PLATELET RICH PLASMA FOR TREATMENT OF OSTEOARTHRITIS

HEALTH TECHNOLOGY ASSESSMENT SECTION
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DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

Osteoarthritis (OA) refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. It is the most prevalent chronic rheumatic diseases and is a leading cause of pain and disability in most countries worldwide. The goal of OA treatment is to control symptoms and to prevent disease progression. Recently, platelet rich plasma (PRP) has been attracting attention as an innovative and promising procedure to stimulate repair or replace damaged cartilage in patients with osteoarthritis.

This information was requested by the Head of Service for Orthopaedic, Ministry of Health Malaysia due to the concern in terms of socio-economic costs and national health levels that PRP procedures are used indiscreetly without sufficient medical evidence.

Objective/aim

To assess the efficacy, safety and cost -effectiveness of platelet rich plasma for the treatment of osteoarthritis.

Results and conclusions

Two systematic reviews, two 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

Methods

Literature was searched through electronic databases which included MEDLINE, Cohrane Library via Ovid, EMBASE, PubMed and general databases such as Google Scholar.

The search strategy used these terms either singly or in various combinations: Platelet rich plasma, growth factors, thrombocytes rich plasma, autologous platelet rich plasma, osteoarthritis, degenerative joint disease ans osteoarthrosis.

The search was limited to human study. The last searched was conducted on 10 April 2013.

PLATELET RICH PLASMA FOR TREATMENT OF OSTEOARTHRITIS

1. INTRODUCTION

Osteoarthritis (OA) refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. OA is a metabolically active repair process that takes place in all joint tissues and involves localised loss of cartilage and remodelling of adjacent bone.[1]

OA is the most prevalent of the chronic rheumatic diseases and is a leading cause of pain and disability in most countries worldwide. The prevalence of OA increases with age and generally affects women more frequently than men. Most of the OA disability burden is attributable to the hips and knees.[2] In the Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) study involving 2594 people in Malaysia, 14.4% complained of pain in the joints and/or musculoskeletal pain and 11.6% had low back pain. The knee was responsible for 64.8% of all complaints pertaining to the joints, and more than half those examined with knee pain had clinical evidence of OA.[3]

The goal of OA treatment is to control symptoms and to prevent disease progression.[4] The management of OA can be divided as pharmacological and non-pharmacological. Pharmacological treatment includes oral analgesics, topical treatments and intra-articular injections. Non-pharmacological treatment includes exercise, manual therapy, weight loss and electrotherapy.[1]

Recent research showed that imbalance between anabolic and catabolic mechanisms, growth factors and inflammatory mediators played an important role in pathophysiology of OA.[4] Growth factors are a group of biologically active polypeptides produced by the body that can stimulate cellular division, growth, and differentiation. In articular cartilage, numerous growth factors work in concert to regulate development and homeostasis of articular cartilage throughout life.[5]

Recently, platelet rich plasma (PRP) has been attracting attention as an innovative and promising procedure to stimulate repair or replace damaged cartilage due to the pools of growth factors stored in the α-granules of platelets which is a natural concentrate of autologous growth factors from the blood.[6] PRP is not only used in orthopaedics and sports medicine but also used in the fields of dermatology, plastic surgery, dentistry, otolaryngology, urology, ophthalmology and neurosurgery.

However there are conflicting views on the effectiveness of PRP since most growth factors are secreted within one hour after intraarticular PRP injection, PRP may not be able to alter the pathophysiology of chronic diseases such as

osteoarthritis, and it is difficult to expect that cartilage that is already worn out will regenerate with that short exposure of growth factors.[7]

This information was requested by the Head of Service for Orthopaedic, Ministry of Health Malaysia due to the concern in terms of socio-economic costs and national health levels that PRP procedures are used indiscreetly without sufficient medical evidence.

2. OBJECTIVE/AIM

To assess the efficacy, safety and cost -effectiveness of platelet rich plasma for the treatment of osteoarthritis.

3. TECHNICAL FEATURES

Platelet rich plasma is defined as autologous blood with a concentration of platelets above baseline values. Some authors are more precise and consider PRP platelet concentrations to be approximately five times above normal. More specific elements of PRP have not been uniformly defined in the literature. A commonly accepted PRP concentration is approximately 400% of the peripheral blood platelets count, and it should contain 1 million platelets or more per microlitre.[4]

PRP is also a concentration of several fundamental protein growth factors proved to be actively secreted by platelets to initiate mesenchymal tissue healing. These growth factors stimulate cell proliferation, migration, differentiation, and matrix synthesis and can affect chondrocyte metabolism, chondrogenesis and improve cartilage healing in vivo. PRP also contains plasmatic proteins such as fibrin, fibronectin, and vitronectin, which act as mesenchymal cell adhesion molecule.[8]

Autologous PRP was first used in 1987 by Ferrari et al following open heart surgery. Since that time, PRP has been used in sports medicine, orthopaedics, dentistry, dermatology, ophthalmology, and plastic, cardiothoracic and maxillofacial surgery.

