IN BRIEF

Subchondral Bone Injections for the Treatment of Knee Osteoarthritis

E. Carlos Rodriguez-Merchan, MD, PhD

Research performed at Department of Orthopedic Surgery, La Paz University Hospital, Madrid, Spain

Received: 1 June 2025 *Accepted: 23 June 2025*

Abstract

The existing literature on whether subchondral bone injections in knee osteoarthritis is advisable for relieving patient pain is minimal and the level of evidence is low. A recent case series (2023) analyzed 30 individuals with knee OA (Kellgren-Lawrence 2-3). It showed that combined intraarticular and subchondral BMAC (bone marrow aspirate concentrate injections) provided clinical and imaging benefits up to 24 months for the treatment of symptomatic knee OA, with a low failure rate, and a significant reduction of bone marrow edema. Besides, VAS (visual analog scale) pain worsened at the final follow-up, although remained lower compared to the baseline value. Although some studies mention that subchondral bone injections can relieve pain in mild/moderate knee OA, it does not seem reasonable to advise it until better-designed research can confirm the preliminary studies discussed in this article.

Level of evidence: III

Keywords: Efficacy, Knee, Osteoarthritis, Subchondral bone injections

Introduction

Several authors have published on the efficacy of intra-articular injections of various substances [hyaluronic acid, platelet-rich plasma (PRP), ozone] for the treatment of symptomatic knee osteoarthritis (OA).[1-4]

In 2019 Sundaram et al stated that subchondral bone injections had been proposed to expand the therapeutic arsenal by potentially halting knee OA progression and postoponing the need for total knee arthroplasty (TKA) in individuals with early/moderate-stage disease.[5]

The aim of this article was to analyze the existing publications in PubMed from the beginning of its operation until May 30, 2025 on the role of subchondral bone injections in the treatment of knee OA. Using "subchondral injections osteoarthritis" as keywords 595 articles were found of which only 8 were analyzed because they were directly related to the title of this article (inclusion criteria). The rest were therefore excluded.

Main body

In 2021 Hernigou et al found that human bone marrow mesenchymal stem cell (MSC) injection in subchondral lesions of knee (as compared with TKA) had a sufficient effect on pain to delay or avert the TKA in the contra lateral joint of individuals with bilateral OA. Bone marrow lesions were predictive factors for future TKA in the knee with subchondral cell therapy at 15 years follow-up.[6,7]

In a literature review published in 2021 by Hernigou et al it was investigated whether joint, subchondral bone, or/and scaffolds implantation of fresh autologous bone marrow aspirate concentrated (BMAC) containing MSCs would improve OA. The review suggested that both implantation of subchondral BMAC and scaffolds loaded with BMAC could diminish the need for further surgery.[8]

In 2021 Kon et al assessed the safety as well as clinical and MRI (magnetic resonance imaging) results of a combined approach of intraarticular and subchondral BMAC injections. The combined treatment showed safety and positive result up to 12 months of follow-up in individuals with symptomatic knee OA associated with subchondral bone alterations. It was suggested that targeting both subchondral bone and joint environment can render promising results, and that BMAC can be a reasonable option

Corresponding Author: E. Carlos Rodriguez-Merchan, Department of Orthopedic Surgery, La Paz University Hospital, Madrid, Spain

Email: ecrmerchan@hotmail.com

THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

for this combined approach to manage knee OA.[9]

In a review article published in 2022 by Gardner et al it was concluded that injections of orthobiologics into the subchondral bone might be superior to intraarticular injections for the treatment of OA.[10]

In 2023 Kon et al assessed the clinical and imaging findings up to 24 months of follow-up in individuals treated with combined subchondral and intraarticular BMAC injections for the management of painful unilateral knee OA. It was stated that combined intraarticular and subchondral BMAC injections rendered clinical and imaging benefits up to 24 months for the management of symptomatic knee OA (Kellgren-Lawrence 2-3) with durable clinical outcomes, a low failure rate (13%), and a substantial reduction of bone marrow edema.[11]

In an animal study published in 2025 Wu et al investigates the effect of subcutaneous injection of human umbilical cord mesenchymal stem cells (UCMSCs) on OA and its possible therapeutic mechanism compared to intrarticular injection. It was found that the efficacy of UCMSCs for treating OA rats via subchondral bone injection was equivalent to that of intraarticular; and even superior to intraarticular in terms of subchondral bone phenotype via regulating apoptosis and TGF-β/pSmad2 signaling in osteoblasts, suggesting subchondral bone injection of UCMSCs as a potential and promising cell therapy for OA treatment.[12]

All the information from the eight articles analyzed in this article is shown in [Table 1].

