Keele UNIVERSITY
Impact Accelerator Unit

Keele Critically Appraised Topic (CAT Form)

Clinical Question

What is the clinical effectiveness of intra-articular platelet rich plasma (PRP) injections in the management of knee osteoarthritis (KOA)?

Please note 8.6.2023 the Chartered Society of Physiotherapy instructed all physiotherapists to stop providing platelet-rich plasma (PRP) therapy to patients, with immediate effect, after its classification as a medicinal product.

www.csp.org.uk/news/2023-06-08-csp-issues-urgent-update-use-prp-injections

Clinical bottom line

Optimal PRP preparation protocol has not yet been established. (Bennell 2021)

One high quality randomised controlled trial (n=288), using single slower-speed centrifugation cycle for 5 minutes and injections of fresh leukocyte-poor PRP at weekly intervals for 3 weeks, showed that platelet rich plasma injection has no significant effect on pain in mild to moderate knee osteoarthritis (Grade 2-3 radiological) over a 12 month review period. PRP preparations are heterogeneous and lack standardization. Results from this trial may not be generalizable to other PRP preparations. (Bennell, 2021)

Some low quality evidence showed a benefit in pain and function for PRP over saline, corticosteroid and hyaluronic injections in grade 1-2 osteoarthritis but this evidence should be interpreted with caution.

Some low to moderate level studies have found PRP injection had no significant difference in adverse events compared to saline or hyaluronic acid. Why is this important?

State why your question is important. Have you noticed clinical inconsistencies or variation in practice? Is there a cost to the NHS, is it a particular clinical interest to your group? Give your readers an idea of why you chose this question.

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Why is this important?

Knee osteoarthritis (KOA) is a prevalent condition within the UK with varied conservative management options of weight loss; physiotherapy; oral and topical non-steroidal anti-inflammatory drugs (NSAIDS) and analgesics. Intraarticular (IA) injection therapy for KOA is often the first invasive intervention offered to patients. In practice IA injection takes the form of corticosteroid (CSI), hyaluronic acid (HA) or platelet rich plasma (PRP) injection. Recent NICE guidance on management of OA has not discussed PRP and recommended against the use of HA due to potential harm, CSI is discussed for use "when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise" (NICE, 2022). Further intervention in the form of arthroplasty is reserved for patients with more advanced OA changes of grade 3-4 utilising the Kellgren-Lawrence system.

The patient groups affected by KOA often have reduced functional ability and this can impact on all their social and domestic activities. For patients who struggle with first line conservative intervention such as exercise and weight management advice (as required), injection therapy may be offered.

For physiotherapists it is useful and informative to have awareness of the risks and benefits for KOA interventions. As with all injectables, pain at the injection site and infection are risks. Specifically, NICE Interventional procedure guidance on PRP injection (IPG637, published 2019) reported the 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.

Knowledge of the effectiveness of musculoskeletal interventions, is vital for shared decision making with patients. Particularly in scenarios when patients have failed conservative treatment the physiotherapist is often the healthcare professional who is addressing the patients concerns regarding ongoing management. PRP appears to be a suitable alternative to other forms of intraarticular KOA injection and a current evidence-based knowledge of this intervention is important for shared decision-making conversations to inform patient management.

NICE interventional procedure guidance recommends PRP injection to be closely monitored using outcomes and audit as well as ensuring the local consent and governance processes are in place. Within the National Health Service (NHS) PRP injection is recommended by some organisations, for example, the British Orthopaedic Association (BOA) have produced information which includes PRP injection. Orthopaedic departments are likely to have consultants who are considering PRP using clinical judgement, alongside other more established injectable treatment options. The author is aware of injections being undertaken within a local NHS trust by a small number of orthopaedic consultants, however at the time of this CAT question the data being collected by this service has not been fully collated. Nationally, there is no published data on PRP intraarticular injection practice patterns. Through the physiotherapy profession, iCSP enquiries have not revealed any further insights on current UK clinical practice. Anecdotally PRP is reportedly offered

privately but to the authors knowledge there is currently no publicly available data on the recorded outcomes of these interventions.