There are many preparative methods that produce PRP with different characteristics based on the presence of other cells, in particular leucocytes, activation and storage modalities, and many other variables that are not of secondary importance for determining PRP properties and clinical effects.[4]

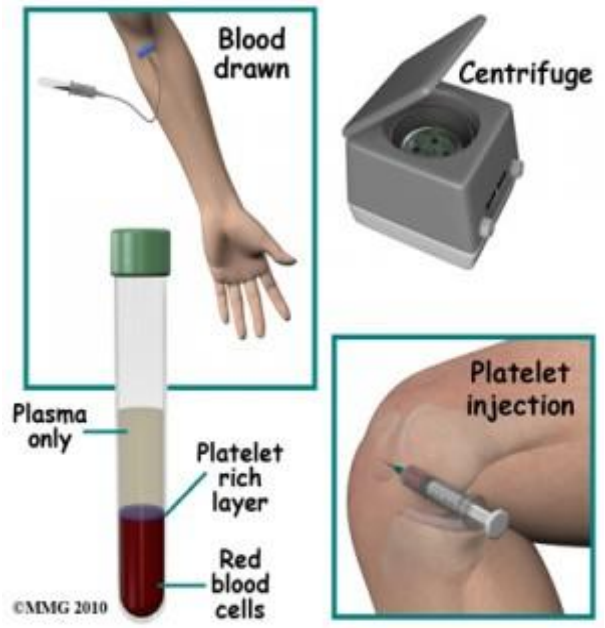

Figure 1. Illustration of PRP procedure

PRP injections are prepared from the patient's own blood with strict aseptic technique. After being centrifuged, the activated platelets are injected into the abnormal tissue releasing growth factors that recruit and increase the proliferation of reparative cells.

One of the methods, used 150 ml venous blood sampled for every knee treated with PRP. Two centrifugations (the first at 1,480 rpm for 6 minutes to separate erythrocytes and the second at 3,400 rpm for 15 minutes to concentrate platelets) produced a unit (20 mL) of PRP.

4. METHODS

4.1. Searching

These scientific databases were searched such as;

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- Embase 1988 to 2013 Week 02
- EBM Reviews - Cochrane Central Register of Controlled Trials- December 2012
- EBM Reviews – Database of Abstracts of Review of Effects (4rd Quarter 2012)
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to December 2012
- EBM Reviews - Health Technology Assessment - 4th Quarter 2012

- NHS Economic Evaluation Database - 4th Quarter 2012
- PubMed

Other database or websites as below were also searched
- EuroScan
- INAHTA
- US FDA

General databases such as Google and Google Scholar were also searched. Animal studies were excluded.

The search strategy used these terms either singly or in various combinations: Platelet rich plasma, growth factors, thrombocytes rich plasma, autologous platelet rich plasma, osteoarthritis, degenerative joint disease ans osteoarthrosis. The last search was conducted on 10 April 2013.

Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients with osteoarthritis
Interventions	Platelet rich plasma,
Comparators	Hyaluronic acid, placebo
Outcomes	Reduction in pain, improvement in joint function, cartilage regeneration, quality of life
Study design	All primary and secondary studies of acceptable quality

Exclusion criteria

Study design	Animal studies
Indications	PRP used for other indications

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US / Canadian Preventive Services Task Force (see Appendix 2)

Data were extracted and summarised in evidence table (see Appendix 3). The data were not pooled and only qualitative analysis was carried out.

5. RESULTS AND DISCUSSION

Two systematic reviews, two randomized controlled trials (RCT) , three non-randomized controlled trial and one retrospective cohort study were included in this review. The two non RCT and one retrospective cohort study were included in one of the systematic review, thus will not be discussed separately. The excluded studies were listed in Appendix 4.

5.1. Safety

PRP is produced from patients' own blood and is not regulated by FDA if it is only minimally manipulated. However the devices used to prepare PRP are regulated and many of these devices have received FDA approval.

