

Injectable orthobiologics for knee osteoarthritis: A review of bias in prospective randomised controlled trials and analysis of professional guidelines

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Background

There is ongoing debate regarding the quality and reliability of the research used to justify use of orthobiologics in knee osteoarthritis (OA). Due to the perceived and demonstrated limitations of traditional injections such as corticosteroids and hyaluronic acid,¹ novel intra-articular injectable therapies have gained increasing attention in both the research community and the public.²

The purpose of this study was to assess the risk of bias amongst randomised controlled trials studying the efficacy of injectable biologics in the management of knee osteoarthritis and compare these conclusions to recommendations from established speciality organisations and expert guidelines.

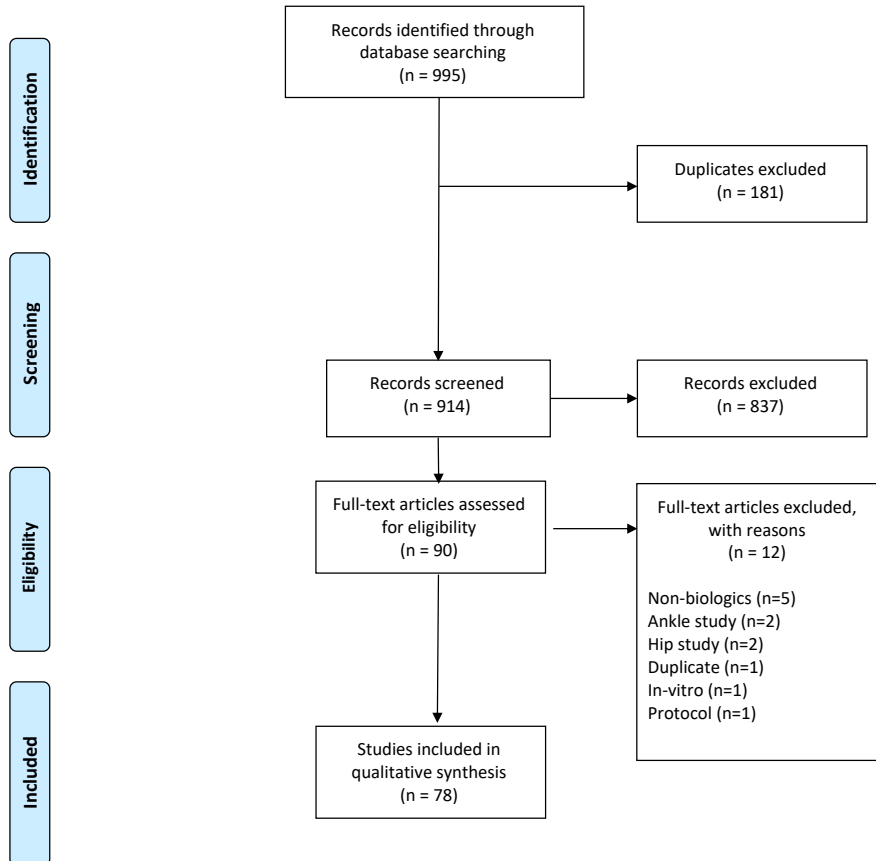


A search of Pubmed and Medline was performed in October 2022 in line with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search terms included 'osteoarthritis', 'orthobiologics' and 'PRP'. The criterion for inclusion was any published, randomised controlled trial studying orthobiologics and knee osteoarthritis.

Studies were assessed for bias using the Cochrane risk-of-bias 2 tool. Professional guidelines were searched via google scholar.





18 studies were ‘high risk’ of bias, 20 were reported as having ‘some concerns’ and 28 were ‘low risk’.

There were a total of 11 professional guidelines identified, with PRP being the most commonly recommended biologic.

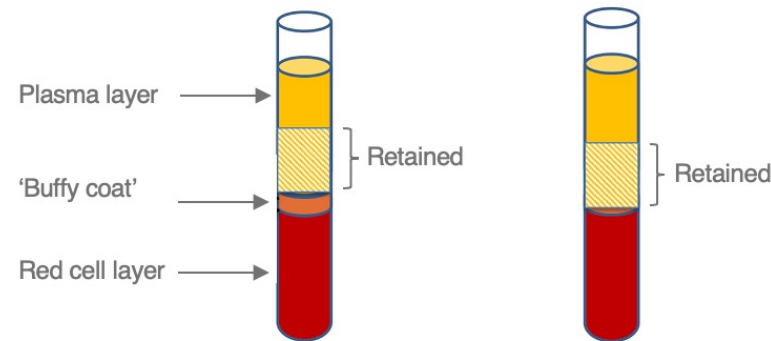
There was no difference in citation factor between those studies which were at risk of bias and those which were not ($p=0.093$). Nor was there a difference in risk of bias for those studies which showed biologics to be superior to controls and those that did not ($p=0.815$).

All studies reported improvement over baseline at final follow up. Orthobiologics were shown to be equivalent or superior to the chosen control group in 87% of studies.

PRP subgroup analysis

- 11 studies = high risk
- 10 studies = some concerns
- 8 studies = low risk

There was no difference in outcomes between LR-PRP and LP-PRP (chi-squared, $p=0.214$). A subgroup analysis of studies analysing PRP outcomes specifically also did not demonstrate differences in risk of bias ($p=0.850$) nor citation factor ($p=0.214$).



