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Review

The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: Osteoarthritis (OA) is a debilitating joint disease characterized by progressive loss of articular cartilage. Intra-articular injections are a mainstay of nonoperative treatment, however, there is controversy as to the optimal injectable for these patients. The purpose of the current study is to perform a network meta-analysis of the randomized control trials in the literature to ascertain whether there is a superior injectable nonoperative treatment for knee OA.

Methods: The literature search was conducted based on the PRISMA guidelines. Randomized control trials (RCTs) evaluating intra-articular injectables in osteoarthritic knees were included. Data was extracted and Visual Analogue Scale (VAS) scores and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, where available were analyzed at 1, 3, 6 and 12 months. Clinical outcomes were compared using a frequentist approach to network meta-analysis, with statistical analysis performed using R. The treatment options were ranked using the P-Score.

Results: Seventy-nine RCTs with 8761 patients were included in this review. Intra-articular injectables evaluated included autologous conditioned serum (ACS), bone marrow aspirate concentrate (BMAC), botulinum toxin, corticosteroids (CS), hyaluronic acid (HA), mesenchymal stem cells (MSC), ozone, saline placebo, platelet-rich plasma (PRP), plasma rich in growth factor (PRGF), and stromal vascular fraction (SVF). At 4–6 weeks and 3 months of follow-up, the treatment with the highest P-Score for WOMAC score was high molecular weight (HMW) HA + CS [P-Score = 0.9500 and 8503, respectively]. At 6-months follow-up, the treatment with the highest P-Score for WOMAC score was PRP [P-Score = 0.7676**]**. At all post-injection time points, the treatment with the highest P-Score for VAS score [P-Score Range = 0.8631–9927] and Womac score at 12 Months [P-Score = 0.9044] was SVF.

Conclusions: The current evidence shows that SVF injections result in the greatest improvement in pain and functional outcomes in patients with knee OA at up to 1 year of follow-up.

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Contents

1. Introduction

Osteoarthritis (OA) is a debilitating joint disease affecting 30 million people in the United State alone, imparting substantial morbidity including disability, reduction in quality of life, and financial burden [1,2]. The knee is the most common site of OA, comprising 80% of the case load globally [3]. Orthopedic surgeons have consequently sought to refine current treatment paradigms in order to improve patient outcomes. Intra-articular (IA) injections remain a central component in nonoperative treatment modalities for OA, as they present a low risk of harm while providing short-term pain reduction and improved joint function [4–7].

Several types of IA injections exist, including corticosteroids (CS), platelet rich plasma (PRP), hyaluronic acid (HA), botulinum toxin type A, autologous conditioned serum (ACS), and stromal vascular fraction (SVF). However, discerning the optimal management for symptomatic OA remains a challenge despite a vast amount of literature on the topic [8,9]. Existing studies are heterogenous, comparing different combinations of treatment modalities at varying time points, which can at times conclude in conflicting results. Furthermore, a recent network meta-analysis [10] pooled varying subtypes of PRP/HA injections with dissimilar biological properties, which may impact the outcomes reported and thus lead to inaccurate results. Additionally, other network meta-analyses exist but have limited their scope to only PRP, HA and CS, failing to include other available therapies.

The purpose of the current study is to perform a network meta-analysis of the randomized control trials in the literature to ascertain whether there is a superior injectable nonoperative treatment for knee OA. Our hypothesis was that orthobiologic therapies would prove superior to other intra-articular injectables in the treatment of knee OA.

2. Methods

2.1. Study selection

Two independent reviewers performed the literature search based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The search results were reviewed, and if any discrepancies existed, a third author reconciliated. All search results were evaluated by title and abstract, and any studies potentially included were then reviewed in full. Additionally, references of all included studies were then screen manually for any additional articles that may meet inclusion criteria.

2.2. Search strategy

The following search terms were used in MEDLINE, EMBASE and The Cochrane Library Database, databases in February 2020 as the search algorithm: [platelet rich plasma OR prp OR autologous conditioned plasma OR bone marrow aspirate OR corticosteroid OR acp OR hyaluronic acid OR ha OR mesenchymal stem cell OR msc OR ozone OR polydeoxyribonucleotide] AND [knee] and [osteoarthritis OR oa OR gonarthrosis OR cartilage]. No time limit was given to publication date.

2.3. Eligibility criteria

The inclusion criteria were: 1) randomized control trial comparing intra-articular injections in the knee, 2) published in a peer reviewed journal, 3) published in English, 4) includes VAS and WOMAC outcome scores, and 5) full text of studies available. The exclusion criteria were the following: 1) non-randomized studies, 2) review studies, 3) does not include patient outcome scores, and 4) basic science studies.

