REVIEW ARTICLE

Role of stem cells in the treatment of osteoarthritis- a review of literature

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Abstract

The purpose of this review was to identify and assess the effectiveness of stem cells in the form of injectables in the treatment of joint osteoarthritis as published in the literature. Studies were searched from multiple databases like Pubmed, Embase and Cochrane Library until June 2022 using multiple keywords. Randomized controlled trials of patients with osteoarthritis (OA) were included which compared the pain and functional outcomes for those getting Mesenchymal Stem Cells (MSCs) injectables as compared to those who received no MSCs injection. Twelve randomized controlled trials, assessing a total of 486 participants were identified and studied. Overall, stem cells injection has no significant effect on pain along with physical function. Stem cells injection could be effective in reducing pain and might also help in improving functional outcome in patients with OA. However, the findings are not yet significant and further clinical trials with larger samples are needed to come to a positive conclusion.

Keywords: Osteoarthritis, Pain, Injections.

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Introduction

Osteoarthritis (OA) is among the most commonly occurring arthritis in adults and causes joint pain resulting in inability to function and subsequent disability. This condition is characterized by loss of the articular cartilage, destruction of the subchondral bone, thickening of synovium, disintegration of ligaments and hypertrophy of capsule[1]. Many treatment regimens have been proposed and marketed for OA, majority of which are modestly efficacious, but are often restricted by adverse events. The primary management of OA includes exercises, lifestyle modifications and pain medications.[2–5] When such interventions are inadequate, many non-invasive therapies have been investigated and applied such as steroids,[6] hyaluronic acid,[7] platelet-rich plasma (PRP)[8] and glucosamine[9].

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Total knee replacement (TKR) is the surgical treatment of choice for painful knee OA that is not controlled using conservative measures. Total knee replacements are associated with significant complications[11,12]. Many of the patients will continue to feel pain in the knee after TKR [13]. Many other complications can occur such as pulmonary embolism, infections and death in around 2 % of patients[12].

The overall health and financial impact of OA has made it a liability which has resulted in working on alternative joint preservation strategies like stem cells. Stem cells have sprouted as a new modality for the management of OA.[14,15] These pluripotent cells have the ability to divide into multiple cell lines.[16] Mesenchymal stem cells (MSCs) are known owing to easy extraction,[17] safety profile[18,19] and ability to differentiate into chondral tissue.[19] They help in immune-modulation by releasing growth factors and cytokines.[20-22] All of these factors could help in the management of OA. These stem cells can be extracted from bone marrow or even adipose tissue and utilised in the form of injection in different joints for degenerative conditions. However, this aspect of stem cells for the management of OA is still open to discussion with no proven data stating its efficacy.[23-25]

Many case series have been identified which do point towards acceptable results of stem cell injections in cartilage disruption[16–17], however, further review into literature is still required. We performed a literature search to evaluate the efficacy of injectable MSCs in reducing pain and enhancing function in advanced OA patients.

Methods

Literature Search: The current review included studies until July 2022. Electronic databases of Pubmed, Cochrane Library, Embase and MEDLINE were searched through the combination of keywords related to OA, stem cell therapy, mesenchymal stem cells and randomized controlled trials (RCT). 152 studies were reviewed initially by name of the title or abstract of the article to assess study inclusion based on criteria.

Study Selection: Studies which met the following criteria were included in the review: (1) RCTs; (2) patients with OA;

(3) pain and functional outcome of patients with OA being reported; and (4) Non-human studies were excluded.

Outcome Measures: The primary goal of the study was to assess the efficacy of pain management and functional improvement by injecting stem cells in various joints. Outcomes assessed included outcomes reported by patients such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score,[3] the visual analog scale (VAS) for pain, and the macroscopic International Cartilage Regeneration & Joint Preservation Society (ICRS) score.[31]

Results

The search of electronic databases and other sources resulted in 152 articles. After removing duplicates, 42 full-text articles were chosen. 11 studies were excluded after reading the full text. Seven were excluded because they were not RCTs or CCTs. In total, 12 studies met the criteria.[26–37] The trials were published between 2011 and 2022.

