Semi-invasive therapies for pain in knee osteoarthritis: a systematic review and network meta-analysis

Siew-Li Goh[1], Melissa Wee Chong[2], Jerri Ling, Zulkarnain Jaafar[3], Zhuang-Li Lim[1], May-Yann Yau[4], Terence Ong[5,6], Jim Richards[7]

1 Sports and Exercise Medicine Research and Education Group, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

2 Sarawak General Hospital, Jalan, Hospital, Kuching, Sarawak, Malaysia

3 Sports Medicine Unit, Department of Orthopedics, Hospital Tengku Ampuan Rahimah Klang, Selangor, Malaysia

4 Sports and Exercise Medicine Unit, Department of Orthopaedics, Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia

5 Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

6 School of Medicine, Taylor's University, Subang Jaya, Selangor, Malaysia

7 Allied Health Research Unit, University of Central Lancashire, Preston, UK

Abstract

Background: The increasing number of semi-invasive pain therapies in knee osteoarthritis poses challenges in decision making. This review aimed to simultaneously compare established intra-articular therapies with newer peri-articular therapies and explore effect modifiers.

Methods: Randomised controlled trials were searched from five electronic databases without date or language restrictions. Study selection and data extraction of reports, retrieved up to May 2024, were performed independently by paired assessors. The primary outcome was six-month pain score. Nine treatments were included. The effect size (ES) for each treatment, relative to placebo, was estimated using standardised means difference and expressed with 95% confidence intervals (CI). The rigour of results was evaluated with subgroup/sensitivity analyses.

Results: A total of 111 studies (14695 participants) were included, with intra-articular hyaluronic acid having the greatest number of participants. Neuro-ablation demonstrated the greatest ES (1.08, 95%CI: 0.07, 2.10). While platelet rich plasma (PRP) ranked second (ES: 0.75, 95% CI: 0.28, 1.22), it was the only intervention demonstrating statistically significant effect at 3, 6, and 12 months. However, this statistical significance was lost in some sensitivity analyses. Larger estimates for biologics and PRP compared to prolotherapy, steroid and hyaluronic acid injections were consistently observed across different time points and in multiple sensitivity analyses. Generally, no statistically significant difference was found between the nine types of therapies.

Conclusion: Although there is robust evidence suggesting greater efficacy of PRP, potentially including biologics, over other interventions, future research is needed to identify the phenotype or patient subgroup that would benefit most from PRP.

1. INTRODUCTION

Despite increases in the understanding of osteoarthritis (OA) pathoetiology, there is still no effective treatment for OA. Supportive therapy, particularly for pain control, remains the mainstay of OA management [1]. In the early stages, OA pain is intermittent, exacerbated by unaccustomed activities and relieved by rest. With disease progression, pain can become more persistent and occur even at rest with increased severity. Universally recommended core therapies such as education and weight loss are the standard of care for the long-term management [1], but they are of limited benefit for acute exacerbation and for unrelenting pain.

Recommendations on pain management involving conventional analgesic agents such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids (IACS) are well debated in various international guidelines[1,2]. Recommendation of these guidelines for newer therapeutic agents (e.g. biologics, prolotherapy), including new therapeutic interventions (e.g. acupuncture, radio-ablation), are less clear due to the uncertainty of current evidence. The multifactorial model of OA pain, along with ongoing effort to improve formularies and their delivery methods, have led to increased challenges in identifying effective pain interventions.

The continuous emergence of new local interventions for pain control is primarily driven by the lack of efficacy and safety of conventional options. NSAIDs and acetaminophen are associated with increased morbidity from organ damage, while IACS have been implicated in deterioration of cartilage quality[3]. The pain relief achieved is often short term, with most treatments having their effects worn off at 6 months[4] which can hamper rehabilitation that aims to restore physical function. Therefore, newer therapeutic agents, especially those with potential to improve structure and quality of cartilage, are appealing because they hold promise in conferring more lasting pain benefits.