2.4. Data extraction/analysis

All relevant information regarding the study characteristics including design, level of evidence, methodological quality of evidence, population, outcome measures, and follow-up time points were collected by two independent reviewers using a predetermined data sheet. Studies were defined as leukocyte poor (LP)-PRP or leukocyte rich (LR)-PRP by the manufacturer's specifications as well as whether they had more or fewer leukocytes than autologous blood. Trials of hyaluronic acid were separated by molecular weight: high molecular weight (HMW) was greater than 1,800,000; middle molecular weight (MMW) was defined as 1,000,000 to 1,799,000; low molecular weight (LMW) was defined as 400,000 to 999,999; small molecular weight (SMW) was 399,999 or less. The level of evidence (LOE) was evaluated based on the criteria by The Oxford Centre for Evidence-Based Medicine. The risk of bias and methodological quality of evidence (MQOE) was assessed for randomized control trials using the Jadad scale, a 5 point scale [12]. Studies with a Jadad score of >3 were considered to have a low risk of bias. The Jadad score of all included studies can be found in the appendix. Despite only including Level I randomized controlled trials, some studies still introduce an element of bias, such as a lack of reporting the outcomes of all recruited patients (including dropouts or loss to follow-up), as well as non-blinded studies.

2.5. Statistical analysis

All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). A frequentist approach to network meta-analysis with a random effects model was performed using the *netmeta* package version 0.9–6 in R [13]. For continuous outcomes, the relative effect sizes were reported as standardized mean differences (MD), and for dichotomous outcomes, the relative effect sizes were reported as odds ratios (OR). The effect sizes were reported with 95% confidence intervals (95% CI). Heterogeneity was quantified using the I^2 statistic [14]. The frequentist analogue to the surface under the cumulative ranking (SUCRA) probabilities called the P-score was used to rank the treatments. This method allows each treatment to be ranked on a scale from 0-1, where 0 indicates the least effective treatment and 1 indicates the most effective [13].

3. Results

3.1. Literature search

The initial literature search resulted in 5594 total studies. Once duplicates were removed and articles were screened by title and abstract, 177 studies were included, and full texts were assessed for eligibility. Ultimately, 79 studies with 8761 patients met inclusion and exclusion criteria (Figure 1).

3.2. Patient demographics

There were 79 RCTs with a total of 8,761 patients. The mean age of included patients was 61.1, the majority of patients were female (64.4%), and the follow-up ranged from 4-weeks to 24-months. The full list of included studies and their characteristics is listed in Appendix 1.

3.3. VAS score

There was no significant difference in VAS score at baseline between any of the groups. At all post-injection time points, the treatment with the highest P-Score for VAS score was SVF [P-Score Range = 0.8922–9923]. The P-Scores for VAS score are shown in Table 1, and the forest plots for VAS score at 4–6 weeks, 3 months, 6 months, and 12 months are shown in Figures 2, 3, 4, 5, and 6 respectively (Table 2).

3.4. WOMAC score

At baseline, the WOMAC score for MMW HA was significantly lower than the control, however, there was no significant difference between the control and any of the groups. At 4–6 weeks and 3 months follow-up, the treatment with the highest P-Score for WOMAC score was HMW + CS [P-Score = 0.9182 and 8735, respectively] At 6-months follow-up, the treatment with the highest P-Score for WOMAC score was PRP [P-Score = 0.9617]. At 12-months follow-up, the treatment with the