Nine articles used the WOMAC score,[5,6,9,24,33]; 7 studies used the VAS; [9,24,29,33] and 5 studies used the macroscopic ICRS score.[6,29,33] The macroscopic ICRS score determines the final outcome of cartilage macroscopically. Grade 1 points towards normal cartilage whereas grade 4 indicates severely damaged cartilage.

Ten randomized controlled trials[26,27,30–37] and two controlled clinical trials[28, 29] were included in this review. All the studies included patients with osteoarthritis and the average age of participants was over 55 years. Five studies[27–31, 33] contrasted stem cells with placebo, which included other interventions as well, such as arthroscopy, rehabilitation regimes, PRP and hyaluronic acid. Two articles[31,32] compared stem cells with HA excluding all other interventions.

Outcomes on Pain: Eight articles[27, 29–35] evaluated the impact of injectable stem cells on pain using a visual analog scale. Inconsistent data extracted showed that stem cells' injection alone, or with other interventions, had an impact on pain in OA but not significantly.

However, when two low quality studies were removed from the review, it resulted in significantly decreased pain scores. Two studies reported that MSCs injection alone was as effective as hyaluronic acid (HA) in reducing pain in OA [30,31].

Outcomes on Function: Seven articles evaluated physical function. Review showed that stem cells alone or in combination with other therapies significantly improved various functional scores (Lysholm score, Lequesne index and OAOS). The Lysholm score of five articles showed significant results[28–32] compared to control group. The rest of the studies utilised the Lequesne index for assessing function between experimental and control groups and showed significant differences[31–33]. However , when six months post injection follow up was studied, neither of the studies showed significant difference between the two groups.

Four studies[31,32,33,34] have been searched in this review which have compared stem cells injection with hyaluronic acid. Evaluation for function was done with Lequesne index and WOMAC at six months and 12 months post injection. The results indicated a significant difference in Lequesne index when the two groups were compared. On the other hand, WOMAC score showed no significant difference.

Discussion

Musculoskeletal conditions requiring alternative regenerative measures are increasing in popularity for treating injuries requiring bone augmentation. Stem cell therapy has sprouted as a fulfilling technique to support bone regeneration[24]. It was the pathologist Cohnheim who claimed that nonhematopoietic cells in the blood travel to injury sites and potentiate tissue regeneration.(Ref)

Frieden stein indicated that bone marrow contains stem cells many years after the discovery of similar cells in rabbits. The research on MSCs has since then resulted in many new researches on their potential for various therapeutic outcomes[35].

MSCs are non haematopoietic stromal stem cells that can be extracted from many sources, like bone marrow, adipose tissue, periosteum, muscle, umbilical cord blood and other mesenchymal tissues as well. They are able to self-replicate themselves and are also able to differentiate into and help in the reproduction of various tissues like bone, cartilage, muscle and adipose tissue. They have been utilised to provide a scaffold for bone grafts using engineered tissues. All this information regarding stem cells paves way for further research and development of newer therapies for bone regeneration using MSCs[38].

In recent years, multiple clinical trials have shown that injectable stem cells have been helpful in the pain management and function outcomes for patients with knee osteoarthritis[30,39-42]. However there are few RCTs describing osteoarthritis in various other joints. Therefore, the outcomes of stem cell therapy on patients of osteoarthritis haven't had a conclusive outcome. Our

review included twelve RCTs[26–37], which fulfilled the inclusion criteria.

On the basis of Jadad scale evaluation, seven of these studies were categorized as high quality and the other five studies fell under low quality. Eight different studies [39,29–35] used VAS for pain evaluation, however, nonsignificant benefit came up of the stem cells injection on improving pain at the last followup. However, it should be noted that owing to the heterogeneity of these studies, the results should be dealt with caution. When two of the mentioned low quality studies were removed from the final results, the remaining high quality articles showed that the injection improved pain relief when compared with the control group. Therefore, this particular outcome of MSCs injection on pain in patients with osteoarthritis can not be significantly concluded.