Filardo et al in an RCT, reported no major complications related to the PRP or hyaluronic acid (HA) injections were observed during the treatment and the 12-month follow-up period. A significantly higher post-injective pain reaction was observed in the PRP group (p=0.039). However, this reaction was self-limiting within a few days and did not compromise the overall outcome.[9] Level 1

In another RCT conducted by Sanchez et al 50 adverse events were reported in 50 patients, 26 in the plasma rich in growth factors (PRGF-Endoret) group and 24 in the HA group. Adverse events were generally mild and evenly distributed between the groups (p=0.811). Most of the adverse events (96% in the PGFR-Endoret group and 92% in the HA group) were not related to the type of treatment. The number of patients who withdrew because of adverse events was similar between groups. One patient who received HA felt numbness in the infiltration area and another patient in this group had itching on the outside area of both thighs. One patient treated with PRGF-Endoret had pain after the third infiltration. All the adverse events disappeared in 48 hours.[10] Level 1

In a non-RCT reported by Spakova et al, no major adverse events or complications were observed in both groups. Mild worsening of pain in the knee joint after application of PRP occurred in six cases. The pain was spontaneously resolved after two days.[8] Level II-1

5.2 Efficacy

Frizziero et al conducted a systematic review (SR) and included two animal studies and six human studies on PRP. The human studies included were four case series[6, 11-13] and two non-randomised controlled trial.[14, 15]

A case series by Sampson et al which was included in Frizziero et al systematic review, evaluated 13 patients with primary and secondary OA. The patients received one injection of PRP every four weeks over 12 weeks. These patients were followed up for 52 weeks. The results showed that six of the 13 patients showed increased femoral articular cartilage at the lateral condyle, medial condyle, and intercondylar notch based on ultrasound measurement. There were significant and linear improvements in the knee injury and osteoarthritis outcome score (KOOS) and in Visual Analogue Score (VAS) scores at 1-year follow-up compared with pre-injection values. Eight patients were satisfied with the treatment.[4 Level II-2]

In another case series by Kon et al, 115 knees in 91 patients were treated with three PRP injections every 21 days for 2 months, and were prospectively evaluated before treatment, at the end of treatment, and at six and 12 months after treatment. A statistically significant improvement in all clinical scores was obtained from the basal evaluation to the end of treatment. These improvements were maintained at six months but the scores tended to be worse at 1 year, but 80% of patients were satisfied. The objective International Knee Documentation Committee (IKDC) scores showed a statistically significant decrease between six and 12 months ($p<0.0005$) and the IKDC scores were significantly worse at 12 months ($p<0.02$). Older patients had a lower improvement at six months ($p<0.049$) than younger patients, and showed more severe changes in the joint ($p<0.0005$). Worst results were seen in women and in patients with higher BMI ($p<0.045$).[4 Level II-2]

Of the 115 knees evaluated, 114 were available for the 2-year follow up which was reported in another paper by Filardo et al. The evaluation performed at 2 years confirmed the same trend with an overall worsening of the results obtained, even though they remained better than the basal level ($p<0.0005$). The level of satisfaction was confirmed at the 24-month evaluation. The median duration of the beneficial effect was nine months. A greater and longer effect was found in young men with a low BMI and degree of cartilage degeneration.[4 Level II-2]

In a non-randomised controlled trial included in the SR, Kon et al compared the efficacy of PRP and HA intraarticular injections for the treatment of OA knees. Statistically significant improvement in all clinical scores relative to the basal evaluation at 2 and 6 months were observed in all treatment groups, with the worst results obtained in older patients and in those with higher degrees of cartilage degeneration. The IKDC and EuroQol Visual Analogue Scale (EQ VAS) scores at 6 months showed better results in the PRP group than in the low

molecular weight (LW) HA and high molecular weight (HW) HA at 6 months. In patients aged 50 years or younger, PRP was more effective than LW HA or HW HA at six months. In patients older than 50 years, the results were equivalent at both two and six months. PRP was superior at six months in those with cartilage degeneration and early OA. None of these procedures resulted in important improvements in OA progression.[4] Level II-2

Another non-randomised study included in the review compared the effects of two different approaches to the production of PRP: single and double spinning procedures. Enrolled in this study were 144 patients who were divided into three groups: degenerative chondral lesion, early OA and advanced OA. Both treatment groups showed statistically significant improvement in all the scores evaluated. The subjective IKDC score showed a statistically significant improvement ($p<0.0005$) at two months, which was maintained at six and 12 months ($p<0.0005$). Similarly, the EQ-VAS score showed statistically significant improvements ($p<0.0005$) at two, six and 12 months with respect to the basal levels. The Tegner score also showed a statistically significant improvement at two months ($p<0.0005$). Further improvement was seen at six months and then the results remained stable at 12 months. The satisfaction levels were similar: 76.4% in the PRGF group and 80.6% in the PRP group. Better results were achieved in younger patients with a low degree of cartilage degeneration.[4] Level II-2