This network meta-analysis aims to cohesively analyse the efficacy of a selected range of semi-invasive interventions for pain control that are, in our opinion, relatively popular and easily accessible in most mainstream health-care services. Apart from summarizing the relative efficacy of the selected interventions, we also performed subgroup analyses to examine if the efficacy of selected treatments, namely intra-articular hyaluronic acid (IAHA) and platelet rich plasma (PRP), have changed over time as a result of improved delivery or formulation.

2. METHOD

The protocol for this review was registered in Prospero (CRD 42021286538). Reports of randomised controlled trials (RCTs) fulfilling the eligibility criteria below were searched using five electronic databases: Pubmed, Medline, SPORTDiscus, Web of Science and Google Scholar. An example of search strategy used for Medline is shown in Appendix 1.

The inclusion criteria were as follows: knee osteoarthritis (OA) had to be diagnosed clinically, excluding patients who were planned for or had already undergone surgical procedures on the knee. One of the treatment groups needed to be assigned an injection or other minimally invasive intervention around the knee, which could include prolotherapy (Prolo), platelet-rich plasma (PRP), biologics (such as plasma rich in growth factor and cell-based therapies), steroids, radio-ablation, viscosupplements (such as hyaluronic acid or hyaluronan), or acupuncture. Comparators could be any of the following: placebo or sham treatments, physiotherapy, or non-invasive pharmacological treatments; however, comparators that combined therapies from different groups (e.g., physiotherapy combined with NSAIDs) were excluded. The study included comparisons between different groups of injections or other semi-invasive interventions (e.g., PRP vs. steroids vs. acupuncture). At least one outcome measure of pain, function, or quality of life (QoL) had to be reported within the primary time

point of interest, which ranged from one month to twelve months post-intervention. For this network meta-analysis (NMA), the focus was solely on pain outcomes. No language or date restrictions were applied to the included studies.

The exclusion criteria were as follows: studies involving mixed cohorts with different locations of osteoarthritis (OA) from which isolated outcomes for knee OA could not be extracted; studies that compared different doses, techniques, or routes without a comparator control group (e.g., ultrasound-guided injection vs. blind injection); studies where the control or comparator group received injections other than prolotherapy, platelet-rich plasma (PRP), biologics, steroids, radio-ablation, hyaluronic acid (HA), or acupuncture; studies with data that were not extractable, such as those presented in graphs or quantified in ways unsuitable for generating a pooled estimate; studies that used the contralateral knee as the comparison, used the knee as the unit of analysis, or had fewer than ten patients in the treatment or comparator group; and participants who had undergone knee surgery.

Paired reviewers (MCW, JL, ZLL, MYL, TO) independently extracted data into standardized forms using Microsoft Access. The extracted data were then compared by SLG. Discrepancies in study characteristics, patient characteristics, outcome measures and risk of bias were resolved through consensus.

Selection of outcome measure in studies with multiple outcomes and time points

In cases where more than one self-reported measure of pain was included, the outcome measures extracted were based on a previously reported hierarchy[5]. Measurements at all reported time points were extracted to explore the pain benefits across 3 months, 6 months and

1 year post intervention. However, 6 months (±4 weeks) was used as the primary time point to evaluate the strength of the evidence for chronic OA pain.

Selection of arm

When a study where the route/dosing regimen varied between groups, the group receiving the most potent intervention was selected for analysis, e.g. If Group A received weekly injections for 3 weeks, Group B received weekly injections for 5 weeks, and Group C received Sham injections, the data from Group B was used to compare with Group C. The non-injectable active comparator was grouped according to physical therapy, exercise, education and pharmacotherapy.

Only crucial information was retrieved using google translate. Risk of bias assessment was not performed on non-English publications.

Analysis

End-point measurement was used to estimate effect size (ES) of each intervention. The ES is expressed as standardised means difference (SMD) estimated by Stata (Release 17. College Station, TX: StataCorp LLC). SMD is calculated by the following equation:

SMD= mean difference between groups/ standard deviation of outcome among participants

Missing values

When not specified, the analysis was assumed to be intention-to-treat (ITT) if the number used for analysis matched the number that were randomised to each arm. If the number used for analysis was not reported, we used the number randomised to obtain a conservative estimate of ES.

