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Comparative effectiveness of nonsurgical interventions in the treatment of patients with knee osteoarthritis

A PRISMA-compliant systematic review and network meta-analysis

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Abstract

Background: To find out, based on the available recent randomized controlled trials (RCTs), if the nonsurgical interventions commonly used for knee osteoarthritis patients are valid and quantify their efficiency.

Methods: The database of MEDLINE and EMBASE were searched for RCTs evaluating nonsurgical treatment strategies on patients with mild to moderate knee osteoarthritis. A Bayesian random-effects network meta-analysis was performed. The primary outcome was the mean change from baseline in the Western Ontario and McMaster university (WOMAC) total score at 12 months. Raw mean differences with 95% credibility intervals were calculated. Treatments were ranked by probabilities of each treatment to be the best.

Results: Thirteen trials assessed 7 strategies with WOMAC at 12 months: injection of platelet rich plasma (PRP), corticosteroids, mesenchymal stem cells (MSCs), hyaluronic acid, ozone, administration of nonsteroidal anti-inflammatory drugs with or without the association of physiotherapy. For treatment-specific effect size, a greater association with WOMAC decrease was found significantly for MSCs (mean difference, −28.0 [95% CrI, −32.9 to −22.4]) and PRP (mean difference, −19.9 [95% CrI, −24.1 to −15.8]). Rank probabilities among the treatments indicated that MSCs had a much higher probability ($P = .91$) of being the best treatment compared with other treatments, while PRP ranked as the second-best treatment ($P = .89$).

Conclusion: In this systematic review and network meta-analysis, the outcomes of treatments using MSCs and PRP for the management of knee osteoarthritis were associated with long-term improvements in pain and function. More high quality RCTs would be needed to confirm the efficiency of MSCs and PRP for the treatment of patients with knee osteoarthritis.

Abbreviations: AARP = American Association of Retired Persons, ASA = amniotic suspension allograft, BMI = Body mass index, BMAC = bone marrow aspirate concentrate, CrIs = credibility intervals, CS = corticosteroids, Dex = dexamethasone, GC = glucosamine chondroitin, GRADE = Grading of Recommendations Assessment, HA = hyaluronic acid, JAGS = Just Another Gibbs Sample, LLLT = Low-Level Laser Therapy (LLLT), MCMC = Markov chain Monte Carlo, MSCs = mesenchymal stem cells, NSAID = nonsteroidal anti-inflammatory, OA = osteoarthritis, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, RCT = randomized controlled trial, SVF = stromal vascular fraction, TENS = Transcutaneous Electrical Nerve Stimulation, TKA = total knee arthroplasty, VAS = Visual Analogue Scale, WOMAC = Western Ontario and McMaster university.

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1. Introduction

Knee osteoarthritis (OA) is a common chronic degenerative disease due to bone and cartilage degeneration affecting up to 19% of adults aged 45 and older,[1] and is a major contributor to functional and social impairment, disability, reduced independence, and poorer quality-of-life.[2,3] Its clinical features mainly include cartilage degenerative lesions, with clinical manifestations such as limited range of motion in the knee, joint swelling, pain, stiffness and deformity (Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A691). Radiographic evidence of knee OA according to the Kellgren and Lawrence classification is present in approximately 30% of adults over the age of 65.[4] Worldwide estimates report that 9.6% of men and 18.0% of women over the age of 60 years have symptomatic OA[5] and that the number of people affected by OA will increase by about 50% over the next 20 years.[6,7] Therefore, there is an increasing need for urgent attention to this disease.

Current knee OA treatment strategies use surgical and non-surgical interventions.[6,8,9] Total knee replacement also known as total knee arthroplasty is considered an effective procedure for treating end-stage knee OA. However, not all individuals with knee OA can or even wish to proceed with surgery due to various comorbidities and/or age or health-related restrictions. Additionally, access to surgical intervention may be limited or delayed in many countries due to budgetary restrictions and limited resources, such as operating time or surgeon availability. Moreover, perioperative complications such as loosening,[10] infection,[11] instability,[12] fractures,[13] pain or discomfort may occur during and after total knee replacement.[14,15] Furthermore, the augmentation in the number of young patients undergoing knee surgery also increases the lifetime risk of requiring revision surgery.[16] For all these reasons, 15% to 30% of patients have reported dissatisfaction after total knee arthroplasty.[17] Therefore, as the majority of non-surgical interventions are safer, have a lower cost, and mobilize a less technical platform, they are required in the first step of the knee OA management before the need for surgery.[6,8] Indeed, these non-surgical interventions are meant to reduce or eliminate pain and improve joint function through cartilage repair which can delay or avoid the need for arthroplasty.

Although there are several guidelines for knee OA management, there has been no consensus reached concerning the efficacy of many available non-surgical treatment strategies. Due to the large number of publications evaluating multiple types of osteoarthritis treatments, recent meta-analyses seem to be an essential way especially with the appearance of new innovative treatments. The aim of our study was to evaluate the long-term efficiency of these treatments published recently by using a Bayesian approach. This method allows comparison of all available non-surgical knee OA strategies.

2. Methods

2.1. Literature search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[18]

The literature was screened and extracted by the authors using the electronic database of MEDLINE (PubMed) and EMBASE. We chose to evaluate a consequent amount of recent studies, namely between January 1, 2017 and March 1, 2020. This led to the evaluation of 864 clinical trials. Titles and abstracts were screened in order to determine if the identified articles met the inclusion and exclusion criteria. The full-text of selected articles was then further evaluated.