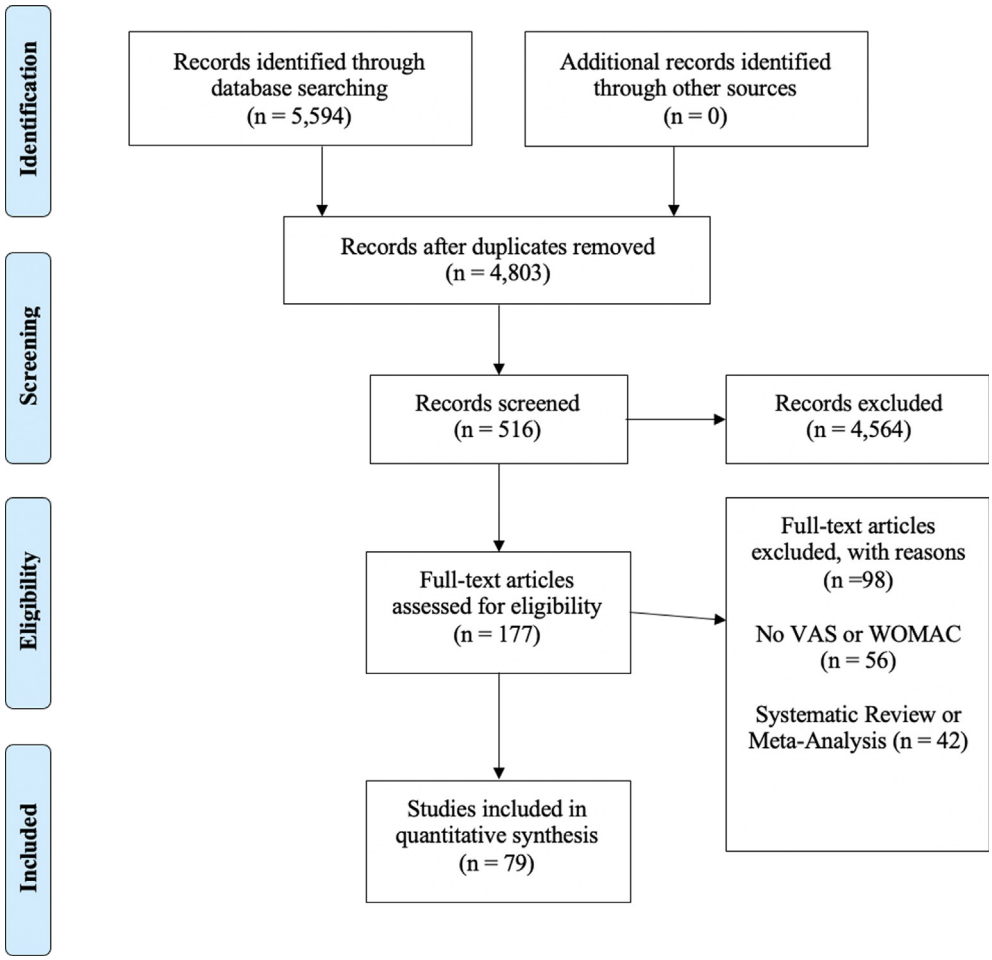

Figure 1. PRISMA Study Selection Flow Diagram.

Table 1
VAS score.

4-6Weeks	3Months	6Months	12Months
SVF: 0.9061	SVF: 0.8922	SVF: 0.9923	SVF: 0.9483
HMW + CS: 0.8519	HMW + LR-PRP: 0.8049	ACS: 0.904	HMW + LR-PRP: 0.871
ACS: 0.8391	ACS: 0.759	LMW + LP-PRP: 0.7947	LR-PRP: 0.7404
HMW + LR-PRP: 0.7391	LR-PRP: 0.6024	HMW + LR-PRP: 0.7771	LP-PRP: 0.7326
LR-PRP: 0.6832	LP-PRP: 0.59	LP-PRP: 0.6921	MSC: 0.5406
CS: 0.6284	LMW: 0.542	LR-PRP: 0.6171	LMW: 0.3823
LP-PRP: 0.5511	LMW + LP-PRP: 0.5095	LMW: 0.454	***Saline: 0.3668***
MMW: 0.4184	HMW: 0.4684	MMW: 0.3912	CS: 0.3004
HMW: 0.4114	HMW + CS: 0.4657	MSC: 0.3808	MMW: 0.287
LMW: 0.3844	MSC: 0.4038	***Saline: 0.3149***	HMW: 0.2158
BoNTA: 0.3788	MMW: 0.3986	HMW + CS: 0.2855	Ozone: 0.1148
Ozone: 0.2796	BoNTA: 0.3803	HMW: 0.2731	
LMW + LP-PRP: 0.2145	***Saline: 0.336***	CS: 0.1231	
Saline: 0.1156	CS: 0.1818	Ozone: 1e-04	
MSC: 0.0984	Ozone: 0.1654		

ACS; autologous conditioned serum, BoNTA; botulinum toxin A, CS; corticosteroids, HMW; high-molecular weight hyaluronic acid, LMW; low-molecular weight hyaluronic acid, MSC; mesenchymal stem cells, MMW; medium-molecular weight hyaluronic acid, PRP; platelet-rich plasma, PRFG; plasma rich in growth factors, SVF; stromal vascular fraction.

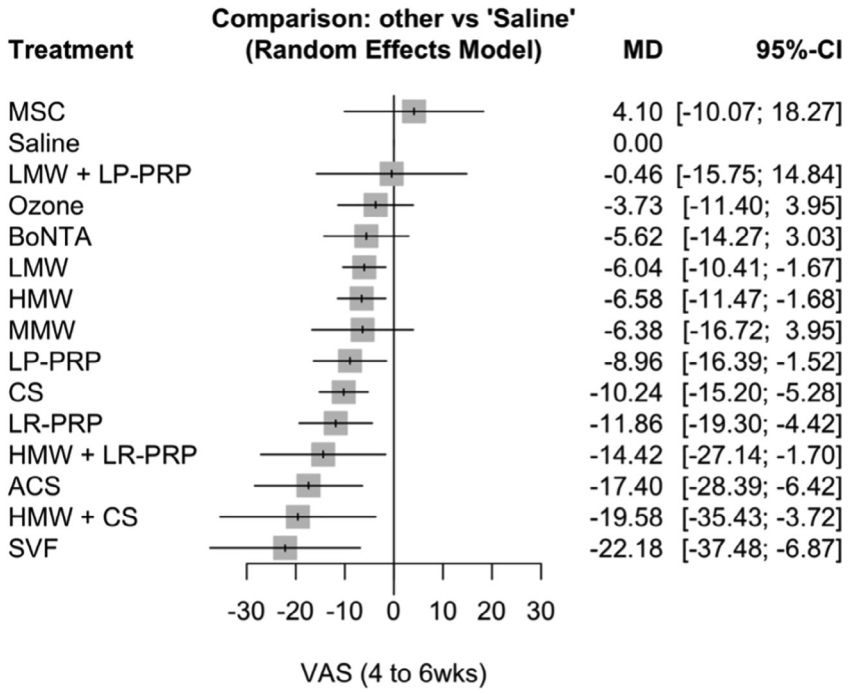

Figure 2. Forest Plot of VAS Score at 4–6-week follow-up.