When variance was not reported, the largest value obtained from other studies with the corresponding measurement tool, was imputed for calculation. In cases where variance was reported for baseline measurements but not for the repeated measures, the baseline variance was extended to the repeated measures from different time points. Random effects based on frequentist approach was used to pool the summary estimates.

Subgroup and sensitivity analysis

Additional analyses were performed to evaluate if the estimates were robust and to examine if the assumptions of transitivity and similarity were violated. The additional analyses made were based on differences in: i) patient characteristics: severity of structural OA, sex distribution; ii) publication date: most recent reports (arbitrarily selected from 2019 to 2022); iii) analysis method: ITT; iv) quality of study as assessed using Cochrane's risk of bias tool (RoB 2.0). Sensitivity analysis to exclude acupuncture was also performed to reduce the heterogeneity that may arise from variations in techniques.

The design-by-treatment interaction model, based on Wald test, was used to evaluate global inconsistency. Local inconsistency between direct and indirect evidence for pairs of comparisons was evaluated using the node-splitting method.

Deviation from registered protocol

The non-injection interventions were analysed as a group, and not primarily classified as pharmacotherapy, non-pharmacotherapy, due to the small number of studies available. We have decided to exclude combinations of different interventions to minimise the heterogeneity of the network and to simplify interpretation.

3. RESULTS

A total of 7253 reports were retrieved from 5 electronic databases (Fig 1 Prisma flow chart). At the end of full text screening, 108 reports were deemed eligible for inclusion based on the registered protocol which covers a few self-reported outcomes. However, we only included 99 reports from 96 studies for this NMA on pain. An updated search in May 2024, provided additional 16 reports to be included. The results reported are therefore based on 111 studies with 14695 participants randomised to the various interventions of interest (Appendix 2).

