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A Comparative Evaluation of Intra-Articular Injections of Hyaluronic Acid, Adipose Mesenchymal Stromal Cells, Platelet-Rich Plasma and Corticosteroids in patients with Knee Osteoarthritis. A Systematic Review

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ABSTRACT

Background: Osteoarthritis (OA) is a persistent bone and joint disease with multiple causes. marked by cartilage damage, which has a negative influence on patient mobility and life quality.
Aim of the study: Estimation of the clinical effects of platelet-rich plasma (PRP), steroids, hyaluronic acid (HA), or adipose mesenchymal stromal cells (MSC) injections in the treatment of knee osteoarthritis (OA).
Patients and Methods: From 2003 to 2021, researchers used Google Scholar, PubMed, Web of Science, Cochrane library, and other databases for randomized clinical trials (RCTs) including patients diagnosed with knee osteoarthritis that compared steroids, HA, adipose MSC, PRP, or head-to-head combination.
Results: There were a total of 24 trials in this study. Steroids are listed as the most useful intervention for pain or function management, whereas multiple PRP and adipose MSC were considered as the least likely to be effective. Despite the fact that there was no statistically significant difference in side effects between the five treatments, except for steroids, single PRP, and HA had a reduced rate of adverse events than placebo. Regarding pain relief, HA outperformed single PRP, but steroids outperformed single PRP by a significant margin. Furthermore, for side effects, corticosteroids were found to be superior to HA.
Conclusion: Our systematic review's ranking data supports using of corticosteroids and HA for selected cases with knee osteoarthritis. Steroids, followed by HA, are most likely the best treatments for pain relief and Adverse Effects (AEs). When compared to the placebo, PRP single, PRP multiple, and adipose MSC injections don't result in a significant reduction in joint pain or improvement in joint function.

Keywords: *Knee Osteoarthritis; Hyaluronic Acid; Platelet-Rich Plasma; Corticosteroids; Adipose Mesenchymal Stromal Cells...*

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INTRODUCTION

Osteoarthritis (OA) is a persistent bone and joint disease with multiple causes. marked by cartilage damage, which has a negative influence on patient mobility and life quality. [1]

Furthermore, the cartilage is devoid of blood vessels, and the cells have limited cellular proliferation in this situation. When cartilage is damaged, its ability to heal is hindered, ultimately resulting in permanent destruction. These consequences have a significant impact on patients' ability to function and independence, particularly in the elderly. [2]

Knee OA affects 50% of individuals over the age of 65, [3] and the most common symptoms are knee pain, effusion, and reduced mobility; It's also linked to a high rate of widespread, late, and significant functional impairment. The purpose of knee OA treatment is to alleviate pain, enhance function and life quality, and decrease disability.

The best method relies on the severity of the patient's symptoms and the condition of their joints. First-line recommendations include patient education, loss of weight, aerobic and strength training. Paracetamol, topical and oral non-steroidal anti-inflammatory medicines (NSAIDs), and a variety of symptom treatment choices, such as manual therapy, transcutaneous electrical nerve stimulation, and other physiotherapy methods, are used in the next stages. When conservative treatment fails, more invasive procedures such as arthroscopy, partial or total arthroplasty may be required. [4] Non-surgical

treatment options include intra-articular injections of Hyaluronic Acid (HA), Adipose Mesenchymal Stromal Cells, Corticosteroids, and Platelet-Rich Plasma (PRP), as well as oral nonsteroidal anti-inflammatory medications and physiotherapy. [5]

The goal of this study was to assess the effect of intra-articular injections of HA, adipose mesenchymal stromal cells, platelet-rich plasma, and corticosteroids on clinical pain, and functional results in patients with knee osteoarthritis (OA).

PATIENTS AND METHODS

Data Sources

Using PRISMA checklist, we conducted a thorough search according to the PRISMA recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

From 2003 to 2021, we conducted a rigorous and a widespread search of the following databases: PubMed, Google Scholar, Embase, Web of Science, Cochrane library, and others, utilizing predeterminate key word combinations related to knee OA.

Knee OA, intraarticular injection, hyaluronic acid, corticosteroids, platelet rich plasma, and adipose mesenchymal stromal cells are some of the terms that will be used in this study.

Study Selection

RCTs with patients with knee OA, Adults aged 19 to 65, Kellgren-Lawrence grades l-lV OA, No or limited favourable effects of previous conservative treatment, and This review includes studies that looked at the mean pain reduction or function scores from baseline, as well as the number of patients who reported AEs or severe AEs after 4 weeks at least, after the last treament dose.