Eligible trials included placebo-controlled RCTs and those comparing any active treatment alone or in combination with another intervention. The inclusion and exclusion criteria are described below:

2.2. Inclusion criteria

- Placebo and active-controlled randomized controlled trials (RCTs).
- Patients with early knee OA (Kellgren–Lawrence grades 1–3).
- At least 6 months of follow up.
- Full version in English.
- Studies that perform a patient global assessment using WOMAC total score and/or visual analogue scale (VAS) for pain.

2.3. Exclusion criteria

Additionally, trials will be excluded if they are:

- Animal studies.
- Studies which evaluated clinical postoperative outcomes after total knee arthroplasty.
- Studies published prior to 2017, or after March 1, 2020.
- Surgical interventions or perioperative treatments.
- Books, reviews, meta-analyses, study protocols, case reports, expert opinions commentary, conference papers, unpublished results.
- Studies evaluating patients with severe OA (Kellgren–Lawrence grade 4).
- Studies focusing only on specific categories of patients (e.g., obese patients).
- Studies with only graphs without available or accessible data.

We chose the WOMAC total score and/or visual analogue scale (VAS) for pain because these instruments are the most used in the literature for their high level of validity and reliability[19,20] in patients with knee osteoarthritis. Furthermore, knee pain and function are likely to be the factors that matter the most to patients, physicians, and caregivers.

The WOMAC is a disease-specific and self-administered questionnaire used in the evaluation of hip and knee OA. It consists of 24 questions, grouped into 3 subscales including pain (5 questions), stiffness (2 questions), and physical function (17 questions) for the activity of daily living during the past 48 hours.[19] In the Likert scale version, each answer is scored on a scale from 0 to 4: 0 represents "none" and 4 represents "extreme." In the VAS version, each answer is scored on a 100-mm VAS: 0 represents "none" and 100 mm represents "extreme," thus, higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

When pain severity was assessed on a 100-mm or 10-cm VAS, higher score indicates greater pain intensity.

2.4. Outcomes and data extraction

The primary outcome was mean change from baseline to 12 months (long-term) with the WOMAC total score. Secondary

outcomes were changes from baseline to 3 months (short-term), to 6 months (middle-term) with WOMAC and from baseline to 3 months, to 6 months, and to 12 months with VAS.

For each outcome, the change from baseline was extracted at each time point if reported; otherwise, numerical data for the outcome were extracted at baseline and at each time point. Other extracted data included baseline demographic characteristics (age, sex, body mass index), clinical characteristics (Kellgren–Lawrence grade), and the dose of each treatment.

Treatments administered at different doses have been considered as a single intervention. If the same trial compared different treatment doses, the trial has been split in more pairwise comparisons against hyaluronic acid (HA) or placebo. This methodological choice has been taken assuming that no correlation structure is evident among different dose effects in the same randomized controlled trial.

Only trials with extractable data were included. No additional information was requested from authors.

2.5. Quality and risk of bias assessment

Quality was assessed independently by the authors. The Quality of the included trials was assessed using the Cochrane Collaboration tool for assessing risk of bias in RCTs.[21] Each study was evaluated as low, high, or unclear risk of bias according to the randomization, allocation concealment, blinding, completeness of outcome data, and selective outcome reporting. The GRADE methodology was used to assess the quality of evidence (GRADEpro, McMaster University, 2020).

2.6. Data synthesis and analysis

The imputation of the correlation method was used when standard deviations were available for absolute baseline and follow-up values, but not for the mean change values[22] by using the correlation value $r = 0.5$. This was selected as a plausible value based on other studies.[23]

When studies did not report mean change, these values were calculated as the arithmetic difference between baseline and follow-up. VAS and WOMAC scale scores were all normalized to a scale from 0 to 100 to ensure comparability between all the studies for each outcome measure.

A Bayesian multiple treatment network meta-analysis[24] with random effects and uninformative priors was performed and considered both placebo- and active-controlled trials. The analysis was performed on the raw mean difference with 95% credibility intervals for the treatment-specific and relative effect sizes for all eligible trials using the WOMAC or the VAS.

The reference treatment group to be compared against is "Placebo." In the case of the absence of placebo "Hyaluronic acid" is used as the reference treatment because HA is widely used by physicians and is also the most commonly used treatment in the trials. The minimum clinical important difference for the total WOMAC score is 10.[25]

The between-study standard deviation was modeled using a uniform distribution of the 0 to 10 interval.[26] A random effects model was computed using Markov chain Monte Carlo methods with Gibbs sampling based on simulations of 200,000 iterations in each of 4 chains.

The number of iterations is considered sufficiently large to produce accurate posterior estimates.

Homogeneity and consistency assumptions were evaluated using node splitting method.

A rankogram plot is used to graph the probabilities of each treatment having each of the different possible ranks among the treatments. The treatment rank probabilities are based on the marginal effect measures. A higher event probability implies a better treatment.

The analyses were conducted using the R-evolution version 4.0.3 and the pcnetmeta package version 2.7 that interfaces with Just Another Gibbs Sample version 4.3.0 for computing a Markov chain Monte Carlo simulation.