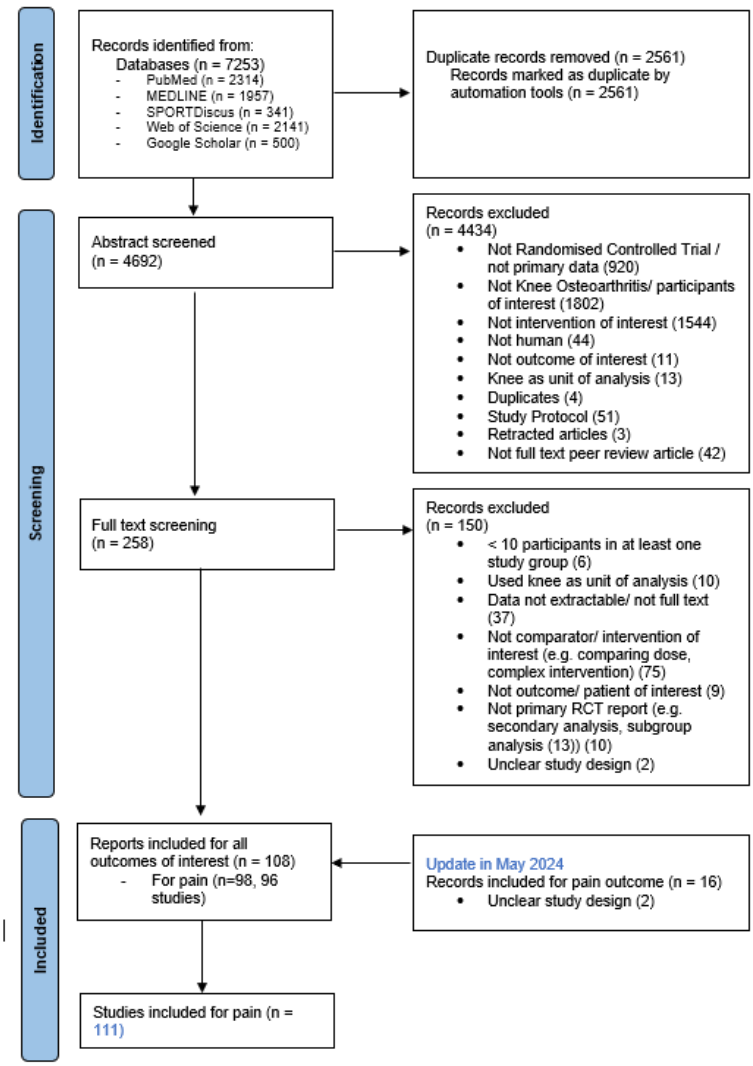


Fig. 1. Prisma flow chart

The network plot for the primary time point of 6 months showed that HA, followed by PRP, were the most considered interventions in terms of sample size (Fig 2 Network plot). The highest number of comparators were found between HA versus PRP and HA versus Placebo. Primarily owing to the semi-invasive nature of the interventions, the RCTs included in the network were graded to be of some concern or high in bias. Studies involving neuro-ablation and biologics are more recent compared to other HA and PRP.

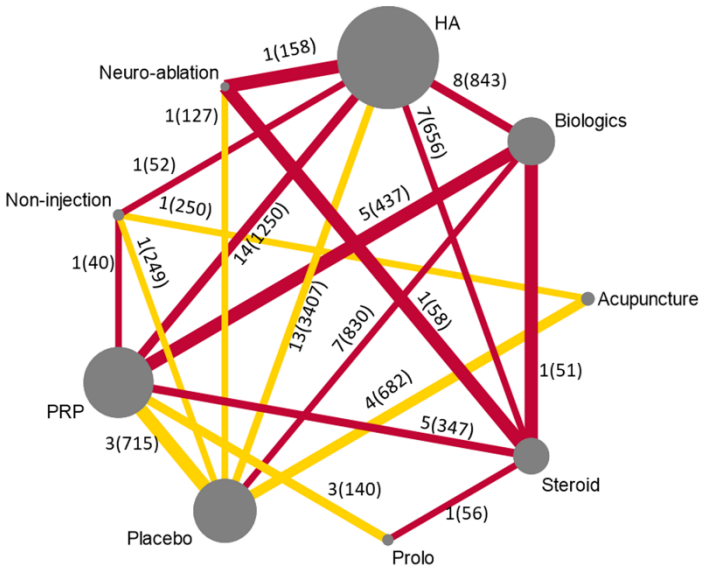
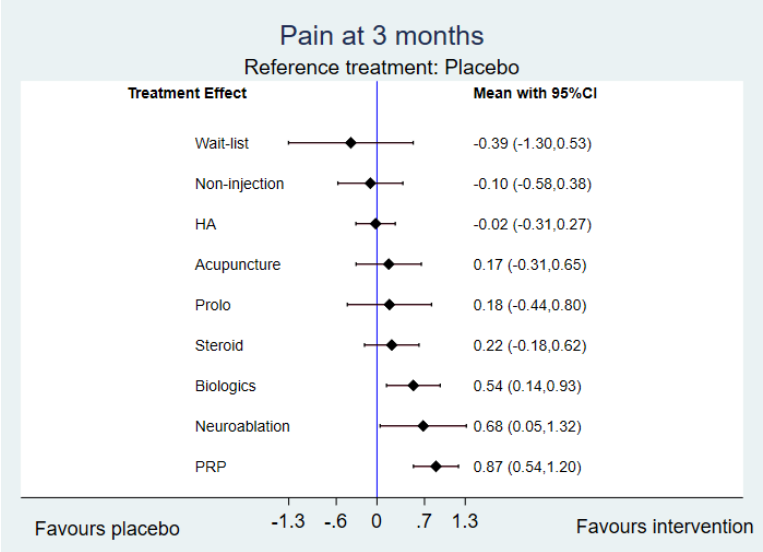


