixth months after treatment ($p<0.001$). Western Ontario and McMaster Universities Osteoarthritis Index values improved significantly ($p<0.001$). Results of six-minute walk test improved at third and sixth months ($p<0.05$). Cartilage thicknesses increased significantly at third and sixth months ($p<0.05$).	Large and longer follow-up studies included in table 2.

Chahla J, Piuzzi NS et la (2016). Intra-Articular Cellular Therapy for Osteoarthritis and Focal Cartilage Defects of the Knee: A Systematic Review of the Literature and Study Quality Analysis. The Journal of Bone and Joint Surgery 98(18):1511-1521	Systematic review N=6 studies 3 studies were on treatment of osteoarthritis (PRP, HTO, MSC) and 3 were on treatment of focal cartilage defects (4 RCTs, 1 prospective cohort study, and 1 retrospective therapeutic case-control study)	124 knees 9oa). Mean follow-up: 21 months The studies of intra-articular cellular therapy injections for osteoarthritis and focal cartilage defects in the human knee suggested positive results with respect to clinical improvement and safety. However, the improvement was modest and a placebo effect cannot be disregarded. The overall quality of the literature was poor, and the methodological quality was fair, even among Level-II and III studies Intra-Articular Cellular Therapy for... (PDF Download Available). Available from: https://www.researchgate.net/publication/308486541_Intra-Articular_Cellular_Therapy_for_Osteoarthritis_and_Focal_Cartilage_Defects_of_the_Knee_A_Systematic_Review_of_the_Literature_and_Study_Quality_Analysis [accessed May 17 2018].	More comprehensive reviews included in table 2.
Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS (2013) Comparative Effectiveness of Platelet-Rich Plasma Injections for Treating Knee Joint Cartilage Degenerative Pathology: A Systematic Review and Meta-Analysis. Archives of Physical Medicine and Rehabilitation. 95(3):562-575	Systematic review N=16 studies [1543 patients] 5 RCTs, 3 quasi-experimental studies and 8 prospective case series. Effect size of PRP treatment from different outcome measurements at 2, 6, and 12 follow-up.	PRP injections in patients with knee degenerative pathology showed continual efficacy for 12 months compared with their pretreatment condition. The effectiveness of PRP was likely better and more prolonged than that of HA. Injection doses ≤2, the use of a single-spinning approach, and lack of additional activators led to an uncertainty in the treatment effects. Patients with lower degrees of cartilage degeneration achieved superior outcomes as opposed to those affected by advanced osteoarthritis	Comprehensive and updated systematic review and meta-analysis included in table 2.

Chen CPC, Cheng CH et al (2017). The influence of platelet rich plasma on synovial fluid volumes, protein concentrations, and severity of pain in patients with knee osteoarthritis. Experimental Gerontology 93, vol, 68-72	N=24 elederly patients with minor to moderate knee OA combined with supra-patellar bursitis treated with 3 monthly PRP injections and evaluated using proteomic approach and clinical evaluation. Follow-up: 3 months	Approximately after the 2nd PRP injection, significant decreases in SF total protein concentrations, volumes, and Lequesne index values were observed. SF proteins associated with chelation and anti-aging physiological functions such as matrilin, transthyretin, and complement 5 increased at least 2-fold in concentrations. Proteins associated with inflammation, such as apolipoprotein A-I, haptoglobin, immunoglobulin kappa chain, transferrin, and matrix metalloproteinase decreased at least 2-fold in concentrations. Therefore, at least two monthly PRP injections may be beneficial for treating patients with minor to moderate knee OA combined with supra-patellar bursitis.	Experimental study assessing proteins concentrations.
Cole BJ, Karas V et al (2016). Hyaluronic acid compared with platelet-rich plasma. A prospective, double blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of Knee osteoarthritis. The American Journal of Sports MEDICINE 45 (2), 339-346.	RCT N=111 patents with symotomatic unilateral knee OA received a series of leukocyte poor PRP (n=49) or HA (n=50) injections. Follow-up 24 weeks	No difference was seen between the groups in WOMAC pain score. A significantly higher IKDC score was seen in the PRP group compared with the HA group at 24 weeks (mean ± standard error [SE], 65.5 ± 3.6 vs 55.8 ± 3.8, respectively; P = .013) and at final follow-up (52 weeks) (57.6 ± 3.37 vs 46.6 ± 3.76, respectively; P = .003). Linear contrasts also identified a statistically lower VAS score in the PRP group compared with the HA group at 24 weeks (mean ± SE, 34.6 ± 3.24 vs 48.6 ± 3.7, respectively; P = .0096) and 52 weeks (44 ± 4.6 vs 57.3 ± 3.8, respectively; P = .0039). An examination of fixed effects showed that patients with mild OA and a lower body mass index had a statistically significant improvement in outcomes. In the biochemical analysis, differences between groups approached significance for interleukin-1β (mean ± SE, 0.14 ± 0.05 pg/mL [PRP] vs 0.34 ± 0.16 pg/mL [HA]; P = .06) and tumor necrosis factor α (0.08 ± 0.01 pg/mL [PRP] vs 0.2 ± 0.18 pg/mL [HA]; P = .068) at 12-week follow-up	Large studies with longer follow-up included in table 2.

Dernek B, Kesiktas FN et al 92017). Effect of platelet concentration on clinical improvement in treatment of early stage-knee osteoarthritis with platelet-rich plasma concentrations. J. Phys. Ther. Sci. 29: 896–901.	Retrospective comparative study N= patients with knee osteoarthritis Group I received platelet-rich plasma kit I, and Group II received platelet-rich plasma kit II. Each injected twice with a one-month interval between injections. Follow-up 6 months	Kits I and II contained 1,000,000 and 3,000,000 platelets/µl respectively. In both groups, initial Western Ontario and McMaster Universities Osteoarthritis Index and Visual Analog Scale scores were significantly higher compared to the latter evaluations. However, no significant difference was observed between groups in terms of clinical evaluations. Similar clinical results were found in groups receiving different platelet concentrations, therefore, a concentration of 1,000,000 platelet/µl is considered sufficient for pain relief and functional recovery.	Study comparing PRP kits with different platelet concentrations.
Dold AP, Zywiel MG, Taylor DW, Dwyer T, Theodoropoulos J. (2014) Platelet-rich plasma in the management of articular cartilage pathology: a systematic review. Clin J Sport Med 24(1):31-43	'Systematic review' n=10 studies (570) joints Follow-up: not reported	No studies reported worse scores compared with baseline at final follow-up. Three of 4 comparative studies reported significantly better clinical and/or pain scores when compared with hyaluronic acid injections at similar follow-up times.	More recent and comprehensive systematic reviews included in table 2.
Duymus TM, Multu S et al (2017). Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc. 25 (2): 485-92.	N=102 patients with mild to moderate knee osteoarthritis (OA) given an intra-articular injection of platelet-rich plasma (n=33 PRP x 2 doses), hyaluronic acid (n=34 HA, single dose) or ozone gas (n=35 , 4 doses). Follow-up: 12 months	At the end of the 1st month after injection, significant improvements were seen in all groups. In the 3rd month, the improvements in WOMAC and VAS scores were similar in Groups 1 and 2, while those in Group 3 were lower ($p < 0.001$). At the 6th month, while the clinical efficacies of PRP and HA were similar and continued, the clinical effect of ozone had disappeared ($p < 0.001$). At the end of the 12th month, PRP was determined to be both statistically and clinically superior to HA ($p < 0.001$). In the treatment of mild–moderate knee OA, PRP was more successful than HA and ozone injections, as the application alone was sufficient to provide at least 12 months of pain-free daily living activities.	Study included in systematic review (Shen 2017) added to table 2.

Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. (2011) Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surgery, Sports Traumatology, Arthroscopy 19 (4): 528-535	n=91 Follow-up: 12 months	IKDC, EQ-VA improved significantly at 12-month follow-up. 80% of patients were satisfied with the outcome of their treatment.	The reporting of outcomes was not conducive for data extraction: results were displayed graphically.
Filardo G, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, Cenacchi A, Fornasari PM, Marcacci M. (2012) Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- compared with double-spinning approach. Knee Surgery Sports Traumatology Arthroscopy	n=144 (72 single spin approach vs 72 double spin approach) Follow-up: 12 months	Statistically significant improvements in IKDC scores were observed in both PRP groups (p values<0.0005). No significant differences were observed between groups (p>0.05)	The reporting of outcomes was not conducive for data extraction: no numbers were reported as results were displayed graphically.
Filardo G, Kon E, Di Martino A, Di Mattio B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M (2012). Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC musculoskeletal disorders. 13: 229 [Online]. Available at: http://www.biomedcentral.com/1471-2474/13/229 (Accessed: 15 October 2013)	Randomised controlled trial N=109 (54 PRP compared with 55 HA) Follow-up: 12 months	Minor adverse events, such as mild pain and effusion after the injections, in particular in the PRP group, where a significantly higher post-injective pain reaction was observed (p=0.039). At follow-up both groups presented a clinical improvement but the comparison between the two groups showed a not statistically significant differences. A trend favorable for the PRP group was only found in patients with low grade articular degeneration (Kellgren-Lawrence score up to 2).	Other randomised controlled trials that reported more outcome measures were available.

Filardo G, Di Matteo et al (2015). Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Compared with Viscosupplementation. A Randomized Controlled Trial. The American Journal of Sports Medicine. 43 (7), 1575-1582.	Randomized controlled trial N=192 patients with knee joint degeneration 3 weekly intra-articular injections of either PRP or HA. Follow-up: 12 months	2 patients reported severe pain and swelling after HA injections, while no major adverse events were noted in the PRP group. PRP presented overall significantly more postinjection swelling and pain. Both treatments proved to be effective in improving knee functional status and reducing symptoms: the IKDC score in the PRP group rose from 52.4 ± 14.1 to 66.2 ± 16.7 at 12 months (P < .0005), and in the HA group it rose from 49.6 ± 13.0 to 64.2 ± 18.0 at 12 months (P < .0005). A similar trend was observed for all the clinical scores used. The comparative analysis of the 2 treatments showed no significant intergroup difference at any follow-up evaluation in any of the clinical scores adopted. PRP does not provide a superior clinical improvement with respect to HA, and therefore it should not be preferred to viscosupplementation as injective treatment of patients affected by knee cartilage degeneration and OA.	Study included in systematic review and meta-analysis (Dai W-Li 2017) added to table 2.
Filardo G, Kon E et al (2015). Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. Knee Surg Sports Traumatol Arthrosc 23 (9): 2459.	Systematic review assessed in vivo, in vitro, preclinical and clinical studies on PRP injections (n=59 studies: 26 in vitro, 9 in vivo, 2 both in vivo and in vitro, and 22 clinical studies)	Preclinical evidence supports the use of PRP injections that might promote a favourable environment for joint tissues healing. Only a few high-quality clinical trials have been published, which showed a clinical improvement limited over time and mainly documented in younger patients not affected by advanced knee degeneration.	More comprehensive and recent systematic reviews included in table 2.
Freitag JB, Barnard A. (2013) To evaluate the effect of combining photo-activation therapy with platelet-rich plasma injections for the novel treatment of osteoarthritis. BMJ Case reports 10: 1136	n=1 Follow-up: 18 weeks	Numerical pain rating scale reduced from 5 to 0 by week 6. The WOMAC global scale improved by 65% at week 6 and remained constant until week 18.	Patient was treated by combination therapy (PRP plus photo activation therapy) making it difficult to ascertain the efficacy of PRP-alone.

Gilani SS, Naeem M et al (2015). Use of platelet rich plasma with exercises in the treatment of knee osteoarthritis. Rawal Medical Journal. 42 (4): 534-536.	Case series N=29 patients with grade 3 osteoarthritis of knee were given 1 PRP injection and combined exercise training program (4 weeks before and 8 weeks after PRP injection). Follow-up: 6 months	All patients completed follow-up. Hospital for special surgery knee scoring system and WOMAC scores were significantly better than pre-injection scores during the follow-up period ($p<0.001$). PRP combined with exercises is a reliable safe and effective treatment for pain relief and functional status.	Large and longer follow-up studies included in table 2.
Gobbi A, Karnatzikos G et al (2012). Platelet-Rich Plasma Treatment in Symptomatic Patients With Knee Osteoarthritis: Preliminary Results in a Group of Active Patients. Sports Health, 4 (2): 162-172	Case series N=50 2 intra-articular PRP injections in active patients with knee OA Follow-up: 12 months	All patients showed significant improvement in all scores at 6 and 12 months ($P < 0.01$) and returned to previous activities. Operated and non-operated patients showed improvement by means of diminishing pain and improved symptoms and quality of life but no significant difference was found between subgroups ($P < 0.01$).	Large and longer follow-up studies included in table 2.
Gobbi A, Lad D et al (2015). The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. Knee Surgery, Sports Traumatology, Arthroscopy.23 (8), pp 2170–2177	Prospective randomised comparative study N=93 (119 knees) 1 cycle (3 PRP injections at monthly interval [n=55]) compared with 2 cycles (n=38 [50 knees randomly selected) (3 PRP injections each given at a monthly interval and repetition after a year) 2 years follow-up.	There was a significant improvement in all scores over time compared to the pre-treatment value ($p < 0.001$). At 12 months, both groups showed similar and significant improvement. At 18 months, except for KOOS (Symptoms) and Tegner score, all other parameters showed a significant difference between the two groups in favour of the patients who had received the second cycle ($p < 0.001$). At 2 years, the scores declined in both groups but remained above the pre-treatment value with no significant difference between the groups despite the patients with two cycles showing higher mean values for all the scores.	Large and longer follow-up studies included in table 2