The sensitivity analyses were conducted to evaluate the robustness of the model. The post hoc sensitivity analyses were performed using alternative statistical methods to those described above.

A sensitivity analysis based on a Fixed effect model instead of the Random effect model has been conducted for each outcome. Furthermore, a sensitivity analysis has been conducted for each outcome based on an empirical informative prior on heterogeneity distribution: inverse-gamma distribution instead of the uninformative prior.

2.7. Ethical approval

Ethical approval was not necessary due to the study design.

3. Results

3.1. Study selection

A total of 838 studies were identified through database searching. After analysis in accordance with the inclusion and exclusion criteria, 19 RCTs (N = 2488 patients) met the eligibility criteria and were included in this meta-analysis. The diagram in Fig. 1 summarizes the selection process.

The mean age of the included patients is 57.65 ± 3.82 and a higher proportion (around 65%) of women than men with a mean body mass index of 28.17 ± 2.04. Ten of the 19 trials included >100 participants in all groups.

Disease severity was defined based on Kellgren–Lawrence radiological grading classification. Among the 19 studies, 5 have included patients with Kellgren–Lawrence grade 1 and 2; 9 studies with Kellgren–Lawrence 2 and 3; 4 studies with Kellgren–Lawrence grade 1–3 and 1 study with Kellgren–Lawrence grade 3.

3.2. Study characteristics

A total of 16 different interventions were studied in these RCTs. The included studies comprised physical and pharmacologic approaches but not any psychosocial or mind-body studies. Injection of platelet rich plasma (PRP) was assessed in 8 trials[27–33,40], HA in 12 trials[28–30,33,34,36–38,40–42,44], mesenchymal stem cells (MSCs) in 2 trials[34,35], corticosteroids (CS) in 2 trials[28,31], nonsteroidal anti-inflammatory drugs (NSAID) in 1 trial[29,45], physical therapy associated with NSAID in 1 trial[35], prolotherapy (dextrose) in 1 trial[27], dexamethasone (Dex) in 1 trial[37], combination of dexamethasone and hyaluronic acid (Dex + HA) in 1 trial[37], ozone injection in 1 trial[33], stromal vascular fraction (SVF) in 1 trial[41], bone marrow aspirate concentrate in 1 trial[43], amniotic suspension allograft in 1 trial[42], administration of Q-Actin in 1 trial[39], glucosamine chondroitin in 1 trial[39], and Chondroitin sulfate in 1 trial[45].