Table 1. Main articles on the role of subchondral bone injections for the treatment of knee osteoarthritis (OA).[5-12]

AUTHORS [REFERENCE]	YEAR	TYPE OF STUDY AND OBJETIVE	METHODS	RESULTS	CONCLUSIONS
Sundaram et al [5]	2019	Systematic review. The aim of this study was to evaluate the effectiveness and safety of subchondral intraosseous injection for the treatment of knee OA.	A systematic review was carried out on PubMed-Medline, and the Cochrane Database of systematic reviews. The minimum follow-up was 6 months. Six studies were included with a total of 163 individuals.	The mean follow-up was 18 months (range: 6-24 months). PROMs, complications, and conversion to TKA were collected. All six studies showed PROMs improvement relative to baseline. Overall, the five studies reporting VAS pain outcomes improved from a baseline mean score of 6.68 to 2.74. Also, KOOS, Tegner-Lysholm, and/or IKDC scores rose compared with baseline scores in all studies. Overall, 2.5% (4/163) of individuals had a complication attributed to study-related treatment. Most individuals (81%, 86/106) remained TKA-free at a 1-year follow-up.	This systematic review exhibited high degree of heterogeneity in both measurement of outcomes and delivery of treatment, with a high risk of bias. Subchondral intraosseous injection should not be used in advanced knee OA. In light of the limitations of the current literature, advising in favor or against these injections for early to moderate knee OA is challenging.
Hernigou, Delambre, et al [6]	2021	Prospective randomized study versus contralateral TKA. The purpose of this study was to determine whether bone marrow lesions on MRI are predictive of risk progression to TKA during the first 10 years after subchondral cell therapy.	This study included 140 adults aged 65 to 90 years. These 140 individuals (mean age 75.4 ± 14.2 years) planned to experience staged-bilateral TKA for medial OA, had "comparable" pain in both knees, and accepted randomization of the knees for surgery. They underwent TKA on one side and a subchondral injection of MSCs (from iliac bone marrow concentrate) on the contralateral knee during the same anesthetic. The bone marrow graft of 20 cm^3 volume (10 cc in the tibia and 10 cc in the femur) contained average 7800 MSCs/mL (range 3120 to 11,560). The baseline volume of BMLs on the tibia and on the femoral condyle determined on MRI was average 3.4 cm^3 (range 0.4 to 6.4 cm^3). The risk of subsequent TKA due to absence of bone marrow lesions regression as well as OA grade was evaluated with Cox proportional-hazards ratio (HR) after control of baseline variables (number of cells injected, age, knee alignment).	After treatment with MSCs injection in bone marrow lesions of the subchondral bone, medial femorotibial compartment BML volume experienced regression over 24 months (mean regression 1.5 cm^3, range 0.8 to 3.2 cm^3). At the most recent follow up (average of 15 years, range 10 to 20 years), a total of 25 (18%) of the 140 individuals experienced TKA carried out at a mean of 10 years (range, 5 to 15 years) after the date of the cell therapy. The overall incidence of TKA after cell therapy was 1.19% per person-year which was equivalent to the risk of a revision for a primary TKA in the contralateral knees of the same patient population (21 revisions, corresponding to 1% revision per person-year; $p = 0.34$). After adjusting for confounders, persistent BMLs larger than 3 cm^3 after cell therapy was a strong independent risk factor for TKA (HR = 4.42 [95% CI = 2.34 to 7.21]; $p < 0.001$), regardless of OA grade, with higher risks demonstrated for larger BMLs. Incidence rates of TKA were also higher for young individuals and for knees presenting severe malalignment.	This study showed that subchondral bone marrow concentrate (as compared with TKA) had a sufficient effect on pain to postpone or avoid the TKA in the contralateral joint of individuals with bilateral OA. BMLs were predictive factors for future TKA in the knee with subchondral cell therapy at 10 years follow-up.