Görmeli G, Görmeli, CA (2017). Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc (2017) 25: 958.	Randomized, double-blind, placebo-controlled trial N=162 patients with different stages of knee OA were randomly divided into four groups receiving 3 IA doses of PRP, one dose of PRP, one dose of HA or a saline injection (control). Then, each group was subdivided into two groups: early OA (Kellgren–Lawrence grade 0 with cartilage degeneration or grade I–III) and advanced OA (Kellgren–Lawrence grade IV). Follow-up: 6 months	There was a statistically significant improvement in the IKDC and EQ-VAS scores in all the treatment groups compared with the control group. The knee scores of patients treated with three PRP injections were significantly better than those patients of the other groups. There was no significant difference in the scores of patients injected with one dose of PRP or HA. In the early OA subgroups, significantly better clinical results were achieved in the patients treated with three PRP injections, but there was no significant difference in the clinical results of patients with advanced OA among the treatment groups. The clinical results of this study suggest IA PRP and HA treatment for all stages of knee OA. For patients with early OA, multiple (3) PRP injections are useful in achieving better clinical results. For patients with advanced OA, multiple injections do not significantly improve the results of patients in any group.	Study included in systematic review added to table 2.
Guo Y, Yu H et al (2016). Treatment of knee osteoarthritis with platelet-rich plasma plus hyaluronic acid in comparison with platelet-rich plasma only. Int J Clin Exp Med;9(6):12085-12090	Cohort study N=126 patients with knee OA 63 cases in PRP plus HA group and 63 cases in PRP group. Follow-up: 12 months	In both groups, VAS scores decreased significantly, and knee function (WOMAC) improved, compared to prior to treatment. No significant difference were observed between the two groups; however, there is a trend that could obtain better functional scores in PRP plus HA group (VAS, P = 0.392; WOMAC, P = 0.082). Six failures occurred in the PRP plus HA group and 11 in PRP group. No major adverse events or complications were observed in both groups.	Larger and longer studies included in table 2.
Halpern B, Chaudhury S, Rodeo SA, Hayter C, Bogner E, Potter HG, Nguyen J (2013) Clinical and MRI outcomes after platelet-rich plasma treatment for knee osteoarthritis. Clinical Journal of Sports medicine 23 (3): 238-239	n=22 Follow-up: 12 months	Statistically significant improvements in VAS and WOMAC scores were observed at 12 month follow-up. MRI scans revealed that 80% (12/15) of knees exhibited no significant change in appearance at follow-up.	Larger studies with more outcome measures were available.

Hassan AS, Mohamed El-Shafey A et al (2014). Effectiveness of the intra-articular injection of platelet rich plasma in the treatment of patients with primary knee osteoarthritis. The Egyptian Rheumatologist (2015) 37, 119–124	Case series N=20 patients with mild to moderate primary knee OA injected intra-articularly with 5 ml PRP for each affected joint, at 1 month intervals for 6 injections. Follow-up: 6 months	After 6 months of PRP, there was a significant improvement in the duration of inactivity stiffness (8.3 ± 2.4 min), VAS score (3.9 ±1.1) and IKDC score (74.3 ±10.2) compared to baseline values (18.7 ±6.5 min, 5.9 ±1.3 and 40.9 ±10.4 respectively; p< 0.001). A significant improvement in Doppler activity (p=0.04) and synovial thickening (p< 0.001) was found. A significant correlation was found between age of patients, body mass index and disease duration with the VAS (p< 0.001)	Large studies with longer follow-up included in table 2.
Huang Po-Hua, Wang Ching-Jen et al (2017). Short-term clinical results of intra-articular PRP injections for early osteoarthritis of the knee. International Journal of Surgery 42, 117-122	Retrospective study in 191 knees (127 patients) with minimum of 12 months follow-up. Repeated intra-articular platelet rich plasma (PRP) injections into the knee in patients with early osteoarthritis.	There were significant improvements in all scores after treatment as compared to the pre-treatment values ($p < 0.05$), except Knee score after 1st and 2nd injection and ROM in three groups. The parameters of Visual Rating Scale (VRS), functional score, and WOMAC Stiffness/Pain/Function score showed significant differences among the three groups in favour of the three injections group ($p < 0.05$). At 12 months, the effects began to decline in one injection and two injections groups, and the data in one injection group showed significant difference compared to two injection group ($p < 0.001$). Three injections group had higher scores and more improvement at 12 months after treatment when compared to the other two groups.	Large studies with longer follow-up included in table 2.

Jang, SJ., Kim, JD. & Cha, SS (2013). Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. Eur J Orthop Surg Traumatol 23: 573	Prospective case series N=65 patients with OA of knee treated with PRP injections. Follow-up: 12 months	Clinical improvement (average VAS score from 7.4 before the procedure to 4.2 at 6 months post-procedure) had been reported, but the symptoms tended to deteriorate to 5.0 1 year after injection. The IKDC score also showed statistical significance ($P < 0.05$). Patients reported relapsed pain 8.8 months after the procedure. Developing degeneration according to the Kellgren–Lawrence grade reduced the clinical effects of PRP ($P < 0.05$) and also accelerated the time for feeling relapsed pain ($P < 0.05$). There was a statistically significant negative correlation between patient age and the PRP potential in the VAS score (slope = 0.1667) and IKDC score (slope = 1.3333). The presence of PFJ degeneration is expected to produce a worse outcome ($P < 0.05$). While intra-articular PRP injection can be used for the treatment of early OA, increasing age, and developing degeneration result in a decreased potential for PRP injection therapy.	Larger studies with more outcome measures were available.
Kavadar G, Demircioglu DT et al (2015). Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: a randomized prospective study. J. Phys. Ther. Sci. 27: 3863–3867.	Prospective randomised study. N=102 patients with grade 3 knee OA were randomly divided into three groups: Group 1 received a single injection of PRP, Group 2 received two injections of PRP two weeks apart, Group 3 received three injections of PRP at 2-weeks intervals. Follow-up: 6 months	Statistically significant improvements were noted in all of the evaluated measures in all of the groups. The mean differences of Group 1-Group 2 and Group 1-Group 3 WOMAC total, WOMAC pain, WOMAC stiffness, and WOMAC function scores were statistically significant. PRP is an effective treatment for functional status and pain in moderate knee osteoarthritis and a minimum of two injections is appropriate.	Large and longer follow-up studies included in table 2.

Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, Gandhi R, Takhar K, Lum G, Chahal J. (2013) The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy. 29(12): 2037-48	Systematic review n = 577 (4 randomised controlled trials and 2 non-randomised comparative studies) Adult patients with mild to moderate knee OA (264 patients in PRP group and 313 in control group [HA or normal saline]). Follow-up: minimum 24 weeks (6 months)	Pooled results using the Western Ontario and McMaster Universities Arthritis Index scale (4 studies) showed that PRP was significantly better than HA or NS injections (mean difference, −18.0 [95% confidence interval, −28.8 to −8.3]; P < .001). Similarly, the International Knee Documentation Committee scores (3 studies) favored PRP as a treatment modality (mean difference, 7.9 [95% confidence interval, 3.7 to 12.1]; P < .001). There was no difference in the pooled results for visual analog scale score or overall patient satisfaction. Adverse events occurred more frequently in patients treated with PRP than in those treated with HA/placebo (8.4% v 3.8%, P = .002).	More recent and comprehensive systematic reviews included in table 2.
Kilincoglu V, Yeter A et al (2015). Short term results comparison of intraarticular platelet-rich plasma (prp) and hyaluronic acid (ha) applications in early stage of knee osteoarthritis. Int J Clin Exp Med;8(10):18807-18812	Retrospective comparative study N=118 patients with early knee OA N=61 PRP compared with n=57 HA injections 3 times 1 week apart. Follow-up: 6 months	In the PRP and HA groups, when pre-treatment KSS and VAS scores were compared with post-treatment three and six-month scores, a statistically significant difference was seen. When the groups were compared with each other, there was no significant difference between pre-treatment KSS and VAS pain scores; however, a significant difference was found between post-treatment three and six-month scores.	Large and more relevant studies included in table 2.
Knop E, de Paula LE et al (2016). Platelet-rich plasma for osteoarthritis treatment. Rev Bras Reumatol; 56(2):152–164	Review N=23 studies (7 RCTs, 2 controlled trials and 14 case series)	In RCTs PRP group showed improvement in pain and joint function compared to placebo and hyaluronic acid. The response lasted up to two years and was better in milder cases. However it was found that there is no standardization in the PRP production method,neither in the number, timing, and volume of applications. Furthermore, the populationsstudied were not clearly described in many studies. Thus, these results should be analyzedwith caution, and further studies with more standardized methods would be necessary fora more consistent conclusion about the PRP role in osteoarthritis.	More recent and comprehensive systematic reviews included in table 2.

Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. (2010) Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surgery, Sports Traumatology, Arthroscopy 18 (4): 472-479	n= 91 (115 knees) Follow-up: 12 months	Statistically significant improvements in IKDC and EQ-VAS scores were observed at 12 month follow-up ($p<0.0005$). There was a significant correlation between age and IKDC scores: As age increased IKDC scores decreased.	The reporting of outcomes was not conducive for data extraction: results were displayed graphically.
Lai. LP, Stitik TP et al (2015). Use of Platelet-Rich Plasma in Intra-Articular Knee Injections for Osteoarthritis: A Systematic Review. American Academy of Physical Medicine and Rehabilitation PM&R 7 (6), 637-648.	Systematic review PRP intra-articular injections for treatment of knee osteoarthritis. 8 studies (4 prospective observational studies, 2 RCTs and 2 prospective comparative studies [3 compared PRP with HA and 1 used saline injection as control]).	Most of the analyses suffered from small sample size and was thus inconclusive, the findings consistently indicated that PRP might have better outcomes in patients with a lesser degree of degeneration and in younger patients. PRP intra-articular injections of the knee may be an effective alternative treatment for knee OA. However, current studies are at best inconclusive regarding the efficacy of the PRP treatment.	More recent and comprehensive systematic reviews included in table 2
Lana JFSD, Weglein A et al (2016). Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. Journal of Stem Cells and Regenerative Medicine. 12 (2): 69-78.	RCT N=105 patients with mild to moderate knee osteoarthritis, were randomly allocated to: HA (n=36), PRP (n=36), or HA+PRP (n=33). Follow-up: 12 months	The study showed that the PRP group have significant reduction in VAS scores at 1 (p= 0.003), 3 (p= 0.0001), 6 (p= 0.0001) and 12 (p= 0.000) months when compared to HA. In addition, the PRP group illustrated greater improvement in WOMAC physical activity scale at 12 months (p= 0.008) when compared to the HA group. Combining HA and PRP resulted in a significant decreases in pain (p=0.0001) and functional limitation (p=0.0001) when compared to HA alone at 1 year post treatment; and significantly increased physical function at 1 (p=0.0004) and 3 (p=.011) months when compared to PRP alone.	Large studies included in table 2.

Laudy ABM, Bakker E WP et al (2015). Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis.British Journal of Sports Medicine 49 (10), 657- 672.	Systematic review and meta-analysis evaluated the effect of PRP injections on knee pain and physical function at 6 and 12 months post-treatment N=10 studies (1110 patients) 6 RCTs, 4 non-randomised clinical trials Comparing PRP with placebo or hyaluronic acid.	Ten trials were included. In these, intra-articular PRP injections were more effective for pain reduction (mean difference (MD) −2.45; 95% CI −2.92 to −1.98; p value <0.00001 and MD −2.07; 95% CI −2.59 to −1.55; p value <0.00001, single and double PRP injections, respectively) compared with placebo at 6 months postinjection. Intra-articular PRP injections were compared with hyaluronic acid and showed a statistically significant difference in favour of PRP on pain reduction based on the visual analogue scale and numeric rating scale (standardised mean difference −0.92; 95% CI −1.20 to −0.63; p value <0.00001) at 6 months postinjection. Almost all trials revealed a high risk of bias.	More recent and comprehensive systematic reviews included in table 2. Results are based on an fixed effects model of Maantel-Haenszel due to significant heterogeneity.
Laver L, Marom N et al (2017). PRP for Degenerative Cartilage Disease: A Systematic Review of Clinical Studies. CARTILAGE Vol. 8(4) 341–364	Systematic review 26 studies PRP for knee OA 3 studies on PRP for hip OA 9 RCTs (8 knee 1 hip), 4 comparative studies, 14 case series and 2 retrospective comparative studies. Narrative synthesis	Overall, all RCTs reported on improved symptoms compared to baseline scores. Only 2 RCTs—one for knee and one for hip—did not report significant superiority of PRP compared to the control group (HA). Nine out of 11 HA controlled studies showed significant better results in the PRP groups. A trend toward better results for PRP injections in patients with early knee OA and young age was observed; however, lack of uniformity was evident in terms of indications, inclusion criteria, and pathology definitions in the different studies.	More recent and comprehensive systematic reviews included in table 2.
Lee GW, Son JH, Kim JD, Jung GH. (2013) Is platelet-rich plasma able to enhance the results of arthroscopic microfracture in early osteoarthritis and cartilage lesion over 40 years of age? European Journal of Orthopaedic Surgery and Traumatology 23 (5): 581-587	n=49 (24 PRP plus microfracture vs 25 microfracture-only) Follow-up: 24 months	Statistically significant improvements in Lysholm were observed within both groups (p<0.021); however, no significant differences were observed between groups (p=0.068).	Larger studies with more outcome measures were available.