Another case series in the review, Napolitano et al included 27 patients which were divided into two groups: those with arthritis of the knee and those with cartilage disease (first or second degree lesions according to the classification of Outherbridge). Patients received three PRP injections (for a total of about 15 ml) at weekly intervals and were prospectively evaluated before treatment and seven and 180 days after the end of treatment. Both groups showed improvement in the long term and pain decreased substantially from the time of the first infiltration, this treatment gave better results in younger patients with less severe joint degeneration. Based on these studies, Frizziero et al concluded that PRP may be useful in the early stages of OA to modulate inflammatory processes. Although the studies are encouraging, more data and long term follow-up are required before PRP can be recommended in the treatment of OA.[4] Level II-1

Another review by Fortier et al on the role of growth factors in cartilage repair included two studies. Sanchez et al conducted a retrospective cohort study on 60 patients where 30 of them received PRGF intra-articular injections and a similar group received HA whilst Kon et al case series which included 100 patients with 115 knees who were treated with four PRP intra-articular knee injections given every 21 days. In Sanchez et al study, the pain rate subscale (Western Ontario and McMaster Universities Arthritis Index, WOMAC) reached 33.4% for the PRP group compared with 10% for the HA group ($p=0.004$). The percent reductions in the physical function subscale and overall WOMAC at five weeks were also associated solely with treatment modality in favour of PRP with $p = 0.043$ and $p = 0.010$ respectively. In Kon et al study, a substantial improvement in IKDC score

and EuroQol (EQ-VAS) scores were noted at the end of therapy at both the 6- and 12- month time points. The IKDC subjective score as well as the EQ-VAS score also demonstrated major improvements at the end of therapy. The authors concluded in their review that the application of growth factors in the treatment of local cartilage defects as well as osteoarthritis appears promising. However, further research is needed at both basic science and clinical levels before routine application. [5] Level II-2

There were two RCTs on PRP or Plasma Rich in Growth Factors (PRGF-Endoret) retrieved.[9, 10]

Filardo et al in a RCT included 109 patients (55 patients treated with HA and 54 patients with PRP), affected with monolateral lesion with a history of chronic (for at least four months) pain or swelling of the knee and imaging findings of degenerative changes of the joint or MRI findings of degenerative changes in patients presenting with no OA x-ray findings. A cycle of three weekly injections was administered. The patients were blinded on the treatment received. All patients were prospectively evaluated before and at 2, 6 and 12 months after the treatment. Preliminary analysis showed statistically significant improvement of all clinical scores from basal evaluation to the 2, 6 and 12 month follow-up in both treatment groups. However, there was no significant different between the two groups.[9] Level 1

In the PRP group, the IKDC subjective score increased from 50.2 ± 15.7 at the basal evaluation to 62.8 ± 17.6 at 2 months, 64.3 ± 16.4 at 6 months, and 64.9 ± 16.8 at 12 months. In the HA group the IKDC score increased from 47.4 ± 15.7 at the basal evaluation to 61.4 ± 16.2 at 2 months, 61.0 ± 18.2 at 6 months and 61.7 ± 19.0 at 12 months.[9] Level 1

The EQ-VAS presented the same trend with improvements in both groups but without any inter-group difference.[9] Level 1

The activity level, evaluated by Tegner score, also showed a similar improvement for the PRP group (from basal 2.9 ± 1.4 to 3.8 ± 1.3 at 12 months of follow-up) but the HA group (from basal 2.6 ± 1.2 to 3.4 ± 1.6 at 12 months of follow-up). Similar results were documented using KOOS score, in all subcategories. [9] Level 1

In another RCT reported by Sanchez et al 176 patients aged between 41 and 74 years old and diagnosed to have OA of the knee based on American College of Rheumatology criteria with radiographic confirmation were included. Eighty nine of the patients received PGRF and 87 received hyaluronic acid. The primary outcome was a 50 % decrease in the summed score for the WOMAC pain subscale where patients on PRGF-Endoret have 14.1% higher points compared to controls (95% CI 0.5 to 27.6, p=0.044). As for the secondary outcomes on normalised WOMAC pain score, normalised WOMAC stiffness score, normalised WOMAC physical function score, normalized WOMAC total score, Lequesne