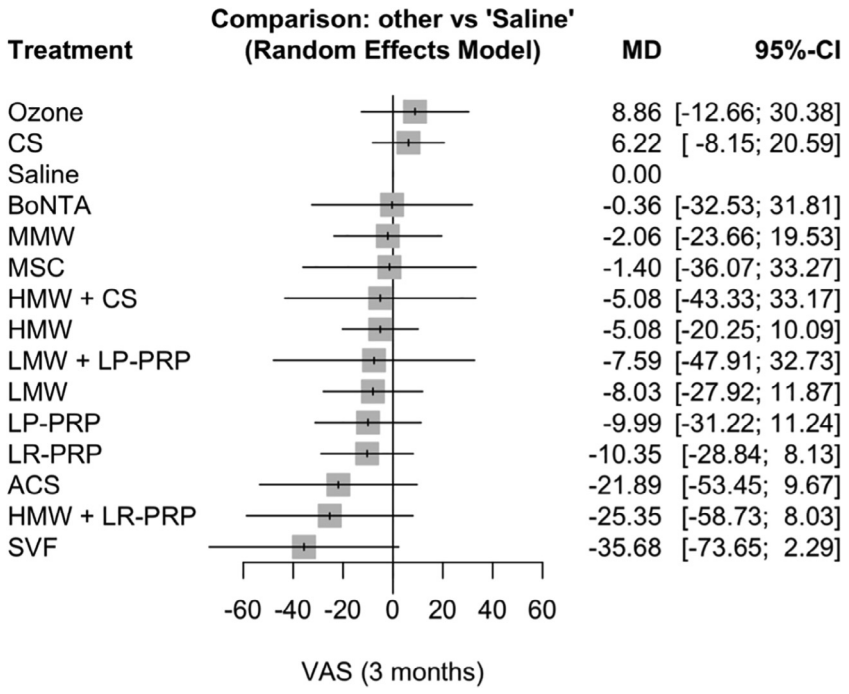

Figure 3. Forest Plot of VAS Score at 3-month follow-up.

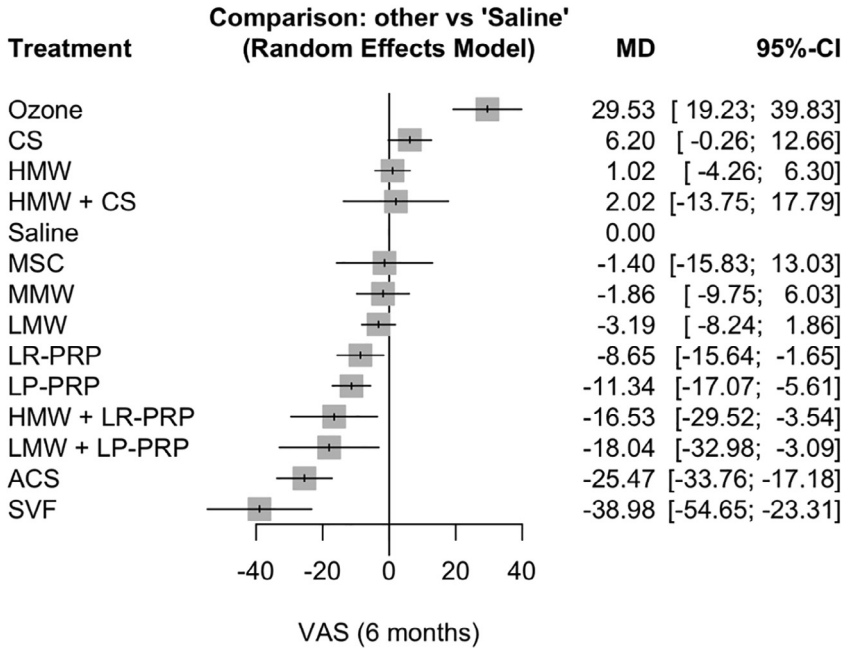

Figure 4. Forest Plot of VAS Score at 6-month follow-up.

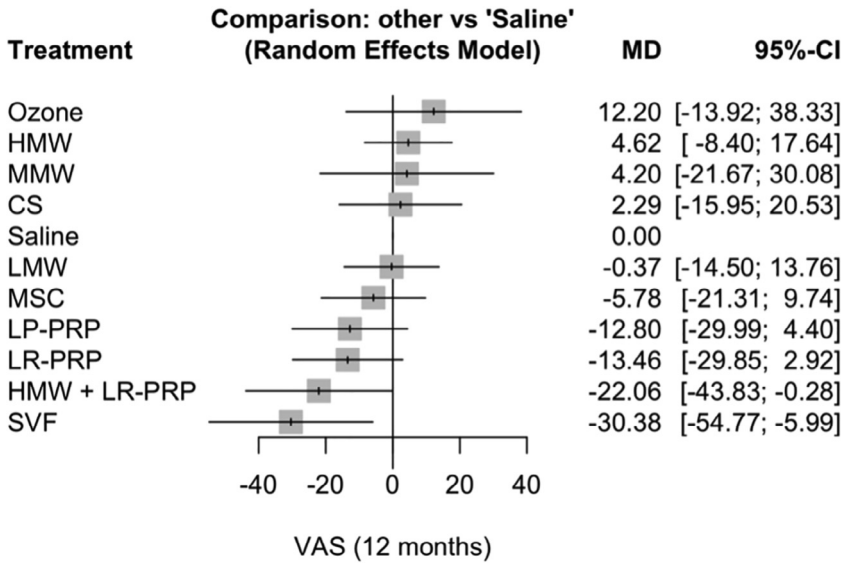

Figure 5. Forest Plot of VAS Score at 12-month follow-up.

highest P-Score for VAS score was SVF [P-Score = 0.9034]. The P-Scores for VAS score are shown in Table 1, and the forest plots for WOMAC score at 4–6 weeks, 3 months, 6 months, and 12 months are shown in Figures 7, 8 and 9 respectively.