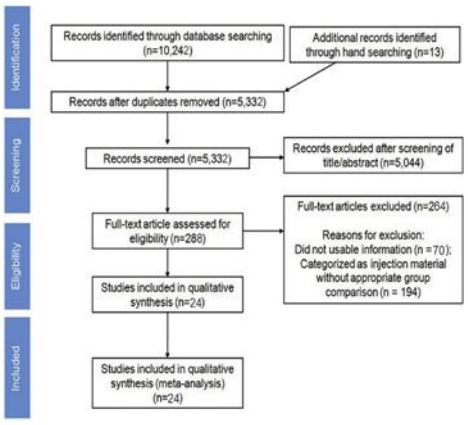

Fig 1. Studies identification and studies selection flow diagram.

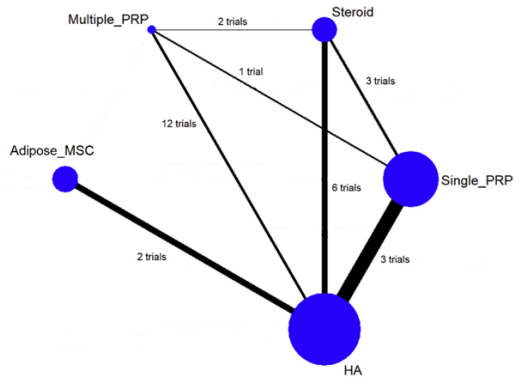

Fig 2. This design established by interventions, as well as direct comparisons between them. The comparisons done within randomized control trials are indicated by the threads connecting treatment nodes. The number beside the line denoted the trials' number. (HA; hyaluronic acid, MSC; mesenchymal stromal cell, PRP; platelet-rich plasma.)

Outcome Measures

In this systematic review, the key endpoint of efficacy and response to treatment for recovery was chosen as The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[6] The function of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) was applied to evaluate function improvement.

Quality Assessment and Data Abstraction

For the studies that were included, a data extraction form was created. First author, year of publication, study location, study design, population size (recurrence/nonrecurrence), sample ages, follow-up length, and risk variables were all retrieved independently by three researchers. The Detsky quality score was utilized to assess randomization of patients, blinding of intervention, consent withdrawals and subjects' dropouts, inclusion and exclusion criteria, treatment regimens, and statistical analysis plan. Studies receiving 75% or more of the maximum Detsky score (15/20) were assigned as excellent quality based on previous published papers. [7] For all components of the Detsky score, we used k values to assess rater dependability.

Data Extraction

The comprehensive analysis includes 24 randomized control trials published between 2003 and 2021, with a mean age ranging from 52.8 to 70.1 years old. One study did not declare a mean age for participants. The features of the involved studies are shown in (Table 1 & 2).

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participant And Personnel	Blinding of Outcome Assessment	Incomplete Outcome	Existence of Selective Reporting	Existence of Other Bias	Level Of Evidence
Houseman et al.,2014. 11	-	-	-	-	-	?	?	I
Leighton et al.,2014. 12	-	-	-	-	-	?	?	I
Louis et al.,2018. 13	-	+	-	-	+	?	?	II
Bisicchia et al.,2016. 14	-	+	-	+	-	?	?	I
Leopold et al., 2003	-	-	-	-	+	?	?	I
Vaquerizo et al., 2013. 15	-	-	-	-	-	?	?	I
Patel et al., 2013. 16	-	+	-	+	-	?	?	I
Lin et al., 2019. 17	-	+	-	-	-	?	?	I
Uslu Guvendi et al.,2018. 18	-	-	+	+	+	?	?	I
Raeissadat et al., 2015. 19	-	+	+	+	-	?	?	I
Huang et al.,2019. 20	+	+	+	+	-	?	?	I
Hong et al., 2019. 21	-	-	-	-	-	?	?	I
Lu et al., 2019. 22	-	-	-	-	+	?	?	I
Cerza et al.,2012. 23	+	+	-	+	-	?	?	I
Caborn et al.,2004. 24	+	+	+	-	+	?	?	I
Cole et al., 2017. 25	-	-	-	-	+	?	?	I
Duymus et al.,2017. 26	-	+	+	+	+	?	?	I
Spakova et al.,2012. 27	+	+	+	+	-	?	?	II
Sanchez et al.,2012. 28	-	-	-	-	+	?	?	I
Su et al., 2018. 29	-	+	+	+	-	?	?	II
Li et al., 2011. 30	+	+	+	+	+	?	?	II
Lana et al., 2016. 31	+	+	+	+	-	?	?	I
Lisi et al., 2018. 32	-	-	-	-	-	?	?	I
Buendia-Lopez et al.,2018. 33	+	+	+	-	+	+	+	II

Table 1: The Twenty-Four Studies included in the systematic review were randomized control trials published between 2003 and 2021, (-) decreased bias risk / (+) increased bias risk / (?) unknown bias risk.