Lee SK, Shetty AS et al 92013). Intra-articular injections of platelet-rich plasma in patients with knee pain of articular cartilage origin (degenerative chondropathy and early OA). Tissue Engineering and Regenerative Medicine, 10(6): 329-35.	Case series N=44 patients with early osteoarthritis and degenerative chondropathy PRP injections within 4 weeks interval.	There were no complications, pain was reduced compared to baseline and was statistically significant. There was a statistically significant improvement in pain during follow-up period.	Larger studies with more outcome measures were available.
Louis ML, Magalon J et al (2017). Growth factors levels determine efficacy of platelets rich plasma injection in knee osteoarthritis: a randomised double blind noninferiority trial compared with viscosupplementation. Arthroscopy: the Journal of Arthroscopic and Related Surgery (article in press).	RCT N=54 patients with symptomatic knee osteoarthritis Single injection of PRP (n=26) compared with hyaluronic acid (n=28) Follow-up: 6 months	Both treatments proved their improvement in knee functional status and symptom relief, with a significant decrease observed at 1 month on all scores except for pain VAS in PRP group and WOMAC function score in the HA group. No difference between groups regarding WOMAC and VAS scores was observed. A higher percentage of responders was observed in the PRP group (72.7%) than in the HA group (45.8%) without significance (P = .064). The quantity of injected PDGF-AB and TGF-β1 correlated with the change in WOMAC scores at 3 months and was lower in responders than in nonresponders (P = .009 and P = .003, respectively).	Large studies included in table 2.
Martini LI, Giai Via A et al (2017). Single Platelet-Rich Plasma Injection for Early Stage of Osteoarthritis of the Knee. Joints 2017;5:2–6.	Case series N=25 patients with grade 1-II primary OA of Knee had single IA-PRP injection Follow-up: 6 months	The median WOMAC score improved from 29.1 points at baseline to 42.41 at final follow-up. Improvements in median KOOS and VAS score have been also found, from 37.49 points and 64.2 mm before injection to 59.71 points and 42.8 mm, respectively. All these improvements were statistically significant ($p < 0.05$). No adverse reactions have been observed.	Large studies included in table 2.

Meheux CJ, McCulloch PC et al (2016). Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 32 (3), 495-505	Systematic review PRP injections inpatients with symptomatic knee osteoarthritis (OA). Narrative synthesis of 6 RCTs.	6 RCTs (n=739) analysed. All studies met minimal clinical important difference criteria and showed significant improvements in statistical and clinical outcomes, including pain, physical function, and stiffness, with PRP. All but one study showed significant differences in clinical outcomes between PRP and hyaluronic acid (HA) or PRP and placebo in pain and function. Average pre-treatment Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were 52.36 and 52.05 for the PRP and HA groups, respectively (P = .420). Mean post-treatment WOMAC scores for PRP were significantly better than for HA at 3 to 6 months (28.5 and 43.4, respectively; P = .0008) and at 6 to 12 months (22.8 and 38.1, respectively; P = .0062). None of the included studies used corticosteroids.	More recent and comprehensive systematic reviews included in table 2.
Milants C, Bruyere O et al (2017). Responders to Platelet-Rich Plasma in Osteoarthritis: A Technical Analysis. Hindawi BioMed Research International Article ID 7538604, 11 pages	Review of RCTs included in systematic reviews (n=19)	There is a lack of standardization in PRP preparation technique for knee osteoarthritis. However it appears that the use of a single spinning technique, a platelet concentration lower than 5 times the baseline, and avoidance of leukocytes should be preferred.	More recent and comprehensive systematic reviews included in table 2.

Mohamed Ghazali IM, Thye MSL et al (2013). Platelet rich plasma for treatment of osteoarthritis. Malaysian Health Technology Assessment section (MaHTAS).	HTA	2 systematic reviews, 2 randomised controlled trials and a non-randomised controlled trial were included in this review. There was insufficient but good level of evidence to support the effectiveness of PRP for the treatment of osteoarthritis. The longest outcome data available was only for 24 months in a study and revealed that the median beneficial results was nine months. Most of the studies available were case series. Studies that have comparisons, used hyaluronic acid as control. In certain countries such as the United Kingdom, intra-articular hyaluronic acid injections are not recommended for the treatment of osteoarthritis. The short term evidence showed that PRP may be beneficial for young (<50 years old) patients with early OA and not overweight or obese. However, the evidence is limited. In terms of safety, no major complications were reported in patients treated with PRP. Further comparative effectiveness study is required before PRP can be recommended for the treatment of osteoarthritis.	More comprehensive systematic reviews and meta-analysis added to table 2.
Montanez-Heredia E, Irizar S et al (2016). Intra-Articular Injections of Platelet-Rich Plasma compared with Hyaluronic Acid in the Treatment of Osteoarthritic Knee Pain: A Randomized Clinical Trial in the Context of the Spanish National Health Care System. Int. J. Mol. Sci. 2016, 17, 1064	double-blind randomized controlled clinical trial. N=55 injecting autologous PRP (n=28) compared with hyaluronic acid (HA, n=27) in knee osteoarthritis follow-up: 6 months	Both groups presented pain reduction at six months. The VAS scores for the PRP group improved by at least 50% from their initial value, particularly at three months following the final infiltration, with results resembling those of the HA group at six months. PRP was more effective in patients with lower osteoarthritis grades. Both treatments improved pain in knee osteoarthritis patients without statistically significant differences between them. However, PRP injection was proved to improve pain three months after the final infiltration and to be more effective in lower osteoarthritis grades.	Study included in a systematic review (Shen 2017) added to table 2.

Muchedzi TA, Roberts SB (2017). A systematic review of the effects of platelet rich plasma on outcomes for patients with knee osteoarthritis and following total knee arthroplasty. The Surgeon 1-9 (Article in Press)	Systematic review on use of PRP in knee osteoarthritis and following TKA. N=17 studies [RCTs and pseudo randomised comparative clinical studies] (n=2328 patients)	Pooled results showed a statistically significant reduction in pain in favor of PRP following TKA but not in non-surgical management of knee OA (P < 0.0001 and 0.13 respectively). No clinical benefit of PRP was found on quality of life and knee function (P = 0.07 and 0.05) following TKA, although a statistical improvement in knee function was demonstrated in patients with knee OA after PRP injection (P < 0.0001). There was no statistically significant clinical benefit of PRP on secondary outcomes including wound scores and length of hospital stay (p = 0.33 and 0.31, respectively). There was no statistically significant difference in respect to blood loss and overall symptoms in favor of PRP compared to control group following TKA (p = 0.37). This systematic review demonstrated no long-term statistically significant improvement in patient validated outcomes and secondary outcomes both in patients with knee OA or following TKA for OA. However PRP has been shown to have short to medium-term benefits in pain control after TKA and activities of daily living in patients with OA.	More comprehensive systematic reviews and meta-analysis added to table 2.
Napolitano M, Matera S, Bossio M, Crescibene A, Costabile E, Almolla J, Almolla H, Togo F, Giannuzzi C, Guido G. (2012) Autologous platelet gel for tissue regeneration in degenerative disorders of the knee. Blood Transfusions 10 (1): 72-77	n=27 (Patients with degenerative cartilage vs patients with osteoarthritis) Follow-up: 6 months	Functional scores improved in both groups.	Study reported quantitative changes in groups; however, no p values were available to ascertain significance levels.