Search timeframe (e.g. 2013-2013)

1948-2021

Search criteria

Population Intervention Comparison Outcomes (PICO) themes	**Description**	**Search terms**
Population and Setting E.g. adults with OA, primary care	Adults, Clinical diagnosis of knee OA and/or Tibiofemoral OA	Adults Over 18, Knee OA, Knee Osteoarthritis.
Intervention or Exposure (i.e. what is being tested) e.g. manual therapy	An intraarticular injection of platelet rich plasma.	Platelet rich plasma injection, PRP injection.
Comparison, if any e.g. usual care, leaflet	N/A	N/A
Outcomes of interest e.g. Visual analogue scale, Range of motion	Increased pain, Improved function, Improved range of motion, Cost to healthcare services.	Pain, Function, Range of movement, Mobility, Cost, Risk/Harm.
Types of studies e.g. Randomised Controlled Trails, Systematic reviews	Meta-analyses', Systematic reviews. RCTs.	

Databases searched

PEDro, BMJ Updates, TRIP, NICE, AMED, Bandolier, The Cochrane Library, Medline, Cinahl, Embase, PsyInfo and Pub med

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Date of search

28/11/2021

Results of the search: include the number in each box

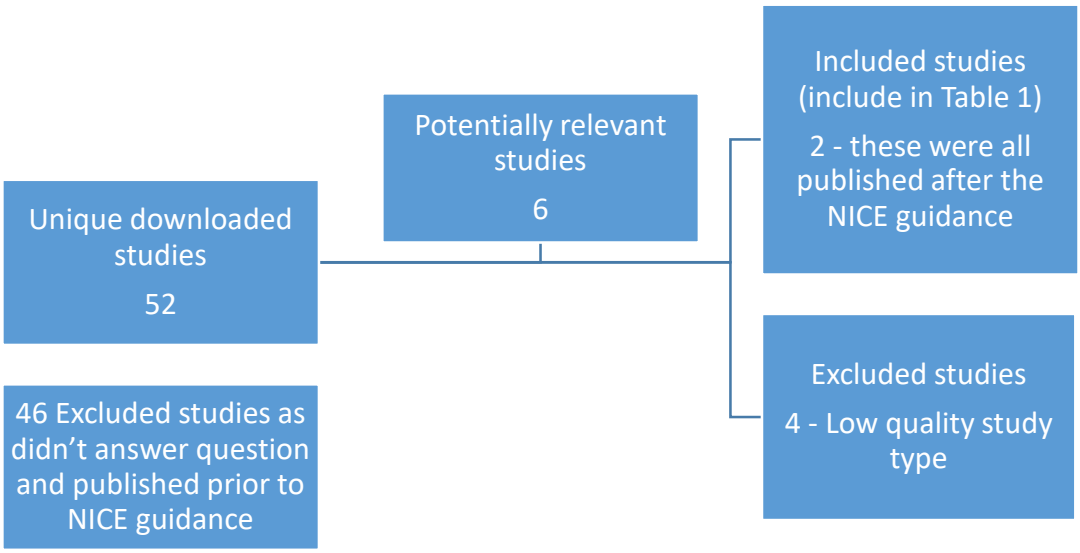

Table 1- Detail of included studies

First author, year and type of study	Population and setting	Intervention or exposure tested	Study results	Assessment of quality and comments
Paper 1 Bennell at al, 2021 Randomized control trail	Randomized 2 group trial, injecting the knee with either saline or with PRP. 144 participants	PRP group – 3x injections at weekly intervals, leukocyte poor, 5ml injection. Compared to injections of 5ml of saline repeated at the same intervals.	Primary Outcomes Improved pain of 2.1 vs 1.8 on VAS scale – not significant between groups measured at 12months.	Good quality study. Clear question and title, study was blinded and participants were randomized and all participants were accounted