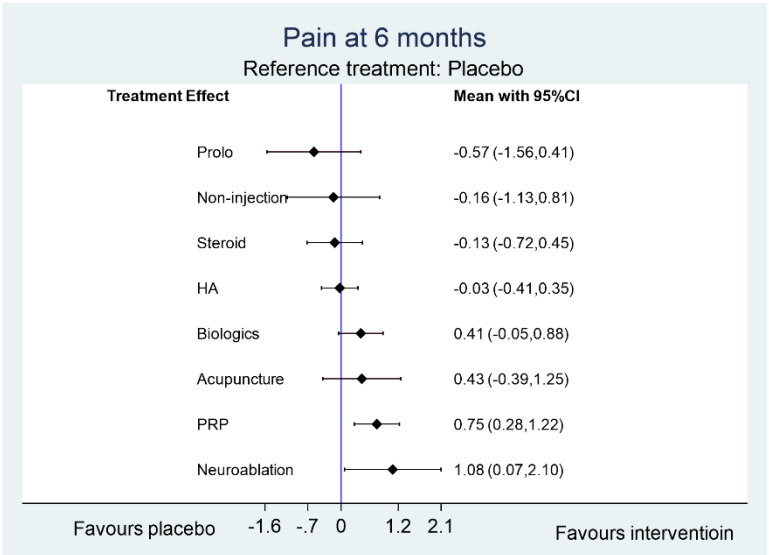
Fig. 2. Network map: Size of node corresponds to number of subjects analysed; thickness of edges corresponds to proportion of recent publications (from 2020); colour of edges represents level of bias (yellow – some concern, red-high risk), number on corresponding line indicates the number of studies and number of participants (in parenthesis) for comparison. (HA, hyaluronic acid; PRP, platelet rich plasma; Prolo, prolotherapy)

Compared to placebo (consisting mainly of sham injections), PRP and neuro-ablation therapies appeared to confer statistically significant pain relieve at 6 months post intervention. Although the ES for neuro-ablation (ES: 1.08, 95%CI: 0.06, 2.11) is the largest, PRP had a more precise estimate as evidenced by a narrower confidence interval (ES: 0.75, 95%CI: 0.27,

1.24). PRP also demonstrated early pain benefits from 3 months and lasting up to 12 months (Figures 3a, 3b,3c).

At the 3 and 12 months' time points, statistically significant pain improvements were also observed for biologic therapies, but not for HA, steroids, non-injectable therapies and Prolo.





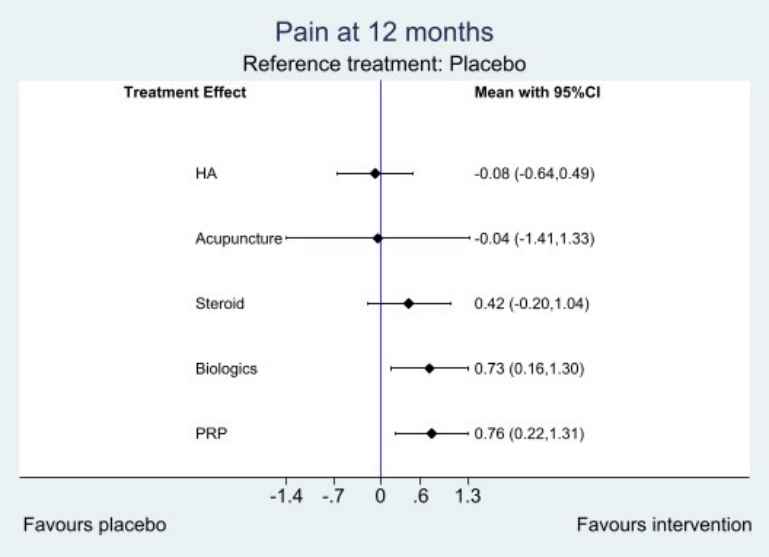


Fig. 3. Summary estimates of interventions at different time points. A: at 3 months (81 studies, 10625 randomised, 10418 analysed, between study standard deviation 0.65); B: at 6 months (primary time point, 69 studies, 10023 randomised, 9274 analysed, between study standard deviation 0.83); C: at 12 months (30 studies, 3871 randomised, 3453 analysed, between study standard deviation 0.67). (HA, hyaluronic acid; PRP, platelet rich plasma; Prolo, prolotherapy)

There is no evidence of inconsistency between direct and indirect estimates for each pair of treatment comparison by node splitting method (Appendix 3) and for global network by Wald test ($p > 0.05$). Visual inspection of the network forest plot (Appendix 4) indicates that the pooled overall estimates are generally in agreement with pooled within design estimates, However, there are a number of within-design studies (e.g., Prolo versus PRP, Steroids versus HA, PRP versus HA) which did not have overlapping confidence intervals.