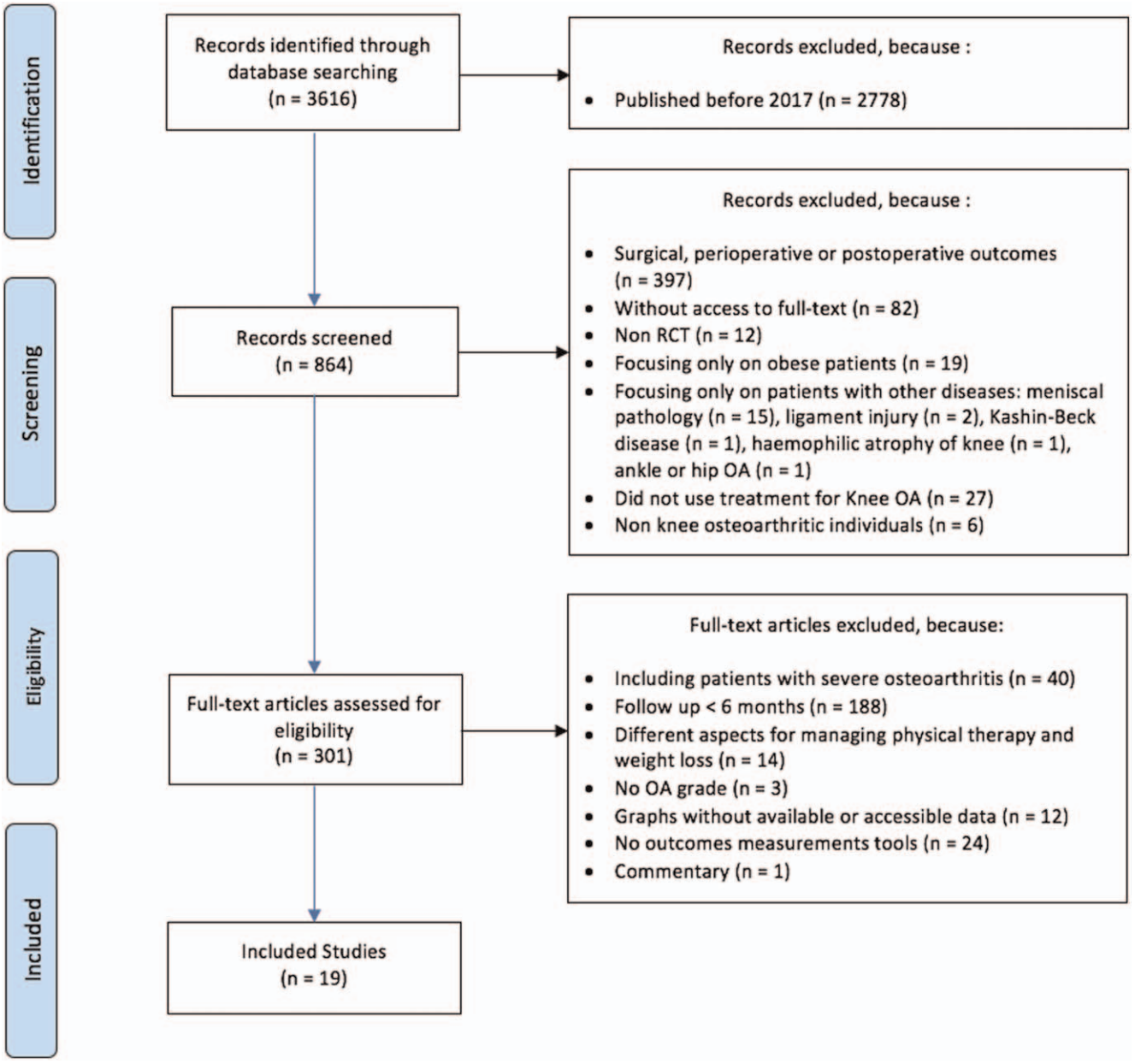

Figure 1. Trial selection process.

Out of the 19 RCTs included, 4 were placebo-controlled and 15 were comparing ≥2 interventions. Included trials are presented by outcome measures: WOMAC in Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A706 VAS in Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A707.

The methodology quality and risk of bias for the included studies are displayed in Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A692 and Table S3, Supplemental Digital Content, http://links.lww.com/MD2/A708. Overall, all patients were randomized to receive an OA treatment. Seven studies maintained allocation concealment but the other studies failed to describe it clearly. The risk of performance bias was high in 13 studies and unclear in 1 study. It might be important for the physicians to be aware of treatments for patient safety. Detection bias was high in 3 studies and unclear in 4 studies. The attrition bias was high in 8 studies and unclear in 1 study. Unlike performance and attrition biases, reporting bias was low in >75% of the evaluated studies.

The quality of evidence for the primary outcome studies according to the GRADE system is presented in Table S5, Supplemental Digital Content, http://links.lww.com/MD2/A710.

The treatments that have been compared together are described in Table S4, Supplemental Digital Content, http://links.lww.com/MD2/A709 by the time point, the outcome measure, number of trials, and number of patients. The total score variation from baseline to the last follow-up are presented for each treatment in Fig. 2 for WOMAC and in Figure S3, Supplemental Digital Content, http://links.lww.com/MD2/A693 for VAS.