All of the included studies evaluated the outcome of MSCs injection on the function of patients with OA. Even though a significant result was observed of stem cells injection as compared with the opposing group, the positive effect was not significant at six months post-injection. As there was a wide variance of these reported outcome measures, we utilized the Lysholm score and Lequesne index to portray the effect of stem cells injection. The final results showed that MSCs injection has had a significant effect on Lysholm score or Lequesne index when compared with the control therapeutic measures.

In order to highlight the comparison between stem cells and hyaluronic acid, four studies[31- 34] were included. One article[36] which studied VAS had a nonsignificant effect on pain reduction with the use of stem cells. When Lequesne index was compared in two studies, it indicated that stem cells were more effective than hyaluronic acid. However, when comparison was made using WOMAC, no significant difference could be associated between the two. However, owing to the limitation of sample size, our findings indicate that stem cells' effect on pain and functional outcome compared with hyaluronic acid cannot be significantly concluded.

A notable limitation keeping this review in mind is that the findings studied and observed have a high risk of bias and being low quality on the basis of evidence studied. Moreover, the studies are limited in number included in this literature search. And even though various different outcome measures of pain and function have been studied in the articles, our main focus has been on Lysholm score and Lequesne index for comparing function between MSCs injection and the control groups. Throughout our review we assumed that no interaction between MSCs and other co-interventions like platelet-rich plasma (PRP) must have taken place without testing this assumption. This adds further limitation.

Finally, only a limited number of small trials have been studied and only twelve studies containing 486 participants in total were included, biases could not be completely appreciated. With such a

limited number of randomized control trials and the data published, only positive outcomes being published is at a high risk while the negative trials are disregarded. Therefore, with such limitations, confidence in the outcomes studied and observed in this literature review is reduced.

Conclusion

The current evidence shows and points out that there could be a potential positive effect of stem cells injection on pain in patients diagnosed with osteoarthritis. There could also be a significant potential positive outcome on physical function in patients with osteoarthritis after the injection. However, the evidence can be considered weak, with some studies being low quality, outcomes not being completely reported and small sample sized studies. Therefore, in conclusion, large sample sized studies and high quality RCTs need to be carried out to prevent such biases, which will evaluate and measure outcomes related to patients' pain relief and functional improvement to support the role of stem cells injection for osteoarthritis patients.

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References

1. Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int 2010;107:152-62. doi: 10.3238/arztebl.2010.0152.
2. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Rheum Dis Clin North Am 2008;34:515-29. doi: 10.1016/j.rdc.2008.05.007.
3. Gouttebarge V, Inklaar H, Backx F, Kerkhoffs G. Prevalence of osteoarthritis in former elite athletes: a systematic overview of the recent literature. Rheumatol Int 2015;35:405-18. doi: 10.1007/s00296-014-3093-0.
4. Gouttebarge V, Inklaar H, Frings-Dresen MH. Risk and consequences of osteoarthritis after a professional football career: a systematic review of the recent literature. J Sports Med Phys Fitness 2014;54:494-504.
5. Kuijt MT, Inklaar H, Gouttebarge V, Frings-Dresen MH. Knee and ankle osteoarthritis in former elite soccer players: a systematic review of the recent literature. J Sci Med Sport 2012;15:480-7. doi: 10.1016/j.jsams.2012.02.008.
6. Jüni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et