Index, the rate of response was higher in the PRGF - Endoret group but there was no statistically significant differences between the two groups.[10 Level 1]

Spakova et al in a non-RCT included 120 patients with OA of the knee joint. Sixty of the patients received PRP and 60 patients received HA. The results measured using WOMAC index, showed improvement in the score from 38.76 ± 16.50 to 14.35 ± 14.18 points at 3-month follow-up and to 18.85 ± 14.09 points at 6-month follow-up in the PRP group. As for the HA group, there was improvement in score from 43.21 ± 13.70 to 26.17 ± 17.47 points at 3-month follow-up and to 30.90 ± 16.57 points at 6-month follow-up. Comparison of the results in the PRP and HA was statistically significant, $p<0.01$.[8 Level II-1] Numeric Rating Scale was also used to measure the outcome. In the PRP group, the results were 5.27 ± 1.87 at baseline, 2.06 ± 2.02 at 3 month follow-up and 2.69 ± 1.86 at 6-months follow-up. In the HA group, the results were 6.02 ± 1.77 at baseline, 3.98 ± 2.27 points at 3-month follow-up and 4.3 ± 2.07 at 6-month follow-up. The comparison of the results between the two groups was statistically significant.[8 Level II-1]

5.3 Cost-effectiveness

There was no retrievable evidence on cost-effectiveness particularly local economic studies. The cost of treatment ranged from USD 500 to USD 2000.[16, 17] If the procedure includes ultrasound guidance, the cost can be higher.

5.4 Limitations

There are several limitations in this review. The selection of the studies was done by one reviewer and checked by another reviewer. Although there was no restriction in language during the search but finally, only English full text articles were included in this report. All the studies included have no placebo group and none of the studies reported long term outcome.

6. CONCLUSION

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 comparison, used hyaluronic acid as control. In some countries such as the United Kingdom, intra-articular hyaluronan injections are not recommended for the treatment of osteoarthritis.[1]

The short term evidence showed that PRP may be beneficial for young patients (<50 years old) 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

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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present
1. Osteoarthritis, Hip/ or Osteoarthritis/ or Osteoarthritis, Spine/ or Osteoarthritis, Knee/
2. (Degenerative adj1 arthriti*).tw.
3. Osteoarthr*.tw.
4. (osteoarthritis adj2 hip).tw.
5. (osteoarthri* adj2 knee).tw.
6. ((spinal or lumbar) adj1 osteoarthritis).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Platelet-Rich Plasma/
9. platelet rich plasma.tw.
10. 8 or 9
11. 7 and 10

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane Database of Systematic Reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS Economic Evaluation Database	
INAHTA	
FDA	
Horizon Scanning Database	
Others	

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomisation.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

9.3 Appendix 3

Abbreviation

BMI	Body Mass Index
HA	Hyaluronic Acid
ICRS	International Cartilage Research Society Visual Assessment Scale
KOOS	knee injury and osteoarthritis outcome score
IKDC	International Knee Documentation Committee
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal stem cell
PBPC	Peripheral Blood Progenitor Cell
PBSC	Peripheral Blood Stem Cell
PRGF	Platelet Rich in Growth Factors
PRP	Platelet Rich Plasma
RCT	Randomised Controlled Trial
US FDA	United States of America Food and Drug Administration
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index

9.4 Appendix 4

EVIDENCE TABLE : PLATELET RICH PLASMA FOR OSTEOARTHRITIS TREATMENT
QUESTION : IS PLATELET RICH PLASMA SAFE AND EFFECTIVE FOR OSTEOARTHRITIS TREATMENT?

Bibliographic citation	Study type and methods	LE	Num. of pts and Pt characteristics	Intervention	Comparison	Follow up	Outcome measures	General comments
Frizziero A, Giannoti E, Ferraro C et al. Platelet Rich Plasma intra-articular injections: a new Therapeutic strategy for the treatment of knee osteoarthritis in sport rehabilitation. A systematic review. Sports Sci Health. 2012;8:15-22.	Systematic review	II-1	2 animal studies and 6 human studies were included The human studies were: Samson 2010 – case series Kon 2010 – case series Filardo 2011 – case series Kon 2011 – non-RCT Filardo 2011 – non-RCT Napolitano 2012 - case series Studies included were on effectiveness and safety of PRP for the treatment of knee OA	Platelet rich plasma, platelet rich growth factor	No control or Hyaluronic Acid	Up to 24 months	PRP has been shown to be an effective and well tolerated treatment option in OA, with greater and longer effects in young men with a low degree of cartilage degeneration. PRP may be useful in the early stages of OA to modulate inflammatory processes. Although the studies are encouraging, more data and long term follow-up are required before PRP can be recommended in the treatment of OA.	Language limitations to English, Italian, French and Spanish.