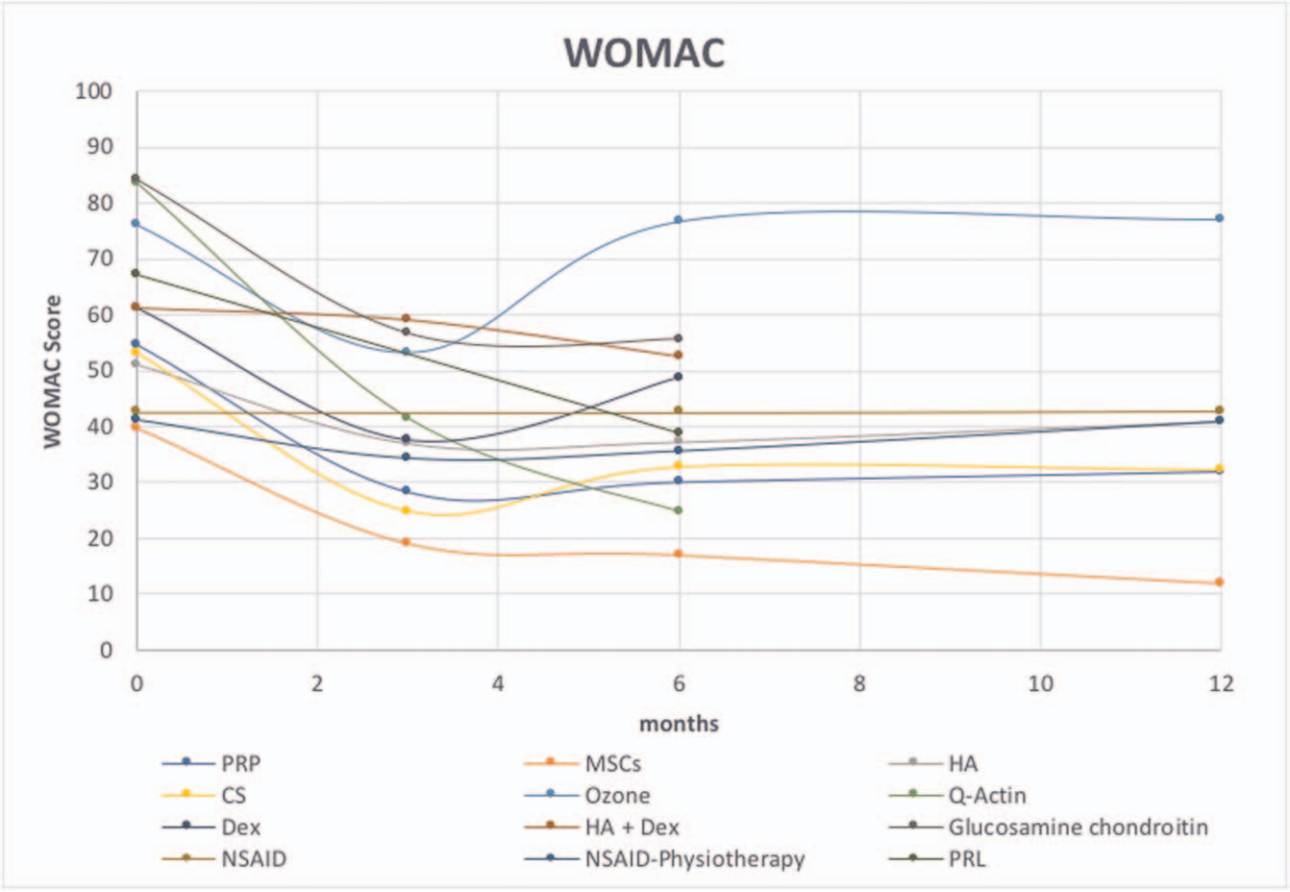

Figure 2. Curves showed the total scores variation of knee OA strategies from baseline to the last follow-up visit according to Western Ontario and McMaster university (WOMAC). OA = osteoarthritis.

Effects estimates were heterogeneous and inconsistent among studies but the node-splitting analysis of inconsistency was statistically insignificant. Consequently, there were no significant differences between the direct and indirect comparisons in the main analysis (Figure S4, Supplemental Digital Content, http://links.lww.com/MD2/A694). A quantitative synthesis of the evidence through a network meta-analysis was appropriate.

3.3. Primary outcome

There were 15 trials assessing 7 strategies with WOMAC at 12 months: PRP, CS, MSCs, HA, Ozone, NSAID, and NSAID with association with physiotherapy (Table S4, Supplemental Digital Content, http://links.lww.com/MD2/A694). The network plot for the primary outcome appears in Fig. 3.

For treatment-specific effect size, a greater WOMAC decrease was significantly found for the MSCs (mean difference, −28.0 [95% CrI, −32.9 to −22.4]) and PRP (mean difference, −19.9 [95% CrI, −24.1 to −15.8]) associated to a clinically significant difference. Moreover, a significant mild improvement in the knee clinical status was found for HA (mean difference, –8.5 [95% CrI, −11.9 to −5.2]) but not for CS (mean difference, −9.5 [95% CrI, −15.0 to –0.7]), NSAID (mean difference, −5.4 [95% CrI, −13.9–0.7]), NSAID associated with physiotherapy (mean difference, –0.2 [95% CrI, −9.6–9.2]) and ozone injection (mean difference, 0.9 [95% CrI, −4.4–6.1]) (Figure S5, Supplemental Digital Content, http://links.lww.com/MD2/A695).

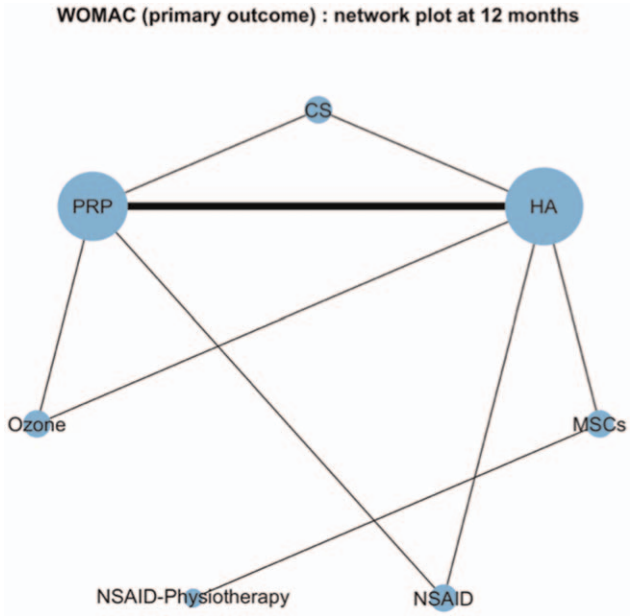

Figure 3. Network plot for the primary outcome. The area of every circle is proportional to the number of randomly assigned patients and indicates the sample size. The width of the lines is proportional to the number of trials that directly compared the 2 strategies.