Study	Detsky Score	Mean Age, Y.	Severity (K-L)	No. of Injections	Pain Outcome Extracted	Time Point Extracted, wk.
Houseman et al.,2014. 11	16/20	60.4	2,3	2/2 (HA/Steroids)	WOMAC	26
Leighton et al.,2014. 12	17/20	61.7	2,3	1/1 (HA/Steroids)	WOMAC	26
Louis et al.,2018. 13	15/20	50.9	2-4	1/1 (Single PRP/HA)	WOMAC, VAS	12, 26
Bisicchia et al.,2016. 14	16/20	70.1	2,3	2/2 (HA/Steroids)	WOMAC	26, 52
Leopold et al., 2003	16/20	65.0	2,3	3/2 (HA/Steroids)	WOMAC, VAS	13, 26
Vaquerizo et al., 2013. 15	16/20	63.6	2-4	3/1 (Multiple PRP/HA)	WOMAC	24, 48
Patel et al., 2013. 16	16/20	52.8	1,2	1/2 (Single PRP/Multiple PRP)	WOMAC, VAS	26
Lin et al., 2019. 17	17/20	62.0	1-3	3/3 (Single PRP/HA)	WOMAC	26, 52
Uslu Guvendi et al.,2018. 18	15/20	61.8	3	1/1/3 (Steroids/ Single PRP/Multiple PRP)	WOMAC, VAS	26
Raeissadat et al., 2015. 19	16/20	59.0	1-4	2/3 (Multiple PRP /HA)	WOMAC	52
Huang et al.,2019. 20	14/20	54.5	1,2	3/1/3 (HA/Steroids/Multiple PRP)	WOMAC, VAS	26, 52
Hong et al., 2019. 21	17/20	NA	2,3	1/1 (Adipose MSCs/HA)	WOMAC, VAS	26, 52
Lu et al., 2019. 22	16/20	57.3	1-3	1/4 (Adipose MSCs/HA)	WOMAC, VAS	26, 52

Cerza et al.,2012. 23	15/20	66.4	1-3	4/4 (Multiple PRP/HA)	WOMAC	12, 24
Caborn et al.,2004. 24	15/20	63.1	2-4	3/1 (HA/Steroids)	WOMAC, VAS	12, 26
Cole et al., 2017. 25	16/20	56.4	1-3	3/3 (Multiple PRP/HA)	WOMAC, VAS	24, 52
Duymus et al.,2017. 26	16/20	60.4	2,3	2/1 (Multiple PRP/HA)	WOMAC	26, 52
Spakova et al.,2012. 27	15/20	53.0	1-3	3/3 (Multiple PRP/HA)	WOMAC	12, 26
Sanchez et al.,2012. 28	17/20	59.7	1-4	3/3 (Multiple PRP/HA)	WOMAC	24
Su et al., 2018. 29	14/20	53.7	2,3	2/5 (Multiple PRP/HA)	WOMAC, VAS	26, 52
Li et al., 2011. 30	14/20	57.9	1-4	3/3 (Multiple PRP/HA)	WOMAC	12, 24
Lana et al., 2016. 31	16/20	60.5	1-3	3/3 (Multiple PRP/HA)	WOMAC, VAS	26, 52
Lisi et al., 2018. 32	17/20	55.3	2,3	3/3 (Multiple PRP/HA)	WOMAC, VAS	26, 52
Buendia-Lopez et al.,2018. 33	NA	56.8	1,2	1/1 (HA/Single PRP)	WOMAC, VAS	26, 52

Table 2: The Twenty-Four Studies included in the systematic review were randomized control trials published between 2003 and 2021 with mean age ranged from 52.8 to 70.1 years. One study failed to provide a mean age for participants. Detsky score is applied for included studies quality evaluation, A score of ≥ 15 points is considered to be high quality. K-L, Kellgren-Lawrence. WOMAC: Western Ontario & McMaster Universities / NA: not applicable / VAS: visual analog scale.