4. Discussion

The most important finding of this study was that SVF resulted in the highest P-Score for VAS score at all time points, indicating that this had the greatest effect on pain post-injection at all time points. Furthermore, SVF had the highest WOMAC score at 12-months post-injection indicating that these patients also had the highest functional outcome scores fol-

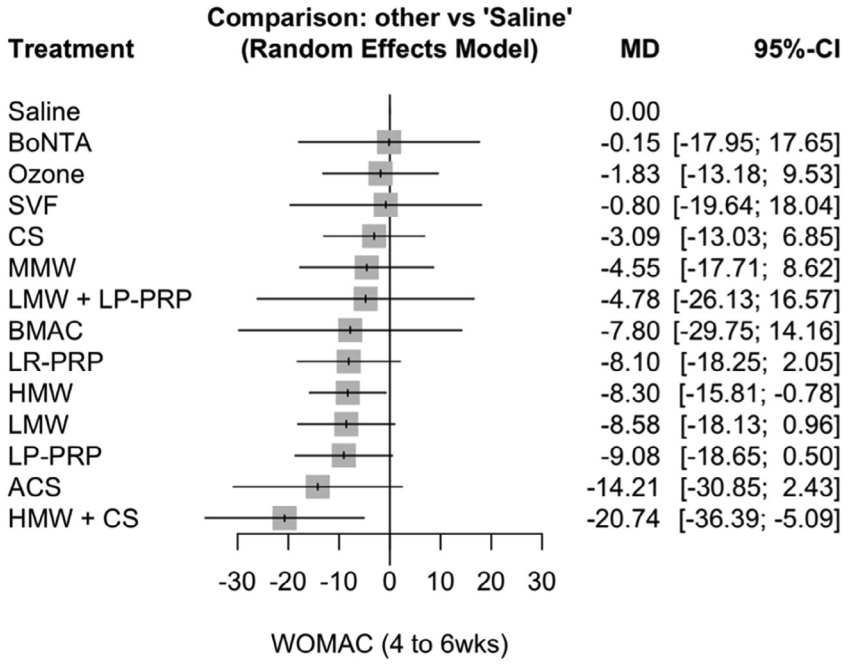

Figure 6. Forest Plot of WOMAC Score at 4–6-week follow-up.

Table 2
WOMAC score.

4-6Weeks	3Months	6Months	12Months
HMW + CS: 0.9182	HMW + CS: 0.8735	ACS: 0.9617	SVF: 0.9034
ACS: 0.7627	LP-PRP: 0.7757	LP-PRP: 0.7514	LP-PRP: 0.8203
LP-PRP: 0.6305	BMAC: 0.7567	MSC: 0.6726	LR-PRP: 0.6559
LMW: 0.608	LR-PRP: 0.723	LMW + LP-PRP: 0.6439	BMAC: 0.5438
HMW: 0.5992	HMW: 0.6552	SVF: 0.6408	MSC: 0.5411
LR-PRP: 0.5839	LMW + LP-PRP: 0.6167	LR-PRP: 0.5772	HMW: 0.4531
BMAC: 0.5425	MMW: 0.5171	HMW + CS: 0.5771	LMW: 0.4064
LMW + LP-PRP: 0.447	LMW: 0.4944	MMW: 0.5343	***Saline: 0.398***
MMW: 0.4296	BoNTA: 0.3456	BMAC: 0.4615	MMW: 0.3872
CS: 0.3576	CS: 0.3118	HMW: 0.4381	Ozone: 0.2017
SVF: 0.3202	SVF: 0.1712	LMW: 0.4045	CS: 0.1892
Ozone: 0.3074	Ozone: 0.146	***Saline: 0.1635***	
BoNTA: 0.2912	***Saline: 0.1131***	CS: 0.1345	
Saline: 0.2021		Ozone: 0.0389	

ACS; autologous conditioned serum, BoNTA; botulinum toxin A, CS; corticosteroids, HMW; high-molecular weight hyaluronic acid, LMW; low-molecular weight hyaluronic acid, MSC; mesenchymal stem cells, MMW; medium-molecular weight hyaluronic acid, PRP; platelet-rich plasma, PRFG; plasma rich in growth factors, SVF; stromal vascular fraction.

lowing treatment. However, it is still worth noting that the majority of intra-articular injections had higher P-Scores than the saline placebo, and thus were shown to be efficacious. The only intra-articular injectable which was found to be consistently worse than the placebo was ozone.

This study performed a network meta-analysis which is an ideal method of comparison of the multiple intra-articular injections utilized in the treatment of knee OA. A network meta-analysis allows for direct and indirect comparison of treatments using common comparators and ranking them with a P-score, a representation of the probability that the treatment option is associated with the optimal result in each outcome measure. The P-Score does not represent the magnitude of difference between the treatment choices, and it does not signify clinically significant differences. Thus, it is important to look at the odds ratio, mean difference and confidence interval between each treatment as seen in the forest plots.