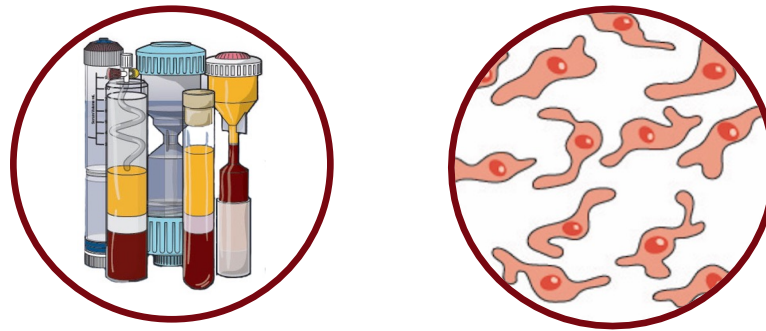
Author	Experimental	D1	D2	D3	D4	D5	Overall
Ahmad et al.	LP-PRP	+	+	+	-	!	-
Angoorani et al.	PRP	-	-	+	-	!	-
Cerza et al.	LP-PRP	!	+	+	+	!	!
Cole et al.	LP-PRP	+	+	+	+	+	+
Di Martino et al.	LR-PRP	+	+	+	+	+	+
Duymus et al.	LP-PRP	!	-	+	-	!	-
Filardo et al.	LR-PRP	+	+	+	+	!	!
Filardo et al.	LR-PRP	+	!	+	!	+	!
Gormeli et al.	LR-PRP	+	!	-	+	!	-
Lana et al.	LR-PRP	+	+	+	+	!	!
Lin et al.	LP-PRP	+	+	+	+	+	+
Lisi et al.	PRP	+	+	+	-	-	-
Montanez-Heredia et al.	LP-PRP	+	-	+	!	-	-
Patel et al.	LP-PRP	+	!	+	+	+	!
Paterson et al.	LR-PRP	+	!	+	+	!	!
Raeissadat et al.	LR-PRP	+	-	+	-	!	-
Raeissadat et al.	LR-PRP	+	!	+	-	!	-
Rahimzadeh et al.	LR-PRP	+	!	+	+	!	!
Sanchez et al.	LP-PRP	+	+	+	+	+	+
Simental-Mendia et al.	LP-PRP	+	+	+	!	+	!
Smith et al.	LP-PRP	+	+	+	+	+	+
Su et al.	LR-PRP	-	-	+	-	!	-
Vaquerizo et al.	LP-PRP	+	+	+	+	+	+
Vaquerizo et al.	LR-PRP x2	-	!	!	-	!	-
Vasavilbaso et al.	LR-PRP	+	+	!	+	+	!
Wu et al.	LR-PRP	+	+	+	+	+	+
Yu et al.	PRP	-	-	!	+	-	-
Joshi Jubert et al.	LP-PRP	+	+	+	+	+	+
Buendia-Lopez et al.	LP-PRP	+	!	+	+	!	!

Society guidance on orthobiologics for knee OA

Association	Year	PRP	APS	ACS	ASA	BMAC	MSC	SVF
American College of Rheumatology	2019	Not recommended	N/A	N/A	N/A	N/A	Not recommended	N/A
Osteoarthritis Research Society International	2019	Not recommended	N/A	N/A	N/A	N/A	Not recommended	N/A
Arthroscopy Association of Canada	2019	Equivocal	N/A	N/A	N/A	Not recommended	Not recommended	N/A
American Academy of Orthopaedic Surgeons	2021	Limited recommendation	N/A	N/A	N/A	N/A	N/A	N/A
National Institute for Health and Care Excellence (Platelet rich plasma)	2019	Limited recommendation	N/A	N/A	N/A	N/A	N/A	N/A
European Society of Sports Traumatology, Knee Surgery and Arthroscopy	2022	Recommended	N/A	Not recommended	N/A	N/A	N/A	N/A
Royal Australian College of General Practitioners	2018	Equivocal	N/A	N/A	N/A	N/A	Not recommended	N/A
American Association of Hip and Knee Surgery	2019	Not recommended	N/A	N/A	N/A	Not recommended	Not recommended	Not recommended
British Orthopaedic Association	2022	Equivocal	Equivocal	Equivocal	N/A	Not recommended	Recommended	Equivocal
National Basketball Association	2021	Recommended	N/A	N/A	N/A	N/A	Not recommended	N/A

Conclusions

There were no professional guidelines which strongly recommended orthobiologics for the management of knee OA. This is despite all RCTs showing improvement over baseline and 87% of studies showing orthobiologics to be equivalent or superior to the chosen control group. Risk of bias and journal citation factor were not associated with favourable results for biologics. PRP was the most commonly recommended biologic with the highest number of RCTs studying its efficacy. There was heterogeneity and contradiction of the professional associations' recommendations of biologics for the treatment of knee OA.



1. Wehling P, Evans C, Wehling J, et al. Effectiveness of intra-articular therapies in osteoarthritis: a literature review. *Therapeutic advances in musculoskeletal disease* 2017;9(8):183-96.
2. Piuzzi NS, Ng M, Chughtai M, et al. The Stem-Cell Market for the Treatment of Knee Osteoarthritis: A Patient Perspective. *J Knee Surg* 2018;31(6):551-56.