			Exclude case reports and letters to editors Language restriction – English, Italian, French and Spanish					

EVIDENCE TABLE : PLATELET RICH PLASMA FOR OSTEOARTHRITIS TREATMENT
QUESTION : IS PLATELET RICH PLASMA SAFE AND EFFECTIVE FOR OSTEOARTHRITIS TREATMENT?

Bibliographic citation	Study type and methods	LE	Num. of pts and Pt characteristics	Intervention	Comparison	Follow up	Outcome measures	General comments
Fortier LA, Barker JU, Strauss EJ, et al. The role of growth factors in cartilage repair. Clin Orthop Relat Res. 2011;469:2706-2715.	Systematic review	II-2	2 studies on PRP were included Sanchez 2008_ retrospective cohort study including 60 patients where 30 received PRGF intra-articular injections and a similar group received HA And Kon 2010 – a case series including 100 patients with 115 knees who were treated with four PRP intra-articular knee injections given every 21 days.	Platelet rich plasma	Hyaluronic acid Or no comparison	5 weeks and 12 months	Sanchez – the pain rate subscale (WOMAC) reached 33.4% for the PRP group compared with 10% for the HA group (p=0.004). The percent reductions in the physical function subscale and overall WOMAC at 5 weeks were also associated solely with treatment modality in favour of PRP with p = 0.043 and p = 0.010 respectively. Kon et al – a substantial improvement in International Knee Documentation Committee (IKDC) and EuroQol (EQ-VAS scores was noted at the end of therapy at both the 6- and 12- month time points. The IKDC subjective score as well as the EQ-VAS score also demonstrated major improvements at the end of therapy.	Low quality of studies included

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Filardo G, Kon E, martino AD, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. BMC Musculoskeletal Disorders. 2012;13(229): 8 pages.	Randomised controlled trial	I	109 patients (55 treated with HA and 54 with PRP) Patients affected with monolateral lesion with a history of chronic (for at least 4 months) pain or swelling of the knee and imaging findings of degenerative changes in patients presenting with no OA x-ray findings All patients underwent harvesting to obtain autologous PRP	Platelet Rich plasma 150 ml venous blood was sampled for every knee treated with PRP. 2 centrifugations (the first at 1,480 rpm for 6 minutes to separate erythrocytes and the second at 3,400 rpm for 15 minutes to concentrate platelets) produced a unit (20 mL) of PRP. The unit of PRP was divided into 4 small units of 5 mL each. 1 U sent for analysis of platelet concentration --3 U were stored at -30°C.	Hyaluronic Acid	12 months	**Efficacy** Preliminary analysis showed statistically significant improvement of all clinical scores from basal evaluation to the 2, 6 and 12 month follow-ups in both treatment groups. No significant different between the two groups. In the PRP group, the IKDC subjective score increased from 50.2 ± 15.7 at the basal evaluation to 62.8 ± 17.6 at 2 months, 64.3 ± 16.4 at 6 months, and 64.9 ± 16.8 at 12 months. In the HA group the IKDC score increased from 47.4 ± 15.7 at the basal evaluation to 61.4 ± 16.2 at 2 months, 61.0 ± 18.2 at 6 months and 61.7 ± 19.0 at 12 months. The EQ-VAS presented the same trend with improvements in both groups but without any inter-group difference. The activity level, evaluated by Tegner score, also	Blinding

				One week after blood harvesting the injection cycle was started, with 3 weekly injections of PRP or HA.			showed a similar improvement for the PRP group (from basal 2.9 ± 1.4 to 3.8 ± 1.3 at 12 months of follow-up). And HA group (from basal 2.6 ± 1.2 to 3.4 ± 1.6 at 12 months of follow-up). Similar result were documented using KOOS score, in all subcategories **Safety** No major complications related to the injectionswere observed during the treatment and follow-up period. A significantly higher post-injective pain reaction was observed in the PRP group (p=0.039). However, this reaction was self-limiting within a few days and did not compromise the overall outcome.	