al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015;2015:CD005328. doi: 10.1002/14651858.CD005328.pub3.
7. Richette P, Chevalier X, Ea HK, Eymard F, Henrotin Y, Ornetti P, et al. Hyaluronan for knee osteoarthritis: an updated meta-analysis of trials with low risk of bias. RMD Open 2015;1:e000071. doi: 10.1136/rmdopen-2015-000071.
8. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy 2016;32:495-505. doi: 10.1016/j.arthro.2015.08.005.
9. Kongtharvonskul J, Anothaisintawee T, McEvoy M, Attia J, Woratanarat P, Thakkinstian A. Efficacy and safety of glucosamine, diacerein, and NSAIDs in osteoarthritis knee: a systematic review and network meta-analysis. Eur J Med Res 2015;20:24. doi: 10.1186/s40001-015-0115-7.
10. de Campos GC, Tieppo AM, de Almeida CS Jr, Hamdan PC, Alves WM, de Rezende MU. Target-based approach for osteoarthritis treatment. World J Orthop 2020;11:278-84. doi: 10.5312/wjo.v11.i6.278.
11. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthr. Cartil 2022;30:184-95. Doi: 10.1016/j.joca.2021.04.020.
12. Dowsey MM, Brown WA, Cochrane A, Burton PR, Liew D, Choong PF. Effect of Bariatric Surgery on Risk of Complications After Total Knee Arthroplasty: A Randomized Clinical Trial. JAMA Netw Open 2022;5:e226722. doi: 10.1001/jamanetworkopen.2022.6722.
13. Batushansky A, Zhu S, Komaravolu RK, South S, Mehta-D'souza P, Griffin TM. Fundamentals of OA. An initiative of Osteoarthritis and Cartilage. Obesity and metabolic factors in OA. Osteoarthritis Cartilage 2022;30:501-15. doi: 10.1016/j.joca.2021.06.013.
14. Gilbert SJ, Bonnet CS, Blain EJ. Mechanical Cues: Bidirectional Reciprocity in the Extracellular Matrix Drives Mechano-Signalling in Articular Cartilage. Int J Mol Sci 2021;22:13595. doi: 10.3390/ijms222413595.
15. Charlier E, Deroyer C, Ciregia F, Malaise O, Neuville S, Plener Z, et al. Chondrocyte dedifferentiation and osteoarthritis (OA). Biochem Pharmacol 2019;165:49-65. doi: 10.1016/j.bcp.2019.02.036.
16. Barry F, Boynton RE, Liu B, Murphy JM. Chondrogenic differentiation of mesenchymal stem cells from bone marrow: differentiation-dependent gene expression of matrix components. Exp Cell Res 2001;268:189-200. doi: 10.1006/excr.2001.5278.
17. Carstairs A, Genever P. Stem cell treatment for musculoskeletal disease. Curr Opin Pharmacol 2014;16:1-6. doi: 10.1016/j.coph.2014.01.005.
18. Wolfstadt JI, Cole BJ, Ogilvie-Harris DJ, Viswanathan S, Chahal J. Current concepts: the role of mesenchymal stem cells in the management of knee osteoarthritis. Sports Health 2015;7:38-44. doi: 10.1177/1941738114529727.
19. Osborne H, Anderson L, Burt P, Young M, Gerrard D. Australasian College of Sports Physicians-position statement: the place of mesenchymal stem/stromal cell therapies in sport and exercise medicine. Br J Sports Med 2016;50:1237-44. doi: 10.1136/bjsports-2015-095711.
20. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem 2006;98:1076-84. doi: 10.1002/jcb.20886.
21. Wei CC, Lin AB, Hung SC. Mesenchymal stem cells in regenerative medicine for musculoskeletal diseases: bench, bedside, and industry. Cell Transplant 2014;23:505-12. doi: 10.3727/096368914X678328.
22. Castro-Manrreza ME, Montesinos JJ. Immunoregulation by mesenchymal stem cells: biological aspects and clinical applications. J Immunol Res 2015;2015:394917. doi: 10.1155/2015/394917.
23. Delling U, Brehm W, Metzger M, Ludewig E, Winter K, Jülke H. In vivo tracking and fate of intra-articularly injected superparamagnetic iron oxide particle-labeled multipotent stromal cells in an ovine model of osteoarthritis. Cell Transplant 2015;24:2379-90. doi: 10.3727/096368914X685654.