Statistical Analysis

We used a qualitative synthesis of the included studies to see how much evidence was available for each intervention. Nodes represent different therapies, while the threads linking them represent studies comparing between treatment regimens. Size of the node and thickness of the connecting lines means the number of patients. [8] The proportion of patients who developed adverse events and sever AEs was estimated using a binary logistic regression model with random-effects model, while weighted averages presented in odds ratios (ORs) and 95% confidence intervals (CI).

We utilized RevMan version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) besides a random-effects model to conduct a pairwise meta-analysis regarding change of pain from baseline scores. We used I2 statistics to determine the degree of heterogeneity. I2 statistics are used to calculate the total variation percentage among trials (I2 of 50% was defined as heterogeneous).

The Network Meta-Analysis -NMA- consistency assumption was tested by the estimation of difference between the effect size from comparisons of study groups within trials and the effect size from indirect comparisons across trials with the same intervention was employed. If the value approaches 1, it implies that the two estimations settle. [8&9]

The mean rank and surface under the cumulative ranking curve are used to report the probability values (SUCRA). The best therapy has an SUCRA rating of 100 percent, whereas the poorest treatment has an SUCRA value of zero%.[8&10] Funnel plots were also used to analyze publication bias

HA	−1.20 (−2.82, 0.43)	0.18 (−0.43, 0.79)	−0.85 (−2.22, 0.52)	−0.26 (−0.93, 0.41)
−0.65 (−3.93, 2.64)	Steroids	1.38 (−0.13, 2.88)	0.35 (−1.66, 2.35)	0.94 (−0.62, 2.50)
−0.26 (−1.19, 0.67)	0.39 (−2.76, 3.53)	Single PRP	−1.03 (−2.36, 0.30)	**−0.44 (−0.86, −0.02)**
−1.92 (−4.03, 0.18)	−1.28 (−5.03, 2.47)	−1.66 (−3.71, 0.38)	Multiple PRP	0.59 (−0.71, 1.90)
−0.21 (−1.25, 0.83)	0.44 (−2.78, 3.66)	0.05 (−0.64, 0.74)	1.72 (−0.29, 3.72)	Adipose MSC
0.53 (−0.81, 1.86)	1.17 (−2.13, 4.48)	0.79 (−0.22, 1.79)	**2.45 (0.31-4.59)**	0.73 (−0.37, 1.84)

Table 3: Meta-Analyses Comparison of Pain Difference (White) and Function Difference (Gray) Results at Follow-Up Time Points from Baseline.Each compartment has an SMD with a 95 percent confidence interval (CI) in parentheses. A -ve SMD favours the lower-right intervention in any cell, while a +ve SMD prefers the upper-left intervention in any cell. The most important findings are highlighted in bold language. CI stands for confidence interval; HA stands for hyaluronic acid; MSC stands for mesenchymal stromal cell; PRP stands for platelet-rich plasma; and SMD stands for standardised mean difference.

	Pain Outcomes		Functional Outcomes		Adverse Effects		Severe Adverse Effects	
Treatment	SUCRA	Mean Rank	SUCRA	Mean Rank	SUCRA	Mean Rank	SUCRA	Mean Rank
Adipose MSC	0.1	5.4	0.4	3.8	0.4	4.2	0.3	4.4
HA	0.7	2.4	0.5	3.7	0.7	2.6	0.5	3.4
Multiple PRP	0.2	5.0	0.1	5.6	0.1	5.4	0.5	3.4
Single PRP	0.4	4.1	0.5	3.4	0.4	3.8	0.7	2.6
Steroids	1.0	1.0	0.9	1.6	1.0	1.1	0.4	4.0

Table 4: Treatment Results from a Network Meta-Analysis for Pain, Functional Outcomes, Adverse Effects, and Severe Adverse Effects. Based on a simulation with 10,000 replications, SUCRA values (0-100) and mean ranks are shown. Treatments with higher SUCRAs and lower mean rankings perform better. PRP, platelet-rich plasma; SUCRA, surface under cumulative ranking curve. MSC: mesenchymal stromal cell/ HA: hyaluronic acid/ PRP: platelet-rich plasma.

RESULTS

Between 2003 and 2021, 24 trials were published. The patient age ranged from 33 to 73 years (median 60 years) in the 24 trials for which data was available, while the proportion of women ranged from 27% to 100% (with a median 60%). The follow-up period range was from 6 to 104 weeks and a median 37 weeks as shown in (Table 2).