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Sanchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (prgf-endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. The Journal of Arthroscopy and Related Surgery. 2012;28(8):1070-1078.	Randomised controlled trial	1	176 patients aged between 41 an d74 years old and diagnosed to have OA of the knee based on American College of Rheumatology criteria with radiographic confirmation Exclusion – BMI >32 Inability to meet radiographic criteria	Plasma-Rich in Growth Factor (PRGF-Endoret) Three treatment given at weekly interval N=89 36 ml of blood extracted through venupuncture directly into 4 extraction tubes containing 3.8% sodium citrate as anticoagulant . The extracted blood was centrifuged at 580 g for 8 minutes at room temperature. Once the blood tubes were centrifuged, the plasma fractions was physically separated by pipeting under	Hyaluronic Acid (3 injections weekly) N=87	24 week	Primary outcome – 50% decrease in the summed score for the WOMAC pain subscale – Patients on PRGF-Endoret has 14.1% higher points compared to controls (95% CI 0.5 to 27.6, p=0.044) Secondary outcomes on normalised WOMAC pain score, normalised WOMAC stiffness score, normalised WOMAC physical function score, normalised WOMAC total score, Lequesne Index, the rate of response was higher in PRGF-Endoret group but there was no significant differences. **Safety** 50 adverse events were reported in 50	Allocation concealment Blinding Intention to treat analysis done

				sterile conditions.			patients, 26 in the PGRF-Endoret group and 24 in the HA group. Adverse events were generally mild and evenly distributed between the groups (p=0.811). Most of the adverse events (96% in the PGFR-Endoret group and 92% in the HA group) were not related to the type of treatment. The number of patients who withdrew because of adverse events was similar between groups. One patient who received HA felt numbness in the infiltration area and another patient in this group had itching on the outside area of both thighs. One patient treated with PRGF-endoret had pain after the third infiltration. All the adverse events disappeared in 48 hours.	

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Spaková T, Rosocha J, Lacko M, et al. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. American Journal of Physical Medicine & Rehabilitation. 2012;91(5):411-417.	Non-randomised clinical trial	II-1	120 patients with OA of the knee joint. Mean age 53 years (range 19-77 years). Mean BMI 27.9 ± 4.1 kg/m^2 in the PRP group and 28.3 ± 4.0 (range, 22.1 – 36.9) kg/m^2 in the HA group	N=60 PRP 27 ml blood sample was drawn into three 10-ml vacutainer tubes, each containing 1 ml of 0.106 M sodium citrate. An aliquot was removed to determine the initial platelet count. The blood sample then centrifuged for 15 minutes at 3200 rpm at 22°C resulting in the three following layers: the inferior layer composed of erythrocytes, the intermediate layer composed of leucocytes, and the superior layer made up of	N = 60 Hyaluronic Acid (Erectus 1.2% CSC Pharmaceuticals Handels GmbH)	6 months	The platelet count in the whole blood had a mean value of 150 ± 30 x 10^6 platelets/ml, and platelet count in PRP had a mean value of 680 ± 132 x 10^6 platelets/ml. **WOMAC index** PRP gp – improvement in score from 38.76 ± 16.50 to 14.35 ± 14.18 points at 3-month follow-up and to 18.85 ± 14.09 points at 6-month follow-up. HA gp – improvement in score from 43.21 ± 13.70 to 26.17 ± 17.47 points at 3-month follow-up and to 30.90 ± 16.57 points at 6-month follow-up. Comparison of the results in the PRP and HA was statistiscally significant, p<0.01 **Numeric Rating Scale** PRP gp – 5.27 ± 1.87 at baseline, 2.06 ± 2.02 at 3 month follow-up and 2.69 ± 1.86 at 6-months follow-up. HA gp – 6.02 ± 1.77 at	No randomisation

				plasma. The buffy coat layer together with the plasma layer was collected, and the third centrifugation step at 3200 rpm for 10 minutes was performed to obtain a two-part plasma: the upper part consisting of platelet-poor plasma and the lower part consisting of PRP. The platelet –poor plasma was first discarded. The tubes were shaken vigorously for 30 secs to suspend platelets. The buffy coat layer, consisting of platelets, was then aspirated into a syringe in a volume of 3 ml of plasma and used for the intra-articular injection within 30 mins.			baseline, 3.98 ± 2.27 points at 3-month follow-up and 4.3 ± 2.07 at 6-month follow-up. The comparison of the results between the two gps was statistically significant. No major adverse events or complications were observed in both groups. Mild worseding of pain in the knee joint after application of PRP in six cases, which was spontaneously resolved after two days.	