24. Jing XH, Yang L, Duan XJ, Xie B, Chen W, Li Z, et al. In vivo MR imaging tracking of magnetic iron oxide nanoparticle labeled, engineered, autologous bone marrow mesenchymal stem cells following intra-articular injection. Joint Bone Spine 2008;75:432-8. doi: 10.1016/j.jbspin.2007.09.013.
25. Shim G, Lee S, Han J, Kim G, Jin H, Miao W, et al. Pharmacokinetics and in vivo fate of intra-articularly transplanted human bone marrow-derived clonal mesenchymal stem cells. Stem Cells Dev 2015;24:1124-32. doi: 10.1089/scd.2014.0240.
26. Varma HS, Dadarya B, Vidyarthi A. The new avenues in the management of osteo-arthritis of knee--stem cells. J Indian Med Assoc 2010;108:583-5.
27. Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy 2013;29:2020-8. doi: 10.1016/j.arthro.2013.09.074.
28. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. Knee 2012;19:902-7. doi: 10.1016/j.knee.2012.04.001.
29. Koh YG, Kwon OR, Kim YS, Choi YJ. Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study. Arthroscopy 2014;30:1453-60. doi: 10.1016/j.arthro.2014.05.036.
30. Orozco L, Munar A, Soler R, Alberca M, Soler F, Huguet M, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: two-year follow-up results. Transplantation 2014;97:e66-8. doi: 10.1097/TP.0000000000000167.
31. Gan FY, Tang C, Guo DB, Xiao LX. The treatment of mesenchymal stem cell transplantation for knee osteoarthritis: a clinical observation study. Modern Diagn Treat 2014;1:3512-3.
32. Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A, et al. Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. Transplantation 2015;99:1681-90. doi: 10.1097/TP.0000000000000678.
33. Lee WS, Kim HJ, Kim KI, Kim GB, Jin W. Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. Stem Cells Transl Med 2019;8:504-11. doi: 10.1002/sctm.18-0122.
34. Murphy C, Mobasheri A, Táncos Z, Kobolák J, Dinnyés A. The Potency of Induced Pluripotent Stem Cells in Cartilage Regeneration and Osteoarthritis Treatment. Adv Exp Med Biol. 2018;1079:55-68. doi: 10.1007/5584_2017_141.
35. Lamo-Espinosa JM, Prósper F, Blanco JF, Sánchez-Guijo F, Alberca M, García V, et al. Long-term efficacy of autologous bone marrow mesenchymal stromal cells for treatment of knee osteoarthritis. J Transl Med 2021;19:506. doi: 10.1186/s12967-021-03160-2.
36. Dulic O, Rasovic P, Lalic I, Kecojevic V, Gavrilovic G, Abazovic D, et al. Bone Marrow Aspirate Concentrate versus Platelet Rich Plasma or Hyaluronic Acid for the Treatment of Knee Osteoarthritis. Medicina (Kaunas) 2021;57:1193. doi: 10.3390/medicina57111193.
37. Chen CF, Hu CC, Wu CT, Wu HH, Chang CS, Hung YP, et al. Treatment of knee osteoarthritis with intra-articular injection of allogeneic adipose-derived stem cells (ADSCs) ELIXCYTE®: a phase

I/II, randomized, active-control, single-blind, multiple-center clinical trial. Stem Cell Res Ther 2021;12:562. doi: 10.1186/s13287-021-02631-z.

38. Tan Y, Jiang M, Yu HY, Li JL, Qing ZY. Therapeutic effect of arthroscopy combined with autologous bone marrow stem cell grafting on knee osteoarthritis. J Tradit Chin Orthop Traumatol 2013;10:35-8.
39. Wakitani S, Okabe T, Horibe S, Mitsuoka T, Saito M, Koyama T, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. J Tissue Eng Regen Med 2011;5:146-50. doi: 10.1002/term.299.
40. Koh YG, Jo SB, Kwon OR, Suh DS, Lee SW, Park SH, et al. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. Arthroscopy 2013;29:748-55. doi: 10.1016/j.arthro.2012.11.017.
41. Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. Int J Rheum Dis 2011;14:211-5. doi: 10.1111/j.1756-185X.2011.01599.x.
42. Jo CH, Lee YG, Shin WH, Kim H, Chai JW, Jeong EC, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells 2014;32:1254-66. doi: 10.1002/stem.1634.