Table 1. Continued

Hernigou, Bouthors, et al [7]	2021	Prospective randomized controlled clinical trial. Its aim was to know what would better drive OA stabilization to postpone total TKA: targeting the synovial fluid by injection or targeting on the subchondral bone with MSCs implantation.	This study was carried out between 2000 and 2005 in 120 knees of 60 individuals with painful bilateral knee OA with a similar OA grade. During the same anesthesia, a bone marrow concentrate of 40 mL containing an average 5727 MSCs/mL (range 2740 to 7540) was divided in two equal parts: after randomization, one part (20 mL) was delivered to the subchondral bone of femur and tibia of one knee (subchondral group) and the other part was injected in the joint for the contralateral knee (intraarticular group). MSCs were counted as CFU-F (colony fibroblastic unit forming). Clinical outcomes of the patient (Knee Society score) were obtained along with radiological imaging outcomes (including MRIs) at 2 year follow-up. Subsequent revision surgeries were identified until the most recent follow-up (average of 15 years, range 13 to 18 years).	At 2 year follow-up, clinical and imaging (MRI) improvement was higher on the side that received cells in the subchondral bone. At the most recent follow-up (15 years), among the 60 knees treated with subchondral cell therapy, the yearly TKA incidence was 1.3% per knee-year; for the 60 knees with intraarticular cell therapy, the yearly TKA incidence was higher ($p = 0.01$) with an incidence of 4.6% per knee-year. For the side with subchondral cell therapy, 12 (20%) of 60 knees experienced TKA, while 42 (70%) of 60 knees experienced TKA on the side with intraarticular cell therapy. Among the 18 individuals who had no subsequent surgery on both sides, all preferred the knee with subchondral cell therapy.	Implantation of MSCs in the subchondral bone of an osteoarthritic knee was more effective to postpone TKA than injection of the same intraarticular dose in the contralateral knee with the same grade of OA.
Hernigou, Vertongen, et al [8]	2021	Literature review. This study analyzed the evidence for each different approach to treat OA.	These authors investigated whether joint, subchondral bone, or/and scaffolds implantation of fresh autologous BMAC containing MSCs would improve OA.	There was in vivo evidence that suggested that all these different approaches (intraarticular injections, subchondral implantation, scaffolds loaded with BMAC) can improve the patient. These authors encountered that the utilization of intraarticular injections resulted in a significant alleviation of pain symptoms in the short run and was maintained in 12 months. However, the clinical trials indicated that the application of autologous bone marrow concentrates in combination with scaffolds or in injection in the subchondral bone was superior to intraarticular injection for long-run outcomes. The tendency of MSCs to differentiate into fibrocartilage affecting the outcome was a common issue faced by all the studies when biopsies were carried out, except for scaffolds implantation in which some hyaline cartilage was encountered.	This review suggested that both implantation of subchondral BMAC and scaffolds loaded with BMAC could diminish the need for further surgery.
Kon et al [9]	2021	Prospective, multicenter, pilot study. The aim of this study was to assess safety as well as clinical and MRI results of a combined approach of intraarticular and subchondral BMAC injections.	Thirty individuals (19 men, 11 women, 56.4 ± 8.1 years) with symptomatic knee OA were treated with a combination of an intraarticular and two subchondral BMAC injections (femoral condyle and tibial plateau). Individuals were assessed at baseline and at 1-3-6-12 months of follow-up with the IKDC subjective, VAS, KOOS, and EQ-VAS scores. The MRI assessment was carried out with the WORMS score.	No major complications were found and only two individuals were considered treatment failures, requiring a new injective or surgical treatment. The IKDC subjective score improved significantly from 40.5 ± 12.5 to 59.9 ± 16.1 at 3 months, 59.1 ± 12.2 at 6 months, and 62.6 ± 19.4 at 12 months ($p < 0.0005$). A similar improvement was reported for VAS pain and all KOOS subscales at all follow-ups, while EQ-VAS did not show any significant improvement. The MRI analysis showed a significant bone marrow edema reduction ($p = 0.003$), while the remaining WORMS parameters did not show any significant changes.	The pilot evaluation of this combined BMAC injective treatment showed safety and positive outcome up to 12 months of follow-up in individuals with symptomatic knee OA associated with subchondral bone alterations. These findings suggested that targeting both subchondral bone and joint environment can provide promising results, and that BMAC can be a valid option for this combined approach to treat knee OA.