Ornetti P, Nourissat G et al (2016). Does platelet-rich plasma have a role in the treatment of osteoarthritis? Joint Bone Spine. 83 (1), 31-36	Review	Most of the randomized trials in knee osteoarthritis support a slightly greater effect in alleviating the symptoms compared to visco-supplementation, most notably at the early stages of the disease, although only medium-term data are available. Many uncertainties remain, however, regarding the best administration regimen. Serious adverse effects, including infections and allergies, seem rare, although post-injection pain is more common than with other intra-articular treatments for osteoarthritis.	Review
Paterson KL, Nicholls M et al (2016). Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: a double-blind, randomized controlled pilot study. BMC Musculoskeletal Disorders 17:67.	double-blind randomized controlled pilot study N=23 people with knee OA received PRP (n=12) or HA (n=11). Follow-up: 12 weeks	Minor pain and swelling during the injection period was reported by two participants from the PA-PRP group. The PA-PRP group demonstrated significant improvements in the VAS ($p < 0.01$, ETA = 0.686), KOOS Pain ($p < 0.05$, ETA = 0.624), KQoL Physical ($p < 0.05$, ETA = 0.706) and KQoL Emotional subscales ($p < 0.05$, ETA = 0.715) at four and 12 weeks. The PA-PRP group also significantly improved hoping ($p < 0.05$, ETA = 0.799) and knee bends ($p < 0.01$, ETA = 0.756) at four or 12 weeks. The HA group showed improvements on only the KOOS Function subscale at 12 weeks ($p < 0.01$, ETA = 0.602). After controlling for baseline values, there were no significant between-group differences at either time-point.	Study included in systematic review added to table 2.
Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. (2013) Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. American Journal of Sports medicine 41 (2): 356-364	Randomised controlled trial N=78 (27 one PRP injection vs 25 two PRP injections vs 26 placebo) Follow-up: 6 months	Statistically significant improvement in all WOMAC parameters was noted in groups A and B. In group C, the scores deteriorated from baseline to final follow-up. Mild complications such as nausea and dizziness, which were of short duration, were observed in 6 patients (22.2%) in group A and 11 patients (44%) in group B. A single dose of WBC-filtered PRP in concentrations of 10 times the normal amount is as effective as 2 injections to alleviate symptoms in early knee OA. The results, however, deteriorate after 6 months. Both groups treated with PRP had better results than did the group injected with saline only.	Other randomised controlled trials that reported more outcome measures were available.

Pourcho AM, Smith J et al (2014). Intraarticular platelet-rich plasma injection in the treatment of knee osteoarthritis: review and recommendations. Am J Phys Med Rehabil. 2014 Nov;93(11 Suppl 3):S108-21.	Review outlines the variables involved in the use of PRP, summarises current literature and suggests avenues for further research.	Intraarticular platelet-rich plasma (PRP) injection has emerged as a promising treatment for knee osteoarthritis. Studies to date, including multiple randomized controlled trials, have shown that PRP is a safe and effective treatment option for knee osteoarthritis. Intraarticular PRP is similar in efficacy to hyaluronic acid, and seems to be more effective than hyaluronic acid in younger, active patients with low-grade osteoarthritis. Treatment benefits seem to wane after 6-9 mos. There are numerous PRP treatment variables that may be of importance, and the optimal PRP protocol remains unclear. Future investigations should control and analyze the effects of these variables in PRP treatment. High-quality randomized controlled trials are needed to optimize PRP treatment methods and better define the role of PRP in osteoarthritis management in the knee and, potentially, in other joints.	Review
Raeissadat, S. A., Rayegani, S. M., Babaee, M., and Ghorbani, E. (2013). The effect of platelet-rich plasma on pain, function, and quality of life of patients with knee osteoarthritis. Pain Research and Treatment 165967 [Online].	Cases series n=60 Follow-up: 6 months	Statistically significant improvements in total WOMAC scores were observed at 6 month follow-up. Furthermore, statistically significant improvements were observed in SF-36 domains for pain, physical function, social functioning and physical role at 6 month follow-up.	Larger studies with longer follow-up periods were available.
Raeissadat SA, Rayegani SM (2015). Knee Osteoarthritis Injection Choices: Platelet- Rich Plasma (PRP) Compared with Hyaluronic Acid (A one-year randomized clinical trial). Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2015:8, 1-8	Non-placebo-controlled randomized clinical trial. N=160 patients with knee OA treated with PRP 2 injections every 4 weeks (n=87) compared with HA (n=73) 3 injections every 1 week. Follow-up: 12 months	At the 12-month follow-up, WOMAC pain score and bodily pain significantly improved in both groups; however, better results were deter-mined in the PRP group compared to the HA group (P , 0.001). Other WOMAC and SF-36 parameters improved only in the PRP group. More improve-ment (but not statistically significant) was achieved in patients with grade 2 OA in both the groups. This study suggests that PRP injection is more efficacious than HA injection in reducing symptoms and improving quality of life and is a therapeutic option in select patients with knee OA who have not responded to conventional treatment.	Study included in systematic review added to table 2.