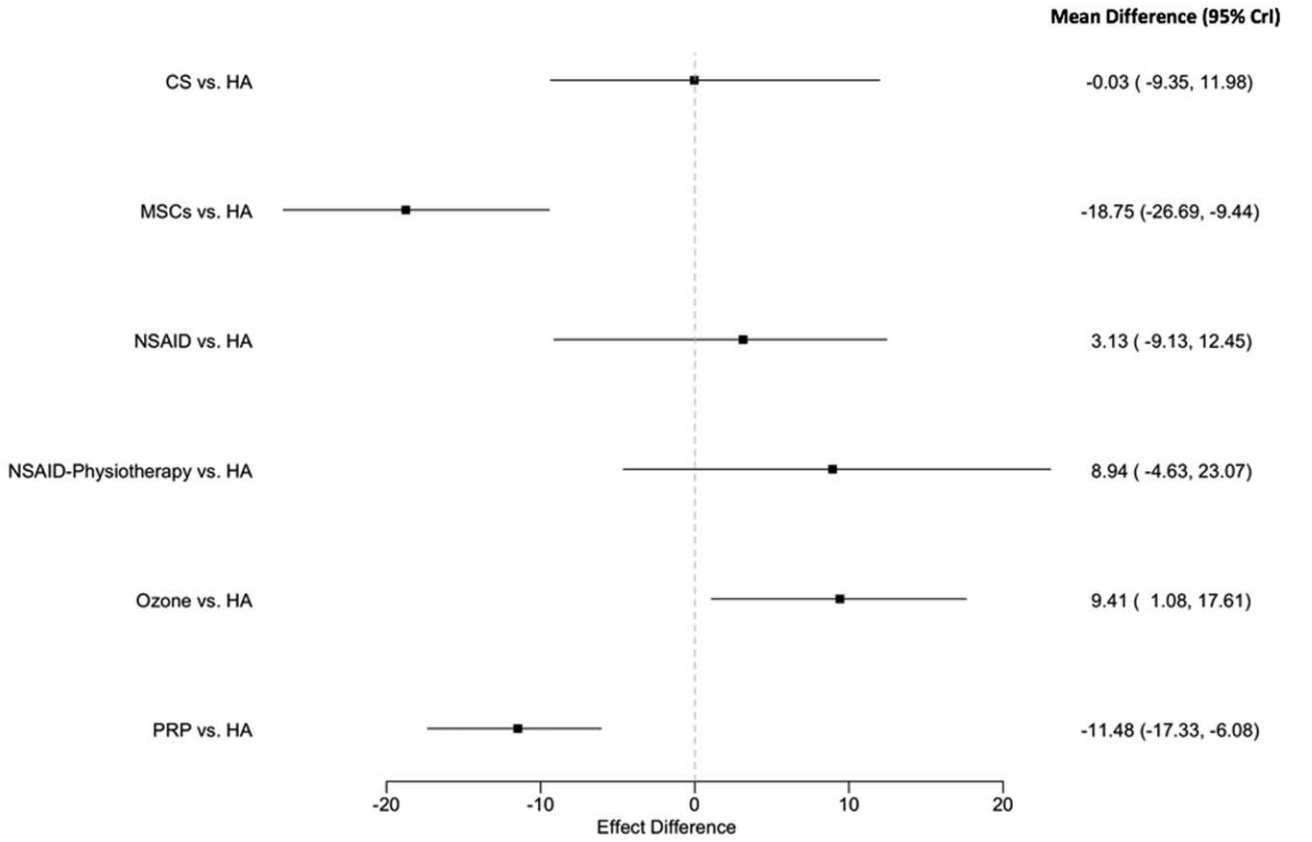

Figure 4. Forest plot for the strategies' effects compared with the reference treatment for primary outcome (WOMAC score at 12 months). Estimates are expressed on a 0 to 100 scale. Point estimates refer to the posterior mean. The bars indicate 95% credibility intervals (CrIs). WOMAC = Western Ontario and McMaster university.

By comparing the treatments to hyaluronic acid "the reference treatment," significant differences were observed between MSCs versus HA and PRP versus HA with an association with improvement in the WOMAC (decrease) for these 2 strategies but not for the 4 other strategies (Fig. 4).

Rank probabilities indicate that MSCs have a much higher probability ($P = .91$) of being the best treatment among the treatments, however, PRP has a higher probability of being the second-best treatment ($P = .89$). CS and HA are ranked as the third and the fourth best treatments ($P = .40$ and $P = .32$, respectively). Figure 5 shows the plots of treatment rank probabilities.

Injection of ozone was significantly associated with increasing in WOMAC and worse knee status compared with the pretreatment. The injection of HA was significantly better than ozone injection for knee osteoarthritis.

3.4. Secondary outcomes

- WOMAC at 3 and 6 months

The strategies were compared with hyaluronic acid (network plots appear in Figures S6a, Supplemental Digital Content, http://links.lww.com/MD2/A696 and S6b, Supplemental Digital Content, http://links.lww.com/MD2/A697). A significant difference was only found between Q-Actin versus HA and associated with improvement in the WOMAC at 3 months (mean difference, −21.3 [95% CrI, −28.4 to −13.1]).

At 6 months, there is significant differences between CSE versus HA, MSCs versus HA, and PRP versus HA. Q-Actin showed a greater improvement in WOMAC (mean difference, −42.4 [95% CrI, −49.3 to −34.7]), compared with MSCs (mean difference, –9.2 [95% CrI, −15.6 to −2.9]) and PRP (mean difference, –8.8 [95% CrI, −13.4 to −4.8]). (Forest plots are presented in Figures S7a, http://links.lww.com/MD2/A698 , Supplemental Digital Content, and S7b, http://links.lww.com/MD2/A699, Supplemental Digital Content).

- VAS at 3, 6 and 12 months

Four of 16 RCTs with VAS have used placebo as the control group. The placebo group was defined as the reference treatment in order to make comparisons between the strategies. (Network plots appear in Figures S8a, Supplemental Digital Content, http://links.lww.com/MD2/A700, S8b, Supplemental Digital Content, http://links.lww.com/MD2/A701, and S8c, http://links.lww.com/MD2/A702, Supplemental Digital Content).

A significant difference was found between autologous adipose-derived stromal vascular fraction (SVF) and placebo associated with decreasing in pain at 3 months (mean difference, –12.7 [95% CrI, −24.1 to −3.3]) but not for other strategies.

At 6 months, SVF (mean difference, –19.9 [95% CrI, −31.8 to −10.7]), chondroitin sulfate (mean difference, –10.7 [95% CrI, −22.3 to 0.5]), and MSCs (mean difference, –10.0 [95% CrI, −20.3 to −0.2]) showed a significant difference associated with pain decrease compared with placebo.