Subgroup and sensitivity analysis

Overall, the pain benefits for the therapies of interest were not statistically significant compared to placebo with the exception of PRP and neuro-ablation on selected analyses. There was a trend suggesting acupuncture, PRP, biologics and neuro-ablation conferred greater pain benefits than placebo. Differences between PRP and other interventions did not reach statistical significance but the direction of effect for PRP largely remain positive. The point estimates for steroid, HA and non-injection therapy on the other hand, were mostly in favour of placebo. When studies with high risk of bias were removed, the estimates for steroids approached that of PRP.

The between-studies SD was reduced from 0.83 to 0.34 by excluding studies with high risk of bias, and to 0.51 by excluding severe structural OA (Table 1). Excluding older studies published before 2020, on the other hand, increased the heterogeneity.

Table 1: Subgroup and sensitivity analyses based on selected patient and study characteristics

Intervention	**Subgroups** **Number of studies/ Number randomised/ Number analysed/ Between study standard deviation**						
	Primary analysis (6 months) 69/ 10023/ 9274/ 0.83	Studies since 2020 22/ 3777/ 3630/ 1.30	#ITT 34/ 4812/ 4697/ 0.71	Excluded acupuncture 66/ 9626/ 8930/ 0.86	KL grade < 4 26/ 4042/ 3750/ 0.50	Female >50% 58/ 8743/ 8223/ 0.90	Excluded high risk (overall) studies 19/ 3931/ 3636/ 0.34
Acupuncture	0.43 (-0.39, 1.25)	0.34 (-1.48, 2.16)	0.47 (-0.59, 1.53)	NA	0.44 (-0.57, 1.44)	0.45 (-0.45, 1.34)	0.44 (0.00, 0.88)
Biologics	0.41 (-0.05, 0.88)	0.71 (-0.87, 2.54)	0.11 (-0.46, 0.67)	0.41 (-0.07, 0.89)	0.12 (-0.39, 0.62)	0.52 (-0.07, 1.11)	0.31 (-0.20, 0.81)
Hyaluronic acid	-0.03 (-0.41,0.35)	-0.38 (-1.67,0.90)	-0.25 (-0.68, 0.18)	-0.03 (-0.43, 0.36)	-0.29 (-0.67, 0.09)	0.01 (-0.44, 0.46)	-0.19 (-0.48, 0.09)
Neuro-ablation	1.08 (0.07, 2.10)	0.51 (-1.81, 2.82)	-0.11 (-1.77, 1.54)	1.08 (0.04, 2.13)	2.25 (1.16, 3.33)	1.12 (0.01, 2.23)	2.25 (1.43, 3.06)
Non-injection	-0.16 (-1.13, 0.81)	NA	-0.19 (-1.86, 1.48)	-0.2 (-1.24,0.84)	NA	-0.09 (-1.15, 0.98)	-0.30 (-0.96, 0.35)
Platelet-rich plasma	0.75 (0.28, 1.22)	1.19 (-0.07, 2.44)	0.50 (-0.16, 1.17)	0.75 (0.26, 1.24)	0.43 (-0.03, 0.90)	0.95 (0.37, 1.52)	0.06 (-0.45,0.57)
Prolotherapy	-0.57 (-1.56, 0.41)	-1.94 (-4.89,1.00)	-1.50 (-2.78, -0.21)	-0.58 (-1.59, 0.44)	NA	-0.55 (-1.77, 0.68)	-0.88 (-1.94,0.17)
Steroid	-0.13 (-0.72, 0.45)	0.23 (-1.78, 2.25)	-0.55 (-1.29, 0.19)	-0.14 (-0.74, 0.46)	-0.73 (-1.42, -0.04)	-0.06 (-0.74, 0.61)	0.09 (-0.57, 0.75)

#studies stated ITT was used and studies without dropout. Estimates are presented as Standardised means difference with corresponding (95% confidence intervals).