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Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. The Journal of Arthroscopy and Related Surgery. 2011;27(11):1490-1501.	Non randomised clinical trial	II-1	150 consecutive patients affected by cartilage degenerative lesions, early OA and severe OA	PRP N=50 150 ml venous blood was sampled for every knee treated with PRP. A complete peripheral blood count was also collected at the time of initial blood draw. Then, 2 centrifugations (the first at 1,480 rpm for 6 minutes to separate erythrocytes and the second at 3,400 rpm for 15 minutes to concentrate platelets) produced a unit (20 mL) of PRP. The unit of PRP was divided into 4 small units of 5	2 control group (50 in each groups) 1. High-molecular weight (HW) HA (30 mg/2 mL of HA with molecular weight 1,000 to 2,900 kDa) 2. Low-molecular weight (LW) HA (20 mg/ 2 mL of HA with molecular weight 500 to 730 kDa)	6 month	**Efficacy** Analysis at 6-month follow up showed better IKDC results in the PRP group compared with the LW HA group (p=0.003), as well as compared with patients treated with HW HA (p=0.005), and the same results were found with the EQ VAS (PRP vs LW HA, p=0.001; PRP vs HW HA, p=0.002) After 2-month follow-up (at which the same results were obtained from the PRP and LW HA groups) a significant difference was documented over time, p=0.001, with a further improvement inthe PRP group and a worsening of the results obtained in the patients treated with LW HA injections.	No blinding No randomisation

				mL each. -1 U sent for analysis of platelet concentration -1 U used for the first injection -2 U were stored at -30°C. Injections administered every 14 days; for the second and third treatments, the samples were thawed in a dry thermostat at 37°C for 30 minutes just before application. Before the injection, 10% calcium chloride was added to the PRP unit to activate platelets.			The analysis of the improvements from 2 to 6 months showed a different trend for the different treatments for the pathology subgroup analysis. Patients affected by cartilage degeneration improved further at 6 months in the PRP group, whereas those in the LW HA group worsened at 6 months. Patients affected by early OA presented stable results in the PRP group whereas those in the LW HA group worsened. On the contrary, in the PRP group the IKDC results of patients with advanced OA worsened from the 2-month follow-up to the 6-month follow-up, whereas the group receiving LW HA injections showed more stable results in the higher degree of knee degeneration. PRP and LW HA treatments offered similar results in patients aged over 50 years and in the	

							treatment of advanced OA. PRP showed a better performance compared with HA in younger patients affected by cartilage lesions or early OA. **Safety** No complications related to the infiltrations were observed during the treatment and follow-up period.	

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Sanchez M, Anitua E, Azofra J, et al. Intra-articular injection of an autologous preparation rich in growth factors for the treatmnet of knee oa; a retrospective cohort study. Clinical and Experimental Rheumatology. 2008;26:910-913	Retrospective Cohort Study Both treatments were administered in series of three intra-articular injections at one-week intervals.	II-2	60 patients diagnosed according to the American College of Rheumatology Criteria. Matched according to age, sex, BMI, and radiographic severity. Exclusion Patients with OA secondary to joint inflammatory disease	PRGF (n=30) 34 cc of peripheral blood was collected into 9 cc tubes containing 3.8% (wt/vol) sodium citrate. Tubes were centrifuged at 640g for 8 min and 2 cc plasma fraction located just above the buffy coat was aspirated and dispensed into an empty tube under vertical air flow conditions. Few minutes prior to the infiltration, calcium chloride was added at a final concentration of 22.8 mM.	Hyaluronic Acid (n=30) 2 cc	5 weeks after the third injection	PRGF therapy - This method resulted in moderate enrichment in platelet number a 2.0 ± 0.5 fold increase. **Efficacy** A significant change from baseline in the WOMAC pain subscale was attributed to treatment modality, p= 0.004. The observed success rate by week 5 for the pain subscale reached 33.3% for the PGRFgroup and 10% for the control group. The changes from baseline in the physical function subscale and overall WOMAC were also associated with treatment modality p= 0.043 and p=0.010 respectively. **Safety** Mild injection pain and inflammation of short duration was reported by some patients and	

							reaccumulation of effusion occurred commonly in both groups.	

EXCLUDED STUDIES

1. Gobbi A, Karnatzikos G, Mahajan V et al. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. Sports Health: A Multidisciplinary Approach. 2012;4(2):162-172
2. Jang SJ, Kim JD, Cha SS. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. Eur J Orthop Surg Traumatol. 2012;7 pages. Doi 10.1007/s00590-012-1037-5
3. Wang-Saegusa A, Cugat R, Ares O et al. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. Arch Orthop Trauma Surg. 2010;7pages. Doi 10.1007/s00402-010-1167-3