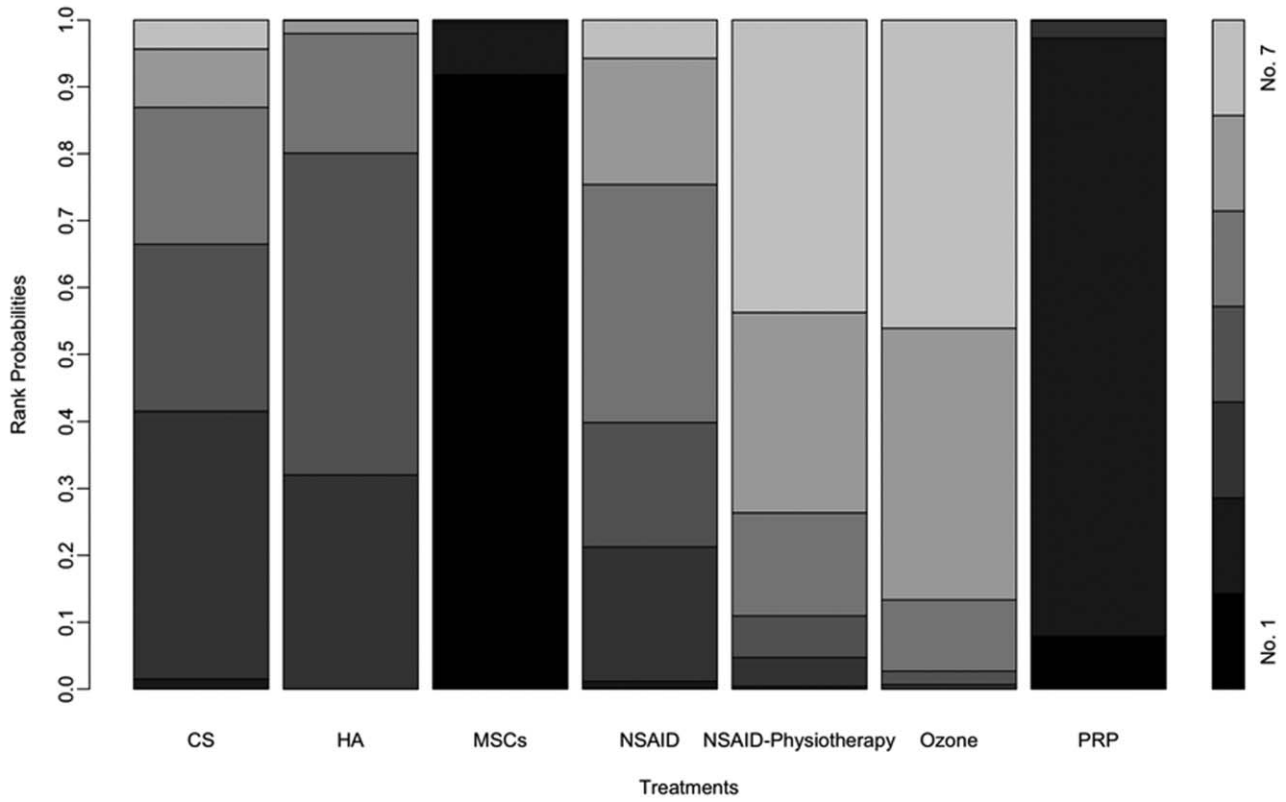

Figure 5. Plots of treatments rank probabilities for primary outcome. A darker area indicates the probability of being a higher rank, thus the black areas show the probabilities of being the best treatment.

A significant difference associated with decreasing in pain was found between SVF (mean difference, –23.2 [95% CrI, −32.0 to −15.7]), MSCs (mean difference, –20.6 [95% CrI, −28.1 to −12.6]), and PRP (mean difference, –15.0 [95% CrI, −20.7 to −11.4]) compared with hyaluronic acid (forest plots are presented in Figures S9a, http://links.lww.com/MD2/A703, Supplemental Digital Content, S9b, http://links.lww.com/MD2/A704, Supplemental Digital Content, and S9c, http://links.lww.com/MD2/A705, Supplemental Digital Content).

3.5. Sensitivity analyses

The sensitivity analyses were partially consistent with the results of the main analysis (Tables S6a–S6b, Supplemental Digital Content, http://links.lww.com/MD2/A711, http://links.lww.com/MD2/A712) when alternative statistical methods were used.

4. Discussion

In this systematic review and network meta-analysis, we chose to evaluate recent available randomized clinical trials in order to reflect contemporary practice. The interventions had different effects on the participants suffering from knee OA. In primary outcome (WOMAC at 12 months), MSCs and PRP were significantly better than the chosen control and associated with improvement in knee status. Otherwise, CS improved outcomes but did not perform better than the control.

Ozone injection is the only intervention for which knee pain and/or function got worse at the end of the study compared with the baseline. Ozone injection showed no improvement in pain and function at 12 months (+5.55% and +1.31%, respectively). In addition, the results of NSAID alone or with physical exercise (physiotherapy) were not associated with improvement in pain and function compared with the injection of HA. Otherwise, the combination of hyaluronic acid and dexamethasone was not associated with improvement in WOMAC at 3 and 6 months compared with the injection of hyaluronic acid alone.