Previous network meta-analyses have been conducted on the treatment of knee OA, and have come to differing conclusions, primarily due to differences in methodologies. Firstly, this study included SVF which was found to have the highest P-Score, and this was not included in the majority of other network meta-analyses in the literature. SVF is comprised of adipose

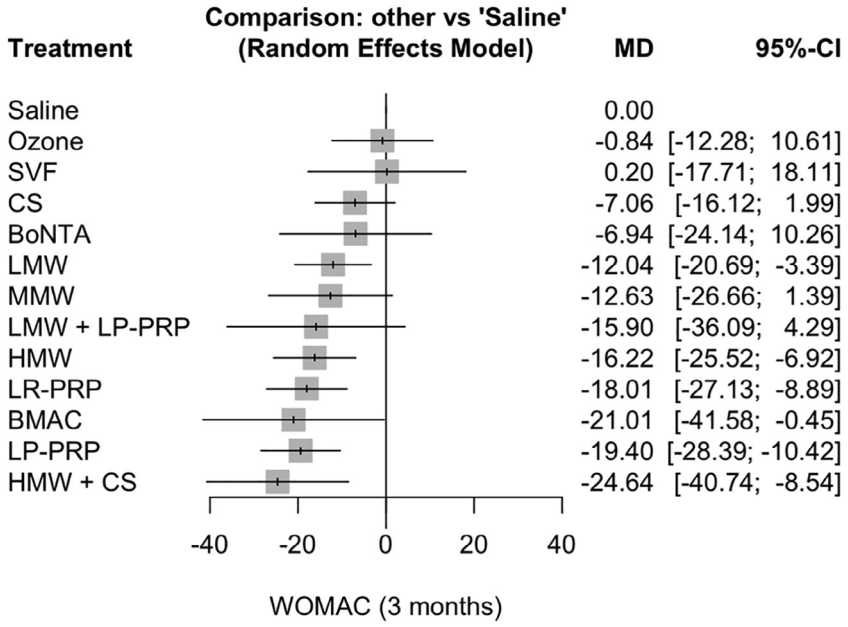

Figure 7. Forest Plot of WOMAC Score at 3-month follow-up.

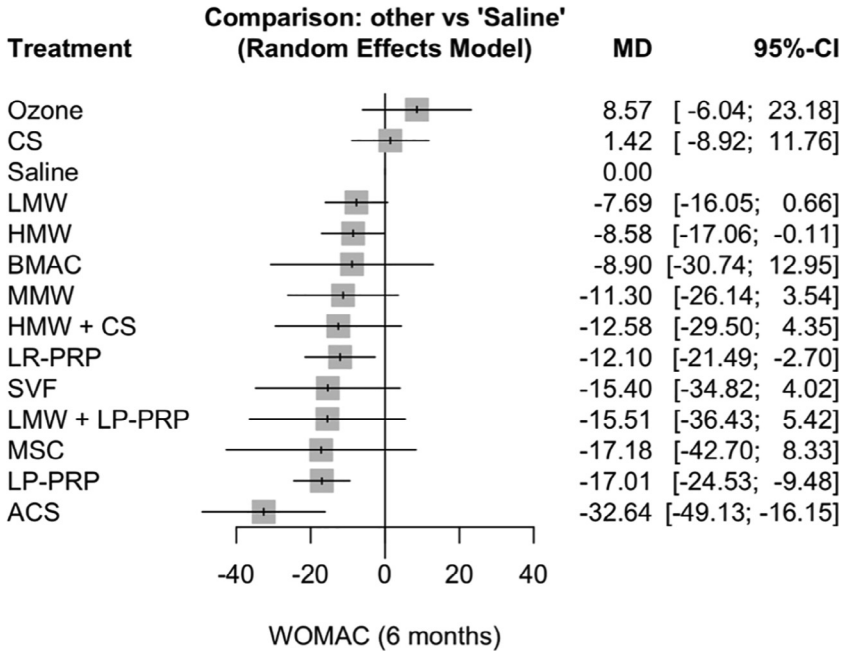

Figure 8. Forest Plot of WOMAC Score at 6-month follow-up.

derived mesenchymal stem-cells, pericytes, vascular adventitia cells, fibroblasts, preadipocytes, monocytes, macrophages, and red blood cells. SVF is harvested from adipose tissue, an attractive source of mesenchymal-stem cells due to the abundance of adipose tissue and ease of accessibility.