Figure-1 summarizes the study's identification, inclusion, and exclusion criteria. The systematic review comprised a total of 24 studies, as shown in table 1. Figure 2 depicts the intervention network. Most trials assigned a Kellgren-Lawrence (K-L) grade of 1, 2, or 3 to patients' severity (8 studies: K-L grade of 2,3 / 6 studies: K-L grade of 1-3 / 3 studies: K-L grade of 1-4 / 3 studies: K-L grade of 2-4 / 3 studies: K-L grade of 1,2 / 1 study: K-L grade of 3).

Depending on the preparation, the number of interventions ranged from one dose to five weekly injections. On effect modifiers like age and injection frequency, there was a lot of heterogeneity between comparisons, excluding the severity of OA in the knee. The patients in the 24 trials we looked at were randomly assigned to one of five different injections (HA, single PRP, steroids, multiple PRP, and adipose MSC).

Safety

Regarding the 24 trials, although most treatments were not significantly superior to one another, single PRP demonstrated a lower number of AEs compared with the other interventions (HA 0.40, 95% CI 0.19-0.85; steroids 0.51, 95% CI 0.28-0.93; adipose MSC 2.49, 95% CI 1.18-5.26; and multiple PRP 6.08, 95% CI 1.33-27.68). There was no evidence for inconsistency between direct and indirect estimates (AEs, P ¼ .79; SAEs, P ¼ 1.00).

Steroids (SUCRA value of 100.0 and a mean rank of 1.1) are most likely the best treatment for AEs, followed by HA (SUCRA value of 70.0 and a mean rank of 2.6), and multiple PRP (SUCRA value of 70.0 and a mean rank of 2.6). (SUCRA value of 10.0 and a mean rank of 5.4).

In terms of SAEs, single PRP is most likely the best therapy (SUCRA value of 70.0 and a mean rank of 2.6), while adipose MSC came in last (SUCRA value of 70.0 and a mean rank of 2.6). (SUCRA value of 30.0 and a mean rank of 4.4). After excluding trials with low methodological quality, no statistically significant difference could be seen between the results of our secondary analysis and those of our primary analysis, showing that the conclusions were unaffected by data collection decisions.

DISCUSSION

Corticosteroids have been linked to resolution of pain and improvement of function in osteoarthritic knees, particularly if there is an inflammation and edema, but only for a short period of time. [34&35] In this study, steroids were demonstrated to consistently offer favorable outcomes in reducing pain and enhancing function for knee OA for at least 26 weeks when used as a solo treatment. 1 reason we saw better results in individuals using corticosteroids in this trial could be due to the possibility of variable responses depending on the degree of the OA and the inflammation level. As a result, patients with KL grade 4 and no inflammation were typically excluded from most trials.

Our results are consistent with recent Randomized Control Trials and other systematic reviews, which found that corticosteroids are beneficial for knees OA in KL grades 1-3. [34&36] However, there is a paucity of clinical evidence on efficacy of corticosteroid injection for osteoarthritic knees in terms of pain relief for 26 weeks or longer. Unlike AEs or SAEs, it is not proper to share them in a systematic review research of pain and function because of discrepancy that may be caused by other confounding factors that influence the results of indirect comparison. As a result, we emphasize the importance of conduction of high quality RCTs with long-term follow-up to investigate the efficacy of this treatment modality.

According to prior studies, PRP and adipose mesenchymal stromal cells are favorable treatments that offers short, medium and long-term benefits in osteoarthritic knees.[37-40]

Furthermore, patients with KL grade 1-3 knee OA could receive PRP in 2 to 4 sessions spaced 2 to 4 weeks apart, implying that 2 or less injections could impair therapy efficiency. [41-42]

However, when compared to single PRP, our data showed for repeated PRP did not alleviate pain or improve knee function. Furthermore, repeated PRP and adipose MSC exhibited the minimal effect on

both pain and function in this study. Additional difficulties could be to blame for these findings, such as a lack of clarity on distinct adipose handling for injection, the role of WBCs filtering during preparation, and most crucially, the patients' inclusion with varying grades of OA severity. [43-47]