Among all the interventions studied, the results of MSCs and PRP were the most consistent and associated with improvement in pain and articular function on the long-term. Moreover, Q-Actin (CSE) was associated with greater improvement in WOMAC at 3 and 6 months and the results of SVF were associated with greater improvement in pain found from the first evaluation at 3 months to the long-term evaluation. More studies with multiple outcomes should be carried out on the long term to confirm the results of these strategies.

MSCs had the highest probability to be the best treatment with primary outcome and also associated with improvement in pain and function especially at mid and long term. Moreover, the greatest improvement of pain and function at 12 months compared with baseline were observed in MSCs intervention groups (–66.36% with WOMAC and –74.47% with VAS). However, MSCs injections were performed in trials in absence of a matrix, mimicking the natural cellular environment, and therefore cartilage regeneration could not be achieved. Indeed, stem cells need a support that provides a 3D environment for their proliferation, differentiation, and regeneration of cartilage.[46,47] Injection of PRP combined with MSCs and in the

presence of a matrix implanted on bone and/or cartilage lesions could be an innovative strategy for treating knee osteoarthritis but larger RCTs are needed to confirm this hypothesis.

According to Kellgren–Lawrence and Outerbridge OA classifications, the articular cartilage fissures do not reach the subchondral bone for patients with grade II but only for grades III and IV. For this reason, it seems important to carry out studies evaluating OA treatments on groups of patients according to the severity of osteoarthritis, because this allows to have more relevant results and to select the most appropriate treatment for each patient.

The interventions using PRP or MSCs were not recommended by the American College of Rheumatology (ACR) guideline[48] for the management of knee osteoarthritis.

Actually, this guideline reviewed studies published until 2018 which could explain why the interventions of our included studies were not recommended. However, more recent studies published after 2018 show the efficacy and safety of some of these treatments such as PRP injections that are becoming more popular nowadays and recommended by the European League Against Rheumatism (EULAR) who considered in 2020 that intraarticular injections of PRP are an efficient treatment of early or moderate symptomatic knee osteoarthritis and may be useful in severe knee osteoarthritis.[49]

According to a 2013 article in American Association of Retired Persons, US hospitals charge $50,000, on average, for a total knee replacement. However, the mean price for a single unilateral knee PRP injection was $714 (95% CI: $691–737) and the cost of a single stem-cell treatment for osteoarthritis was estimated at $5156 (95% CI $4550–5762) based on data from 273 centers in the United States.[50] A medico-economic study focused on knee OA strategies appears crucial in order to provide information to public health decision-makers. Moreover, literature highlighted the important value of a medico-economic evaluation for knee OA treatment strategies.

Knee OA is considered a chronic disease and this study cannot confirm the efficiency of the evaluated interventions due to several limitations. First, the high statistical heterogeneity >75% for PRP strategy probably due to variation in protocols used in the included studies in important variables such as the volume of PRP, the frequency of the injections, and the control strategy.

Furthermore, overall quality of evidence, as qualified by GRADE was very low which means that further research is likely to show different results.

Second, the largest number of knee OA treatments studies published since 2017 evaluated different interventions on the short term. Only a small number of RCT studies evaluated interventions on the long-term (≥1 year of follow-up), although knee OA is considered a chronic disease. Furthermore, according to several studies, 50% of clinical trials go unreported, often because the results are negative,[51] which may also have introduced a bias.

Third, the small number of patients (<30 participants) included and evaluated for some strategies may introduce bias due to small study effects.

Fourth, the small number of publications using other outcome measures than VAS and WOMAC represents an important issue making it difficult to evaluate interventions according to other outcomes. Thus, the development of a universal outcome scale combining items as pain, function, and quality of life may be a solution to evaluate knee OA patients without the necessity to use many instruments. It would be beneficial to facilitate and strengthen the processing of future comparative studies.

Fifth, Freitag et al[35] showed better improvement in the MSCs groups compared with the control group represented by conservative treatments as exercise program prescribed by a physiotherapist or medical practitioner for at least 8 weeks, weight loss, analgesia, and biomechanical management. However, these interventions should be evaluated apart in a meta-analysis for a better understanding of the effectiveness of each one. In addition, many interventions have been excluded from our study (e.g., low-level laser therapy, transcutaneous electrical nerve stimulation, therapeutic ultrasound, Curcuma, etc) which may also have introduced bias.

Finally, the rank probabilities were used to compare the effectiveness between the different interventions, nevertheless, they show limitations, and the results should be interpreted with caution. For example, the safety of patients as well as the level of satisfaction and quality of life were not an outcome measures which is also considered a limitation to this study.

5. Conclusions

In this systematic review and network meta-analysis, the outcomes of treatments using MSCs and PRP for the management of knee osteoarthritis were associated with long-term improvements in pain and function. We suggest that more high quality randomized controlled trials would be needed to confirm the efficiency of MSCs and PRP for the treatment of patients with knee osteoarthritis.

Author contributions

Anne-Marie Musset, Damien Offner, and Moustafa Naja contributed in the conception and design of this article. Moustafa Naja and Damien Offner performed searches, analyses, and interpretations. Gabriel Fernandez De Grado provided statistical expertise. Moustafa Naja wrote the article. Damien Offner and Anne-Marie Musset contributed to the corrections. Nadia Benkirane-Jessel, Dominique Scipioni, and Henri Favreau made revision of the article for intellectual content. All authors have read and approved the final submitted manuscript.

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