Risk of bias results

More than 75% of the included studies were considered to suffer from high risk of bias. The most common source of bias was the domain associated with blinding of treatment (i.e. bias in outcome measurement). Approximately 60% of the included studies were affected by biases in expectation of the outcome.

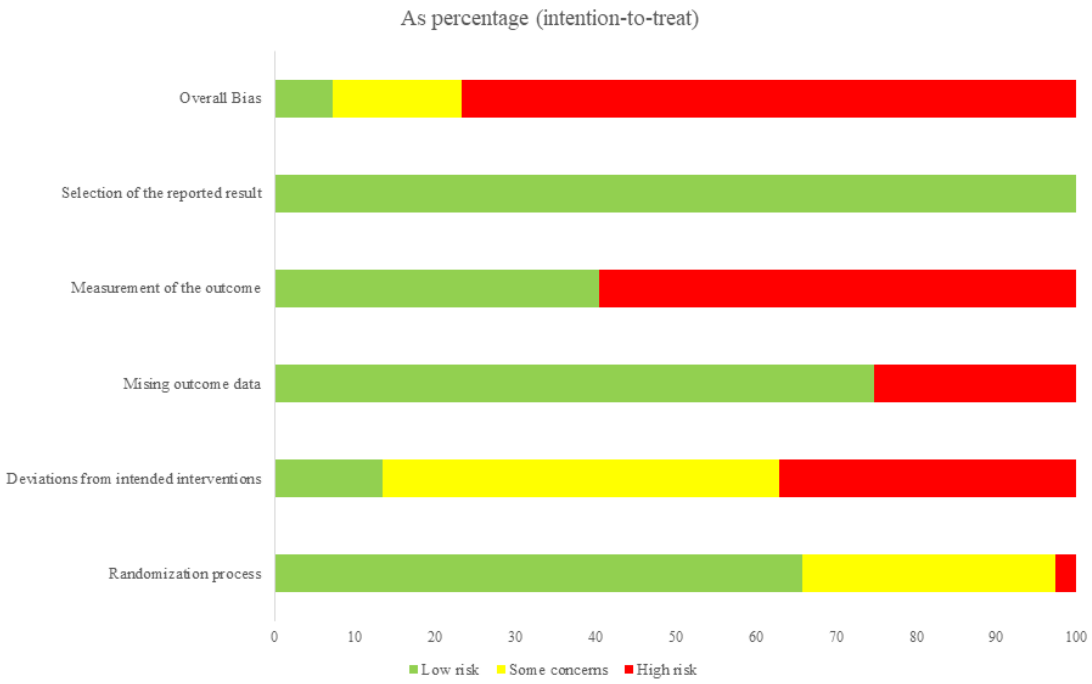


Fig. 4. Risk of bias: Most of the studies are of high risk of bias.

4. DISCUSSION

This NMA incorporated various pragmatic treatment options in outpatient practices and is not restricted to only intra-articular injections, but also peri-articular injections and non-injection therapies. We aimed to facilitate decision making in clinical practice when semi-invasive therapies are being contemplated. Attention was also given to evaluate the robustness of the results, through subgroup and sensitivity analyses, to enhance the confidence during decision making. Despite

some variations in pooled estimates, our analysis revealed a consistent hierarchical trend in efficacy over 3, 6, and 12 months, with prolotherapy being the least effective, followed by hyaluronic acid, steroids, biologics, and PRP showing the highest efficacy. Although the effect size for PRP is consistently larger than most therapies, there is no statistical significance between PRP and other therapies.

Platelet-rich plasma (PRP) and other biologics are designed to promote long-term healing and modulate inflammation[6]. PRP is abundant in growth factors and cytokines, which facilitate tissue healing and regeneration, mechanisms crucial for addressing the underlying causes of chronic OA pain[7]. The enrichment of PRP with growth factors may result in a more direct and targeted relief compared to non-biologic injections. PRP use in OA treatment additionally operates as a complex regenerative treatment through a more mechanisms that extend beyond the delivery of growth factors[8] which may explain its greater efficacy compared to other therapies. There is evidence to show that its pain benefits may last for 6-12 months[9,10].