Significant chondrogenic effects from the application of adipose derived mesenchymal stem-have been shown in in-vitro studies, proposing that SVF possess the CD73, CD90, CD105 and CD106 markers, which are surface markers required for cell differentiation into cartilage [15–17]. Furthermore, there is also a paracrine effect of SVF on OA chondrocytes as they pro-

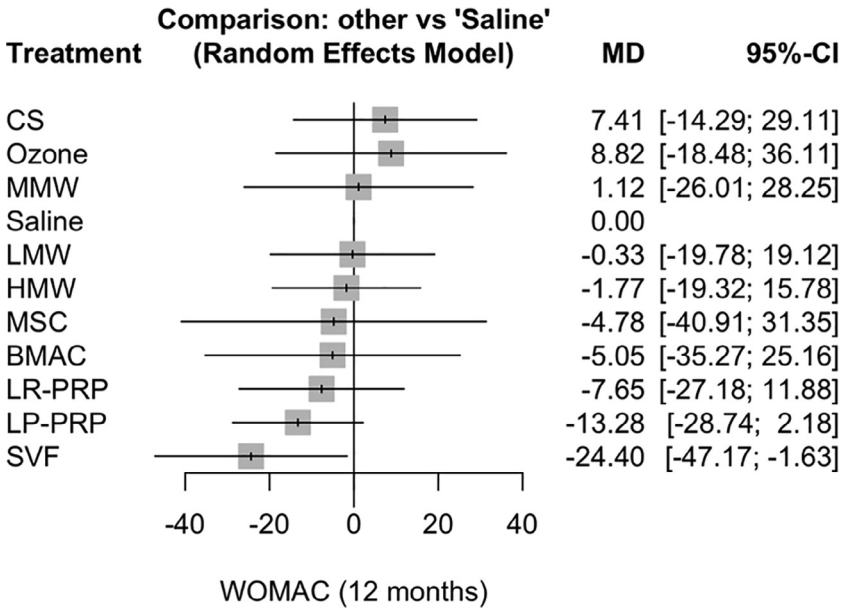

Figure 9. Forest Plot of WOMAC Score at 12-month follow-up.

mote inhibitory macrophages and T regulatory cells, which may decrease inflammatory markers and result in the pain relief and functional improvement as shown by this network meta-analysis [15,16]. However, it is important to note that the harvest method of SVF in the majority of studies involves the use of collagenase to separate the adipose and it is important that collagenase digestion cannot be used in the United States due to FDA regulations. Therefore, for SVF to be utilized in the United States, it requires mechanical fractioning to separate the SVF from the adipose tissue.

Our study performed subgroup analysis based on the leukocyte concentration of the PRP preparations, and the molecular weight of HA, as these are important biologic variables which may impact the results. LP-PRP has been shown in basic science studies to stimulate endogenous HA production and decrease cartilage catabolism and suppress the inflammatory mediators and expression of their genes in synoviocytes and cartilage [18]. The reduction in inflammatory mediators plays a role in the pain reduction following LP-PRP injections. Cole et al. [19] found in their RCT that with LP-PRP there was a decrease in the pro-inflammatory cytokines as measured by ELISA. In contrast, there may be concern with utilizing LR-PRP for knee OA as it may be pro-inflammatory based on basic science evidence. However, Mariani et al. [20] found that this did not alter the inflammatory cytokines as measured by ELISA. Although our study found LP-PRP resulted in higher P-Scores than LR-PRP, which would support that the decreased leukocyte concentration results in improved clinical outcomes.

Higher molecular weight in HA injections has been suggested to be more efficacious as it more closely resembles the HA in the knee, which is lost in an osteoarthritic joint [21–24]. Elmorsy et al. [25] found in a rabbit osteoarthritis model HMW-HA has greater chondroprotective effects than LMW-HA. However, in our study there was mixed evidence with different molecular weights having greater effects at different time points, and thus requires further study. Although, it is interesting to note that HA and a concomitant medication such as PRP or CS resulted in superior outcomes at most time points compared to isolated injections. This suggests that there may be a synergistic effect between them, as PRP and CS primarily modulate inflammation, whereas HA offers a chondroprotective effect, and thus the combination could lead to greater clinical improvements.

Corticosteroid injections are often the first line injection for knee OA, however, while they provide initial pain relief due to decreased inflammation, they are not chondroprotective and may cause further cartilage loss [26,27]. While research on the non-operative treatment of knee OA has been rapidly advancing, there are still several areas that require further study. Orthobiologics have been shown to improve symptoms by dampening the inflammatory process and have chondrogenic potential, however, it is still unclear if they prolong the interval time to knee arthroplasty.

5. Limitations

As a systematic review, a major limiting factor is the lack of available data between the included studies. Similarly, discrepancies exist in reported outcome measures as follow-up was obtained at various points during the post-operative period. In the included pooled analyses, the standardization of reporting limited our analysis. Thus, some intra-articular injections could not be added to comparisons at certain time points. However, we mitigated the heterogeneity by including random effects models to control for this.

6. Conclusion

The current evidence shows that SVF injections result in the greatest improvement in pain and functional outcomes in patients with knee OA at up to 1-year follow-up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.knee.2021.08.008.