Rahimzadeh P, Imani F et al (2016). Adding Intra-Articular Growth Hormone to Platelet Rich Plasma under Ultrasound Guidance in Knee Osteoarthritis: A Comparative Double-Blind Clinical Trial. Anesth Pain Med 6(6): E41719	RCT N=54 27 PRP compared with 27 PRP+growth hormone Follow-up: 2 months	WOMAC score in both groups has been significantly reduced after injections (P = 0.030). WOMAC score reduction in group PS in first month was significantly higher than group P, but in secondmonth2, the difference between two groups was not significant (P = 0.235). No complication was observed.	Compared with PRP only combined with growth hormone.
Rayegani SM, Raeissadat SA et al (2014). Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthopedic Reviews 2014; volume 6:5405	Randomized controlled trial N= 62 patients with knee OA 31 in PRP +exercise group and 31 in control group In PRP group 2 courses of leukocyte rich PRP (5.6 fold higher platelet concentration) with a 4-week interval was injected.	Mean changes of total WOMAC, physical component summery and mental component summery of Short Form-36 in PRP group showed better improvement than control group (P<0.05). This study showed that intra articular PRP knee injection combined with therapeutic exercise can be more effective in pain reduction and improvement of stiffness and quality of life, compared with therapeutic exercise alone.	Study included in systematic review (Kanchanatawan 2016) added to table 2.
Rodriguez-Merchan EC (2013). Intraarticular Injections of Platelet-rich Plasma (PRP) in the Management of Knee Osteoarthritis. CURRENT CONCEPT REVIEW. Arch Bone Joint Surg; 1(1): 5-8.	Review of 20 reports	Clinical studies suggest that intraarticular injections of PRP could have preventive effects against osteoarthritis progression. However, presently there is no clear evidence from well-designed clinical trials that intraarticular injections of PRP are efficacious in osteoarthritis. Therefore, at this time the efficacy of PRP requires more investigation, wherein better scientific studies should be performed that include high powered randomized controlled trials.	Review
Sadabad HN, Behzadifar M et al 92016). Efficacy of Platelet-Rich Plasma compared with Hyaluronic Acid for treatment of Knee Osteoarthritis: A systematic review and meta-analysis. Electron Physician. 2016 Mar; 8(3): 2115–2122.	Systematic review N=7 studies |(6 RCTs and 1 retrospective cohort study, PRP compared with HA)	Seven studies with 722 subjects (364 participants in PRP and 358 participants in the HA group) were analyzed. The WOMAC PRP compared to HA, SMD = −0.75 (95% CI: −1.33 to −0.18, I2 = 92.6%) in treatment of knee osteoarthritis was statistically significant and PRP was more effective. The results of this meta-analysis two years after PRP injection showed the efficacy of PRP compared with HA. However, further studies are required to determine the longer-term effects.	Comprehensive systematic reviews added to table 2.

Say, F., Gurler, D., Yener, K., Bulbul, M., Malkoc, M. (2013) Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. Acta Chirurgiae Orthopaedicae et Traumatologiae Cechosl. 2013;80(4):278-83.	Non-randomised clinical trial n=90 (45 PRP vs 45 HA) Follow-up: 6 months	No severe adverse events were observed. The PRP group exhibited significantly greater improvements in KOOS and VAS scores for pain compared with the HA group at 3 month and 6 month follow-up.	Larger studies with longer follow-up periods were available.
Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. (2010) Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. American Journal of Physical Medicine and Rehabilitation 89 (12): 961-969	n=14 Follow-up: 12 months	No significant improvements were observed in KOOS subgroups apart from the pain relief and symptom relief scale s(p values<0.04). Statistically significant improvements in Brittberg-Peterson VAS for pain at rest, pain whilst moving and pain whilst bending were observed at 12 month follow-up (p<0.004)	Larger studies with more outcome measures were available.
Sanchez M, Fiz N et al (2012). A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) compared with hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthroscopy. Aug;28(8):1070-8.	Randomised double-blind clinical trial N=176 patients with symptomatic knee osteoarthritis. PRGF-Endoret an autologous biological therapy for regenerative purposes, compared with hyaluronic acid (HA) (3 injections on a weekly basis)	Compared with the rate of response to HA, the rate of response to PRGF-Endoret was 14.1 percentage points higher (95% confidence interval, 0.5 to 27.6; P = .044). Regarding the secondary outcome measures, the rate of response to PRGF-Endoret was higher in all cases, although no significant differences were reached. Adverse events were mild and evenly distributed between the groups.	Study included in systematic review by Dai W Li 2017 added to table 2.

Sanchez M, Delgado D et al (2016). Combination of Intra-Articular and Intraosseous Injections of Platelet Rich Plasma for Severe Knee Osteoarthritis: A Pilot Study. BioMed Research International, Article ID 4868613, 10 pages	Case series N= 13 patients with severe knee osteoarthritis. Combining intra-articular injections and intraosseous infiltrations of platelet rich plasma.	There was a significant pain reduction in the KOOS from baseline (61.55±14.11) to week 24 (74.60 ± 19.19), after treatment (p = 0.008), in the secondary outcomes (symptoms, p = 0.004; ADL, p = 0.022; sport/rec., p = 0.017; QOL, p = 0.012), as well as VAS score (p < 0.001) and Lequesne Index (p = 0.008). The presence of mesenchymal stem cells in synovial fluid and colony-forming cells one week after treatment decreased substantially from 7.98 ± 8.21 MSC/μL to 4.04 ± 5.36 MSC/μL (p = 0.019) and from 601.75 ± 312.30 to 139.19 ± 123.61 (p = 0.012), respectively.	Combined treatment (Intra-articular and intra-osseous PRP injections).
Sanchez M, Delgado D (2018). Treating Severe Knee Osteoarthritis with Combination of Intra-Osseous and Intra-Articular Infiltrations of Platelet-Rich Plasma: An Observational Study. Cartilage 1–9	Case series N= 60 patients with severe knee OA 30 had combination of intra-articular and intra-osseous infiltrations of plateletrich plasma (PRP) and 30 with only intra-articular injections of PRP used as a control group Follow-up: 12 months	At 2, 6 and 12 months after treatment, IO group had a significant improvement in all KOOS and WOMAC subscales (*P* < 0.05). On the contrary, patients of the IA group did not improve in any of the scores. Sixteen out of 30 IO group patients showed minimal clinically important improvement (MCII) whereas 8 out of 30 IA group patients showed this response at 6 months (26.7%; 95% CI −0.4 to 49.9; *P* = 0.037). At 12 months, 14 patients of IO group and 5 patients of the IA group showed MCII (30%; 95% CI 4.3 to 51.9; *P* = 0.013). No differences between groups were observed at 2 months.	Combined treatment (Intra-articular and intra-osseous PRP injections).
Shi WJ, Tjoumakaris FP et al (2017). Biologic injections for osteoarthritis and articular cartilage damage: can we modify disease? The Physician and Sportsmedicine. 45 (3), 203-223.	Systematic review of 2 treatments PRP and senchymal stem cell treatments (MSC) (biologics). Total 33 studies included (21 on PRP, 9 on MSC and 3 on combination of MSC and PRP) Narrative synthesis.	All PRP studies showed clinical improvement with PRP therapies in outcomes surveys measuring patient satisfaction, pain, and function. Two studies reported no significant difference in improvement compared to hyaluronic acid (HA). The one PRP study that had a 2nd look arthroscopy reported increases cartilage regeneration with PRP. Current data suggests that, of the two treatments, MSC provides more significant disease modifying effect; however, further research needs to be done to compare these two treatments and determine if there is a synergetic effect when combined.	More comprehensive and recent systematic reviews included in table 2.