Prolotherapy and hyaluronic acid (HA) are non-biologic therapies which are also administered for their regenerative potential. However, unlike PRP, the primary mechanisms of these therapies are indirect. Prolotherapy promotes healing by inducing pro-inflammatory response leading to regenerative process[11]. Whereas, HA acts to promote joint environment and cartilage health by inducing the production of endogenous HA, reducing cartilage degeneration and reducing inflammation[12].

Our analysis is in agreement with a few recently published smaller studies that PRP can potentially confer the most significant clinical benefits[13,14]. However, the point estimates obtained were not robust and varies between 0.03 to 1.28. The sensitivity analyses suggested that studies with high risk of bias was the single most important factor responsible for the heterogeneity of the

primary analysis. Between-studies heterogeneity reduced by 50% when the analyses was repeated without studies of high risk of bias.

In contrast, the estimates for acupuncture and non-injection therapies were relatively robust and remained consistent in all subgroup/ sensitivity analyses. Yet, the conclusion for acupuncture still requires further evaluation as the evidence base for acupuncture is scarce in comparison to HA and PRP. Despite its increasing acceptance in modern medicine for treatment of OA[15], there is limited network meta-analyses that have compared acupuncture to intra-articular injection therapies[16,17].

Although the results suggest that non-injection (e.g., electrotherapies, exercise and education) is no better than placebo, it does not imply a poor efficacy of non-injectables. It is imperative that the findings are interpreted in acknowledgement of the 'placebo effect'. The placebos in this analysis are innate injectables which, by virtue of their administration, can bring about positive placebo responses. It has been estimated that placebo effect may account for 75% of pain relieved experienced by patients[18]. Administration of non-injection therapies remained as core therapies and continue to be universally recommended by many groups of exeprts[1, 19].

With a sample size of over 4000 subjects, HA is the most extensively investigated therapy. Its analgesic effect is comparable to non-injection therapy and steroids for up 6 months post intervention. It is also comparable to PRP at 12 months. Overall, the results suggest that the efficacy of the therapies for OA may require consideration of specific pain characteristics as the pain pathway may differ between individuals and require individualised therapy[20]. For instance, OA of inflammation or of low repair phenotype would potentially respond better to steroid or acupuncture and not suitable candidates for PRP [21].

LIMITATIONS

We did not differentiate between the types of biologics (e.g. bone marrow aspirate, stem cells) and PRP (e.g. leucocyte-rich PRP, leucocyte-poor PRP) as there was no convincing evidence of significant difference in pain benefits between these subgroups of therapies[22, 23]. Therefore, we have grouped interventions that shared common features for analysis. This was also performed to facilitate a more 'global' understanding of different semi-invasive therapies which normally precedes the decision on specific injectates, or whether an injection should be offered.

Other potential sources of heterogeneity that may affect the results obtained include patient demographics, nonstandard time points for outcome measurement and the study quality. To address these, we have performed analysis for different time points and sensitivity analyses to investigate the effect of patient demographic and study quality. It appeared that studies with high risk of bias may be the single most important factor responsible for the heterogeneity detected. This was highlighted by the standard deviation between studies which was reduced by 50% when studies of high risk were excluded from the analysis. Additionally, we have attempted to minimise the heterogeneity by pre-emptively excluding other injections (e.g., Ozone injection, intraosseous PRP) which are less commonly available and have limited evidence.

CONCLUSION

There is no convincing evidence to recommend one injection over another mainly because each therapy exhibit specific advantages and mechanisms to address various facets of OA pain. Although the PRP appeared to have the most promising pain benefit, the reliability of its estimated effect size may be compromised by poorly blinded assessors. A patient-centred approach is crucial

in treatment selection to ensure that the individual's unique needs and preference are taken into consideration. Lasting pain relief from semi-invasive therapies, may not be possible in some OA subtypes. Future research is needed to identify the phenotypes or patient subgroups that would benefit most from PRP and other specific therapies. Characterizing OA phenotypes and subgroups from the imaging, clinical and molecular aspects remain a significant challenge, highlighting the need for continued investigation in this area [24].

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