	per arm (288 total). Community based volunteer patients in Melbourne/ Sydney region, Australia. Eligibility criteria of >50years old, mild to moderate OA (grade 2-3)	Secondary measure - Pre and 12 month post MRI to measure the thickness of the medial tibial cartilage volume. They also assessed 25 secondary subjective and 6 MRI based structural secondary outcomes.	No significant difference was found regarding the medial tibial cartilage thickness (0.2% difference between groups) <u>Secondary Outcomes</u> Of the 25 subjective outcomes only global improvement had significant improvement (p=0.02) at 2months favouring PRP. At 12 months the global improvement of function and pain was more commonly stated in the PRP group with p value 0.05. None of the 6 secondary MRI outcomes showed statistically significant benefits of PRP at 12-month follow-up.	for throughout the study. Power calculation and confidence interval calculations were made. The results were reported comprehensively with clear p values and no drop outs. There was a clear record of adverse events (no significance between groups). The participants were appropriately aged and can be compared to a UK population of patients with KOA. No cost benefit analysis was carried out.

PAPER 2 Hong et al, 2021. Systematic review and meta-analysis	Patients suffering with KOA (no grade stated). All 23 included articles were RCT's, this is a total of 2222 patients (2355 knees). Research based in Beijing University and local hospital.	Efficacy & safety of IA PRP. Adverse events were reported for saline and HA. Safety was not reported in comparison to CS injection (111pts). PRP versus placebo (saline) (5 studies – all poor quality & blinding/bias present) PRP vs (HA) (14 studies) Triple versus single PRP (2 studies)	SAFETY: PRP vs saline: no significant difference in safety between the two groups (153pts) PRP vs HA: no significant difference, (383pts) VAS was significantly improved with PRP at 6 months (153 pts total) WOMAC significantly improved with PRP at 1 and 6 months however I^2 was 60% showing poor homogeneity (194 pts). PRP showed significant improvement above HA with VAS at 12 months however I^2 was 81% (199pts). No significant difference in VAS at 1 month or	Poor quality paper. Appropriate PICO inclusion criteria. There is high concern that no comment was made as to how the patients were judged to have KOA within individual articles (i.e. radiological grading or by clinical assessment). Appropriate exclusion criteria. Strong numbers of patients across the total number of RCT's but very limited numbers within each assessed criteria. Substantial heterogeneity remained along with various degrees of

			WOMAC at 3 months (100pts).	reported quality. Confidence interval calculations and forest plots were used for each outcome measure to compare various RCT's but power and homogeneity of patients per arm were poor. Outcome measures were appropriate for the population and intervention.

Summary

The author found many articles were comparative in nature, finding PRP commonly compared to saline (placebo), HA, oral NSAIDs and CSI. Safety of PRP in comparison to other injectables was equivocal, adverse events were not significantly different between any of the injection groups. Establishing the diagnosis of KOA has not been discussed in a large systematic review and meta-analysis published since the NICE guidelines were produced. Generally, there was radiological assessment using the Kellgren-Lawrence system. Certainly, in the management of KOA this seems appropriate in much the same way as how other injectables are used in mild/moderate stages of presentation. More invasive interventions become appropriate in the later stages of KOA, as such all articles excluded Kellgren-Lawrence 4. There was disparity in the studies with the larger RCT using grade 2-3 and other RCT's as part of the meta-analysis using grade 1-2.

Research articles convey that PRP is thought to stimulate synovial membrane activity by means of having an anti-inflammatory effect as well as additional chondroprotective effects.

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NICE report platelets contain growth factors that are thought to stimulate chondrocyte proliferation, leading to cartilage repair.

Additional cost benefit analysis of PRP has not been investigated by the current literature.

NICE have interventional procedures guidance on PRP for KOA (IPG 637) which had a review date of January 2022. When published in January 2019 the review found more high-quality evidence was needed for effectiveness to be recommended. The guidance did not give clear direction on current use for clinical practice. NICE based their findings on 2,717 patients from 3 systematic reviews and meta-analyses as well as 5 RCTs. The NICE guidance has to date not been updated.

Implications for practice

There is moderate level evidence which suggests that PRP has no effect on pain over 12 months compared to saline for patient with grade 2-3 KOA. Bennell et al (2021) also found no difference in the thickness of medial tibial cartilage measured with MRI 2 weeks prior and 12 months following the PRP injections.