Smith PA (2016). Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis: An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial. Am J Sports Med. 2016 Apr;44(4):884-91.	Randomized controlled trial N=30 Leukocyte-poor PRP ACP (n = 15) or saline placebo (n = 15) for a series of 3 weekly injections. Follow-up: 1 year	No adverse events were reported for ACP. Results demonstrated no statistically significant difference in baseline WOMAC scores between the 2 groups. However, in the ACP group, WOMAC scores at 1 week were significantly decreased compared with baseline scores, and the scores for this group remained significantly lower throughout the study duration. At 12 months, subjects in the ACP group had improved their overall WOMAC scores by 78% from their baseline score, compared with 7% for the placebo group.	Study included in Shen 2017 systematic review added to table 2.
Souzdalnitski D, Narouze SN et al (2015). Platelet-rich plasma injections for knee osteoarthritis: Systematic review of duration of clinical benefit. Techniques in Regional Anesthesia and Pain Management. 191(–2), 67-72	Systematic review 24 studies (n=2385 patients) were included in the review.	The results showed a consistent improvement in patient pain scores and functional indexes for 6 months after initiation of injections. The residual clinical effect was typically observed beyond 6 months in most of the studies. Pain and functional scores decreased after 12 months but remained higher than the base scores in the majority of studies. Some suggested that annual injections improved treatment outcomes after 18 months. Data from available clinical reports suggest that the PRP administration results in decreased pain and enhanced functional status. The duration of beneficial clinical effects after administration of PRP or recounted autologous products for patients with knee OA and chondropathy was stable up to 6 months following completion of regenerative therapy. The pain and functional scores worsened after 12 months but were still better than pre-injection scores. The analysis is limited by the wide variability of available studies.	More comprehensive and recent systematic reviews included in table 2.
Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. (2012) Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. American Journal of Physical Medicine and Rehabilitation 91: 411-417	Prospective cohort study n=120 (60 PRP vs 60 HA) Follow-up=6 months	Statistically significant differences were observed in WOMAC scores within groups ($p<0.01$) and between groups ($p<0.01$) at 6 month follow-up.	Other randomised controlled trials that reported more outcome measures were available.

Tietze DC, Geissler K et al (2014). The Effects of Platelet-Rich Plasma in the Treatment of Large-Joint Osteoarthritis: A Systematic Review. The Physician and Sportsmedicine Volume 42 (2): 27-37.	Systematic review PRP injection in the treatment of large-joint OA N=13 studies (12 on knee OA and 1 on hip OA). 1 RCT, 2 nonrandomised controlled studies, 1 cohort study, 9 case series. Narrative synthesis.	All studies showed statistically significant improvement in patient outcome scores with PRP. Platelet-rich plasma has a statistically significant benefit in knee OA when compared with hyaluronic acid. The benefit from PRP appears to last between 6 and 12 months. Platelet-rich plasma may be an effective treatment for knee OA. However, because of the low level of evidence, small sample sizes, and wide variability in treatment, no definitive recommendations can be made at this time.	More comprehensive systematic reviews included in table 2.
Vaquerizo, V., Plasencia, M. A., Arribas, I., Seijas, R., Padilla, S., Orive, G., Anitua, E. (2013) Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) compared with durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: A randomized controlled trial. Arthroscopy - Journal of Arthroscopic and Related Surgery. 29 (10): 1635-1643	n=96 (48 PRP vs 48 HA) Follow-up: 48 weeks	The PRP group exhibited statistically greater improvements in Lequesne scores and total WOMAC scores compared with the hyaluronic acid group at 24 and 48 week follow-up assessments. Furthermore, the PRP group exhibited greater improvements in WOMAC subscale scores for pain, stiffness and physical function compared to the HA group at follow-up. Adverse events were mild and evenly distributed between study arms.	Larger studies with longer follow-up periods were available.
Wu YT, Hsu KC et al (2018). Effects of Platelet-Rich Plasma on Pain and Muscle Strength in Patients With Knee Osteoarthritis. Am J Phys Medical Rehabil 97: 248-254.	RCT N=20 patients with bilateral knee OA Randomised to receiving single PRP injection and single saline injection. Follow-up 6 months.	The PRP group showed a significant reduction in the WOMAC-pain and -total scores compared to normal saline group ($p < 0.05$). Although a significantly greater percentage of knee strength (extensor > flexor) was found in the PRP group during a longer follow-up period, PRP treatment resulted in insignificant differences in muscle strength compared to normal saline. Strength training is recommended to enhance muscle strength recovery.	Large studies with longer follow-up included in table 2.

Xing D, Wang B et al (2017). Intra-articular platelet-rich plasma injections for knee osteoarthritis: An overview of systematic reviews and risk of bias considerations. International Journal of Rheumatic Diseases. 20 (11), 1612-30.	Overview of systematic reviews N=10 systematic reviews included. 4 with low risk of bias and 6 with high risk of bias.	Two systematic reviews conducted by Dai et al and Meheux et al with highest AMSTAR score and low risk of bias were selected as the best evidence. The present overview demonstrates that PRP is an effective intervention in treating knee OA without increased risk of adverse events. Therefore, the present conclusions may help decision makers interpret and choose PRP with more confidence.	More comprehensive and recent systematic reviews included in table 2.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	26/02/2018	Issue 2 of 12, February 2018
HTA database (Cochrane Library)	26/02/2018	Issue 1 of 12, January 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	26/02/2018	Issue 4 of 4, October 2016
MEDLINE (Ovid)	26/02/2018	1946 to February 23, 2018
MEDLINE In-Process (Ovid) and MEDLINE Epubs ahead of print (Ovid)	26/02/2018	February 23, 2018
EMBASE (Ovid)	26/02/2018	February 23, 2018

MEDLINE search strategy

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Platelet-Rich Plasma/
2 Blood Platelets/
3 (Platelet* adj4 Rich* adj4 (Plasma* or fibrin* or therap*)).ti,ab.
4 PRP.ti,ab.
5 ((knee* or platelet* or blood* or plasma* or plasm or thrombocyt*) adj4 (inject* or infus* or jab* or syringe* or needle*)).ti,ab.
6 or/1-5
7 Osteoarthritis, Knee/
8 exp Knee Joint/
9 OA.ti,ab.
10 ((knee* or patella* or meniscal* or articular* or patellofem*) adj4 (OA or osteoarthrit* or cartilag* or degenerat* or diseas* or deteriorat* or injur* or defect*)).ti,ab.
11 ((cartilage* or joint* or cap*) adj4 (degenerat* or diseas* or deteriorat* or injur* or defect*)).ti,ab.
12 Gonarthrosis*.ti,ab.
13 (degenerativ* adj4 arthriti*).ti,ab.
14 or/7-13
15 6 and 14
16 MTF Cascade.ti,ab.
17 Arteriocyte Magellan.ti,ab.
18 Biomet GPS.ti,ab.
19 or/16-18
20 15 or 19
21 limit 20 to ed=20171108-20181231
22 animals/ not humans/
23 21 not 22