Comparison	Adverse Effect	Severe Adverse Effect
Steroids vs HA	0.77 (0.48-1.24)	1.05 (0.52-2.13)
Single PRP vs HA	0.40 (0.19-0.85)	1.22 (0.44-3.41)
Adipose MSC vs HA	0.99 (0.50-1.98)	0.84 (0.28-2.47)
Multiple PRP vs HA	2.42 (0.55-10.73)	1.07 (0.08-13.66)
Single PRP vs steroid	0.51 (0.28-0.93)	1.17 (0.57-2.38)
Adipose MSC vs steroid	1.28 (0.75-2.18)	0.80 (0.33-1.94)
Multiple PRP vs steroid	3.12 (0.74-13.15)	1.02 (0.08-12.49)
Adipose MSC vs single PRP	2.49 (1.18-5.26)	0.69 (0.24-1.97)
Multiple PRP vs single PRP	6.08 (1.33-27.68)	0.88 (0.07-11.11)
Multiple PRP vs adipose MSC	2.44 (0.62-9.61)	1.28 (0.11-15.42)

Table 5: . Comparison of Adverse Effects Results from Network Meta-Analyses. The OR and 95 percent confidence intervals for the data were pooled. Arthralgia, injection site pain and stiffness are some of the side effects. Pneumonia, transient ischemic stroke, cardiac arrest, degenerative joint disease and malignancy are all serious side effects. CI: confidence interval / HA: hyaluronic acid / MSC: mesenchymal stromal cell / OR: odds ratio / PRP: platelet-rich-plasma.

In spite of several changes in the research procedure, PRP injections were found to be more efficacious and last longer in patients with knee OA than other treatments, with no SAEs. [48]

Even while single PRP showed no statistically significant difference from other injections in terms of odds ratio values, the review result in that SUCRA percentage demonstrated that single PRP had a lesser risk of SAEs compared to other injections. However, PRP was proved to have a more risk of discomfort, edema, and moderate effusion than the other therapies, which can reduce after a few days. [49]

Based on the odds ratio values in AEs, our studies suggest that there is a significant difference among single PRP and other therapies. Comparison of single and numerous PRPs, either steroids or HA showed a lower risk of arthralgia, tenderness at site of injection, and decreased range of motion.

In regards to our experience, patient characteristics, symptoms, and clinical findings may indicate a practical approach for IA injections. The CS choice is reasonable in acute and persistent synovitis for patients that cannot be operated. The corticosteroids are effective in short-term.

We prefer HA for obese patients who are older than 60 years and for patients with extremity malalignment. The supposed long-term effect of HA is attractive for these patients who are not willing to be operated.

We prefer PRP for patients who are younger than 60 years, with mild OA and body mass index < 30, and for patients that do not have any extremity malalignment.

If the patients are older than 60 years, or their body mass index > 30, or they have moderate OA, we still apply PRP injection, which is followed by a supplementary single dose of HA injection 2 to 4 weeks after PRP injection.

The ranking statistics like SUCRA values of our systematic review support the use of steroids and HA for appropriate patients with knee OA. For pain relief and AEs, steroids are most likely the best treatment, followed by HA.

Single PRP, multiple PRP, and adipose MSC interventions do not result in a relevant reduction of joint pain nor improvement of joint function compared with the placebo. However, treatment effect differences were small and potentially not clinically meaningful, indicating that other factors, such as cost and patient preferences, may be more important in patients with knee OA.

LIMITATIONS

There are a few flaws in this study. First, we conducted a thorough literature search across several databases, ensuring that no relevant trials were overlooked. However, if relevant trials were published in papers not indexed in those databases, we may have missed them.

Second, because we did not account for the large variation in delivery mechanism and intervention dose, confounding factors may be a concern.

Third, due to the inadequate raw data presented in the original studies, data on independent analyses for the timing or duration of the injection were missing, which are crucial criterion in determining which of the six modalities to recommend.

Fourth, information about the clinical relevance of these therapies is missing, therefore take our findings with caution because statistical significance does not always reflect clinical significance.

Finally, we did not assess unpublished trials; however, funnel plots revealed that publication bias is unlikely among the research included.

CONCLUSION

Our systematic review encourages the usage of corticosteroids and HA for selective patients with knee osteoarthritis. Corticosteroids, followed by HA, are most likely the best treatments for pain relief and AEs.

Adipose MSC, single PRP, and multiple PRP therapies showed no significant reduction in joint discomfort as well, no improvement of joint function when compared to the placebo. Nonetheless, the differences between treatment effect were minimal and may not be clinically profound, suggesting that other factors like treatment cost and patient preferences may be greater importance for management of knee OA.

So, we recommend using corticosteroids followed by hyaluronic acid according to patient's selection criteria. Also, we recommend adding placebo to the comparison in the next review.

Conflict of interest : none

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