References

[1] Nelson AE. Osteoarthritis year in review 2017: clinical. Osteoarthritis Cartilage 2018;26(3):319–25. doi: https://doi.org/10.1016/j.joca.2017.11.014.
[2] White AG, Birnbaum HG, Janagap C, Buteau S, Schein J. Direct and indirect costs of pain therapy for osteoarthritis in an insured population in the United States. J Occup Environ Med 2008;50(9):998–1005. doi: https://doi.org/10.1097/JOM.0b013e3181715111.
[3] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2163–96. doi: https://doi.org/10.1016/s0140-6736(12)61729-2.
[4] Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino A, Mont MA. Knee Osteoarthritis: A Primer. Perm J 2017;21:16–183. doi: https://doi.org/10.7812/TPP/16-183.
[5] Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015;162(1):46–54. doi: https://doi.org/10.7326/m14-1231.
[6] McCabe PS, Maricar N, Parkes MJ, Felson DT, O'Neill TW. The efficacy of intra-articular steroids in hip osteoarthritis: a systematic review. Osteoarthritis Cartilage 2016;24(9):1509–17. doi: https://doi.org/10.1016/j.joca.2016.04.018.
[7] van Middelkoop M, Arden NK, Atchia I, Birrell F, Chao J, Rezende MU, et al. The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. Osteoarthritis Cartilage 2016;24(7):1143–52. doi: https://doi.org/10.1016/j.joca.2016.01.983.
[8] Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment With Platelet-Rich Plasma Is More Effective Than Placebo for Knee Osteoarthritis: A Prospective, Double-Blind. Randomized Trial. Am J Sports Med 2013;41(2):356–64. doi: https://doi.org/10.1177/0363546512471299.
[9] Ornetti P, Nourissat G, Berenbaum F, Sellam J, Richette P, Chevalier X. Does platelet-rich plasma have a role in the treatment of osteoarthritis? Joint Bone Spine 2016;83(1):31–6. doi: https://doi.org/10.1016/j.jbspin.2015.05.002.
[10] Han S-B, Seo I-W, Shin Y-S. Intra-Articular Injections of Hyaluronic Acid or Steroids Associated With Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cells, or Placebo in Knee Osteoarthritis: A Network Meta-Analysis. Arthroscopy 2021;37(1):292–306.
[11] Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016;352:. doi: https://doi.org/10.1136/bmj.i157i157.
[12] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1–12. doi: https://doi.org/10.1016/0197-2456(95)00134-4.
[13] Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15:58. doi: https://doi.org/10.1186/s12874-015-0060-8.
[14] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60. doi: https://doi.org/10.1136/bmj.327.7414.557.
[15] Ragni E, Colombini A, Viganò M, Libonati F, Perucca Orfei C, Zagra L, et al. Cartilage Protective and Immunomodulatory Features of Osteoarthritis Synovial Fluid-Treated Adipose-Derived Mesenchymal Stem Cells Secreted Factors and Extracellular Vesicles-Embedded miRNAs. Cells 2021;10(5):1072.
[16] Ragni E, Perucca Orfei C, De Luca P, Colombini A, Viganò M, de Girolamo L. Secreted Factors and EV-miRNAs Orchestrate the Healing Capacity of Adipose Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis. Int J Mol Sci 2020;21(5):1582. doi: https://doi.org/10.3390/ijms21051582.
[17] Jankowski M, Dompe C, Sibiak R, Wąsiatycz G, Mozdziak P, Jaśkowski JM, et al. In Vitro Cultures of Adipose-Derived Stem Cells: An Overview of Methods, Molecular Analyses, and Clinical Applications. Cells 2020;9(8):1783. doi: https://doi.org/10.3390/cells9081783.
[18] Sundman EA, Cole BJ, Karas V, Della Valle C, Tetreault MW, Mohammed HO, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med 2014;42(1):35–41. doi: https://doi.org/10.1177/0363546513507766.
[19] Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis. Am J Sports Med 2017;45(2):339–46. doi: https://doi.org/10.1177/0363546516665809.
[20] Mariani E, Canella V, Cattini L, Kon E, Marcacci M, Di Matteo B, et al. Leukocyte-Rich Platelet-Rich Plasma Injections Do Not Up-Modulate Intra-Articular Pro-Inflammatory Cytokines in the Osteoarthritic Knee. PLoS ONE 2016;11(6):. doi: https://doi.org/10.1371/journal.pone.0156137e0156137.
[21] Balazs EA, Watson D, Duff IF, Roseman S. Hyaluronic acid in synovial fluid. I. Molecular parameters of hyaluronic acid in normal and arthritis human fluids. Arthritis Rheum 1967;10(4):357–76. doi: https://doi.org/10.1002/art.1780100407.
[22] Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther 2003;5(2):54–67. doi: https://doi.org/10.1186/ar623.
[23] Goldberg VM, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. Osteoarthritis Cartilage 2005;13(3):216–24. doi: https://doi.org/10.1016/j.joca.2004.11.010.
[24] Pelletier JP, Martel-Pelletier J. The pathophysiology of osteoarthritis and the implication of the use of hyaluronan and hylan as therapeutic agents in viscosupplementation. J Rheumatol Suppl 1993;39:19–24.
[25] Elmorsy S, Funakoshi T, Sasazawa F, Todoh M, Tadano S, Iwasaki N. Chondroprotective effects of high-molecular-weight cross-linked hyaluronic acid in a rabbit knee osteoarthritis model. Osteoarthritis Cartilage 2014;22(1):121–7. doi: https://doi.org/10.1016/j.joca.2013.10.005.
[26] Kompel AJ, Roemer FW, Murakami AM, Diaz LE, Crema MD, Guermazi A. Intra-articular Corticosteroid Injections in the Hip and Knee: Perhaps Not as Safe as We Thought? Radiology 2019;293(3):656–63. doi: https://doi.org/10.1148/radiol.2019190341.
[27] McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. JAMA 2017;317(19):1967–75. doi: https://doi.org/10.1001/jama.2017.5283.