Gardner et al [10]	2022	Review article (comparison of subchondral versus intraarticular injections).	This study compared subchondral versus intraarticular orthobiologic injections for the treatment of knee OA.	Compelling data showed that intraarticular orthobiologic injections, such as PRP and MSCs, were effective in providing alleviation of OA symptoms. Besides, some data suggested that injections of orthobiologics into the subchondral bone might be superior to intraarticular injections for the management of OA.	This review highlighted the rationale and current evidence for intraarticular and subchondral bone injections of orthobiologics for the treatment of OA.
Kon et al [11]	2023	Case series. The aim of this study was to assess the clinical and imaging findings up to 24 months of follow-up in individuals treated with combined subchondral and intraarticular BMAC injections for the treatment of knee OA.	Thirty consecutive individuals (19 males, 11 females) aged between 40 and 75 years (mean age 56.4 ± 8.1 years) with unilateral symptomatic knee OA (Kellgren-Lawrence 2-3) were included in the study. Individuals were treated with combined intraarticular and subchondral bone BMAC injections (total 9 ml) under fluoroscopic control. IKDC subjective score, VAS for pain, KOOS, and EQ-VAS were prospectively assessed up to 24 months. Radiographs were carried out at baseline and at 24 months after the procedure. MRI was assessed with the WORMS score at baseline, 6-12 months, and 24 months of follow-up.	No major complications and a 13% failure rate were found. The IKDC subjective score remained stable from 62.6 ± 19.4 at 12 months to 63.4 ± 17.1 at 24 months (both $p < 0.0005$ compared to baseline, 40.5 ± 12.5). Similar improvements were found for all KOOS subscales, while EQ-VAS did not show any significant improvement. VAS pain worsened from 3.0 ± 1.9 at 12 months to 4.4 ± 1.8 at the final follow-up ($p = 0.0001$), although remaining lower compared to the baseline value of 6.3 ± 1.8 ($p = 0.002$). The radiographic assessment did not reveal signs of improvement or deterioration of the OA grade. The MRI findings showed a worsening in marginal osteophytes and synovitis, but a significant reduction of bone marrow edema at 24 months ($p < 0.0005$).	Combined intraarticular and subchondral BMAC injections provided clinical and imaging benefits up to 24 months for the treatment of symptomatic knee OA, with durable clinical results, a low failure rate, and a significant reduction of bone marrow edema.
Wu et al [12]	2025	Animal study. These authors investigated the effect of subchondral injection of human umbilical cord MSCs (UCMSCs) on OA and its possible therapeutic mechanism compared to intraarticular injection.	Male Sprague-Dawley rats with anterior cruciate ligament transection (ACLT) received saline or UCMSC injections via subchondral or intraarticular. Consecutive injections once a week for three weeks and withdrawal for another four weeks, followed by radiographical scanning, histopathological, immunohistochemical, and terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick-end labelling (TUNEL) staining. Cell counting Kit-8 (CCK-8) assay, alkaline phosphatase (ALP), alizarin red staining (ARS), TUNEL, flow cytometry, quantitative real-time polymerase chain reaction (qRT-PCR) and Western blotting were employed in TNFα-induced MC3T3-E1 cells to illustrate the exact pathogenesis mechanism.	Intraarticular and subchondral UCMSC injections preserved cartilage, synovium, and subchondral bone parameters like trabecular bone volume fraction (BV/TV). Subchondral injection uniquely improved trabecular separation (Tb.Sp) and trabecular number (Tb.N). Subchondral and intraarticular injections of UCMSCs demonstrated equivalent efficacy in promoting osteoblastic bone formation and attenuating aberrant angiogenesis of subchondral bone. In addition, these authors demonstrated that osteoblast apoptosis and Smad2-dependent TGF-β were crucial and interactive subchondral bone pathological features in OA. In vivo and vitro studies further revealed that UCMSCs inhibited excessive TGF-β/pSmad2 signaling to regulate aberrant vascularization, osteoblast apoptosis and differentiation imbalance, ultimately maintaining osteochondral homeostasis.	The efficacy of UCMSCs for treating OA rats via subchondral injection was equivalent to that of intraarticular; and even superior to intraarticular in terms of subchondral bone phenotype via regulating apoptosis and TGF-β/pSmad2 signaling in osteoblasts, suggesting subchondral injection of UCMSCs as a potential and promising cell therapy for OA treatment.

Conclusion

According to the literature reviewed, subchondral bone injections have not yet been clearly demonstrated to be a worthwhile treatment for patients with painful knee OA of Kellgren-Lawrence grades 2-3. Much more research on the subject is needed to be able to advice on this type of injections.