Low quality evidence suggests that IA PRP injection for grade 1-2 KOA can be useful in improving patients' pain and function for periods of between 9 and 12 months following single injection. These results must be interpreted with caution due to the risk of bias/ blinding issues and potential differences in PRP sample preparation.

Whilst not delivering this intervention, physiotherapists, first contact physiotherapists and advanced practice physiotherapists will be very likely involved in the management of patients offered or receiving PRP injection therapy. Understanding the evidence base underpinning the effectiveness of treatments offered to patients is important to inform shared decision-making processes and onward referral options.

Some studies considered one versus multiple PRP doses as part of a course of treatment. Best current evidence is unable to recommend the optimal PRP protocol (Bennell et al, 2017). Further research to establish an optimal PRP protocol across future studies is required.

Further research has happened since the NICE guidance of Jan 2019, which is included in this CAT. As stated further good quality evidence is needed to look at specifics of which preparation of PRP are more effective. This may lead to more research into IA PRP injections for joints commonly affected by OA, such as the hip. There can be an added cost associated with the different preparations due to equipment required. Based on the findings of this CAT question, further research within the NHS setting that can establish both the clinical effectiveness and cost effectiveness of PRP therapy is needed before this can become a more widely offered treatment option for KOA.

What would you post on X (previously Twitter)?

A recent high quality RCT using single slower-speed centrifugation cycle for 5 minutes and injections of fresh leukocyte-poor PRP at weekly intervals for 3 weeks, suggests PRP

injections have no statistically significant effect on pain in mild-to-moderate knee osteoarthritis over a 12 month review period.

Generally inconsistencies in PRP protocols remain, further research required.

Please note 8.6.2023 the Chartered Society of Physiotherapy instructed all physiotherapists to stop providing platelet-rich plasma (PRP) therapy to patients, with immediate effect, after its classification as a medicinal product.

www.csp.org.uk/news/2023-06-08-csp-issues-urgent-update-use-prp-injections

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Bennell, K. L., Hunter, D. J., & Paterson, K. L. (2017). Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. Current rheumatology reports, 19(5), 24. https://doi.org/10.1007/s11926-017-0652-x

Bennell, K. L., Paterson, K. L., Metcalf, B. R., Duong, V., Eyles, J., Kasza, J., Wang, Y., Cicuttini, F., Buchbinder, R., Forbes, A., Harris, A., Yu, S. P., Connell, D., Linklater, J., Wang, B. H., Oo, W. M., & Hunter, D. J. (2021). Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial tibial cartilage volume in patients with knee osteoarthritis: the RESTORE randomized clinical trial. JAMA, 326(20), 2021–2030. https://doi.org/10.1001/jama.2021.19415

BOA 2022 Injectable Orthobiologic Treatments for osteoarthritis. https://www.boa.ac.uk/resources/injectable-orthobiologic-treatments-for-osteoarthritis.html

Hong, M., Cheng, C., Sun, X., Yan, Y., Zhang, Q., Wang, W., & Guo, W. (2021) Efficacy and safety of intraarticular platelet-rich plasma in osteoarthritis knee: a systematic review and meta-analysis. Biomedical research international, http://doi.org/10.1155/2021/2191926

NICE 2019 Interventional Procedure Guidance (IPG 637) Platelet-rich plasma injections for knee osteoarthritis. https://www.nice.org.uk/guidance/ipg637

NICE 2022 Osteoarthritis in over 16s: diagnosis and management. NICE guideline [NG226] Published: 19 October 2022 https://www.nice.org.uk/guidance/ng226/chapter/Recommendations#pharmacological-management

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Please tick the box that best reflects your clinical bottom line and include the picture on page 1

CAT image	Evidence quality	Checkbox
	Good quality evidence to support use….	☐
	Insufficient or poor quality evidence OR substantial harms suggest intervention used with caution after discussion with patient…	☑
	No good quality evidence, do not use until further research is conducted OR Good quality evidence to indicate that harms outweigh the benefits….	☐

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