Acknowledgement

N/A

Authors Contribution: Author who conceived and designed the analysis: ECR-M/ Author who collected the data: ECR-M/ Author who contributed data or analysis tools: ECR-M/Author who performed the analysis: ECR-M/Author who wrote the paper: ECR-M

Declaration of Conflict of Interest: The author does NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: The author received NO financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: Our institution does not require ethical approval for reporting retrospective studies.

Declaration of Informed Consent:

The author declares that there is no information (names, initials, hospital identification numbers, or photographs) in the submitted manuscript that can be used to identify patients.

E. Carlos Rodriguez-Merchan, MD, PhD [1]

1 Department of Orthopedic Surgery, La Paz University Hospital, Madrid, Spain

References

1. Rodriguez-Merchan EC. Intraarticular injections of platelet-rich plasma (PRP) in the management of knee osteoarthritis. Arch Bone Jt Surg. 2013;1(1):5-8.
2. Hedayatabad JJ, Kachooei AR, Chaharjouy NT, et al. The effect of ozone (O3) versus hyaluronic acid on pain and function in patients with knee osteoarthritis: a systematic review and meta-analysis. Arch Bone Jt Surg. 2020;8(3):343-354. doi: 10.22038/abjs.2020.46925.2292.
3. Jalali Jivan S, Monzavi SM, Zargaran B, et al. Comparative analysis of the effectiveness of intra-articular injection of platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: results of an open-label trial. Arch Bone Jt Surg. 2021;9(5):487-495. doi: 10.22038/abjs.2021.52003.2569.
4. Rodriguez-Merchan EC, De la Corte-Rodriguez H. The role of intraarticular injections of hyaluronic acid and platelet rich plasma for the treatment of articular pain in knee osteoarthritis. Arch Bone Jt Surg. 2025;13(1):54-61. doi: 10.22038/ABJS.2024.78852.3621.
5. Sundaram K, Vargas-Hernández JS, Sanchez TR, et al. Are subchondral intraosseous injections effective and safe for the treatment of knee osteoarthritis? A systematic review. J Knee Surg. 2019;32(11):1046-1057. doi: 10.1055/s-0039-1677792.
6. Hernigou P, Delambre J, Quiennec S, Poignard A. Human bone marrow mesenchymal stem cell injection in subchondral lesions of knee osteoarthritis: a prospective randomized study versus contralateral arthroplasty at a mean fifteen year follow-up. Int Orthop. 2021;45(2):365-373. doi: 10.1007/s00264-020-04571-4.
7. Hernigou P, Bouthors C, Bastard C, Flouzat Lachaniette CH, Rouard H, Dubory A. Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomized study. Int Orthop. 2021;45(2):391-399. doi: 10.1007/s00264-020-04687-7.
8. Hernigou J, Vertongen P, Rasschaert J, Hernigou P. Role of scaffolds, subchondral, intra-articular injections of fresh autologous bone marrow concentrate regenerative cells in treating human knee cartilage lesions: different approaches and different results. Int J Mol Sci. 2021;22(8):3844. doi: 10.3390/ijms22083844.
9. Kon E, Boffa A, Andriolo L, et al. Subchondral and intra-articular injections of bone marrow concentrate are a safe and effective treatment for knee osteoarthritis: a prospective, multi-center pilot study. Knee Surg Sports Traumatol Arthrosc. 2021;29(12):4232-4240. doi: 10.1007/s00167-021-06530-x.
10. Gardner JE, Williams CW, Bowers RL. Subchondral versus intra-articular orthobiologic injections for the treatment of knee osteoarthritis: a review. Regen Med. 2022;17(6):389-400. doi: 10.2217/rme-2021-0174.
11. Kon E, Boffa A, Andriolo L, et al. Combined subchondral and intra-articular injections of bone marrow aspirate concentrate provide stable results up to 24 months. Knee Surg Sports Traumatol Arthrosc. 2023;31(6):2511-2517. doi: 10.1007/s00167-022-07195-w.
12. Wu C, Xu H, Wu Z, et al. Subchondral injection of human umbilical cord mesenchymal stem cells ameliorates knee osteoarthritis by inhibiting osteoblast apoptosis and TGF-beta activity. Stem Cell Res Ther. 2025;16(1):235. doi: 10.1186/s13287-025-04366-7.